1. 1 Diagnosis

AN EMPIRICAL EVALUATION OF THE ARIZONA SEXUAL EXPERIENCE SCALE (ASEX) QUESTION-NAIRE TO IDENTIFY SEXUAL DYSFUNCTION IN PATIENTS OF THE SCHIZOPHRENIA SPECTRUM

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Objective: The main aims of this paper are threefold: a) to assess the frequency of sexual dysfunction in a sample of out-patients with schizophrenia and schizoaffective disorder under antipsychotic therapy; b) to investigate the effect of different antipsychotics on sexual function; and c) to evaluate the accuracy of the Arizona Sexual Experience Scale (ASEX) to identify sexual dysfunction. Method: A cross-sectional study of sexual function was conducted with one-year consecutive outpatients from the Schizophrenia Program of the Universidade Federal de Sao Paulo (Proesq), from February 2007 to January 2008. Patients, who met DSM IV criteria for schizophrenia or schizoaffective disorder, were asked to fulfill both the Arizona Sexual Experience Scale (ASEX) and the Dickson Glazer Scale for the Assessment of Sexual Functioning Inventory (DGSFi) at a single interview. Results: 137 patients entered the study (86 were males and 51 were females). The sensitivity and specificity of the ASEX at identification of sexual dysfunction in relation with DGSFi scores were respectively: 80.8%, (95% CI = 70.0%–88.5%) and 88.1% (95% CI = 76.5%–94.7%), and the misclassification rate was 9,5%. The ROC curve comparing the ASEX and the DGSFi scores revealed a value of 0.93 (CI = 0.879–0.970), with the optimum cutoff point of ASEX for sexual dysfunction being 14/15. Sexual dysfunction measured by ASEX was higher among females (79.2%) than for males (33.3%), and this difference was statistically significant (χ^2 = 27.41, df = 1, $P < .001$). Conclusion: Patients under antipsychotic treatment showed a high level of sexual complaints, and the ASEX questionnaire showed to be an accurate instrument to identify sexual dysfunction in an out-patient sample of patients with schizophrenia and schizoaffective disorders. Females showed a higher frequency of sexual dysfunctions than males and sexual drive and ability to reach orgasm were the most affected areas. The use of antipsychotics, especially the combinations of medications, was more likely to impair sexual functioning.
ID: 540733

METHODS FOR DETERMINING INTER-RATER RELIABILITY OF THE PANSS: A REVIEW OF THE LITERATURE

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Inter-rater reliability (IRR) is an important consideration in CNS trials, as poor reliability increases error variance, which reduces study power and increases the risk for type II errors. The increasing placebo response in schizophrenia points to renewed examination of the role of clinical ratings. The method for evaluating reliability impacts the reliability figures, eg, observation of tapes results in artificially higher IRR than independent interviews, as the former artificially reduces information variance. Thus, the methodology for determining IRR is a critical factor in interpreting a study's results. To date there has been no systematic review of the methods used in determining reliability of the PANSS, and the relationship between method and level of IRR. We searched Pub Med using keywords "PANSS" and "reliability." In only 53% of studies (18/34), the method for determining reliability was described: these included rating tapes (9/34;26%), joint interviews (8/34;24%), and a combination of both methods (1/34;3%). No studies used independent interviews. Rater training was done in 56% (19/34) of studies. IRR total PANSS score ranged from 0.63 to 0.71 for tapes and from 0.92 to 0.99 for joint interviews. The positive subscale ranged from 0.56 to 0.99 (tapes) and 0.72 to 0.99 for joint interviews, and the negative subscale ranged from 0.27 to 0.90 for tapes and from 0.63 to 0.92 for joint interviews. Methodology for testing IRR is not often cited. Tape rating is the most common method reported. Reliability on the PANSS using joint methods is good, but unknown with independent assessments.
ID: 550710

COMPARING SCHIZOPHRENIA AND BIPOLAR PROBANDS: NEUROPSYCHOLOGY, NEUROPHYSIOLOGY AND FMRI

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A better characterization of similarities and differences between schizophrenia and affective psychoses is needed to define their diagnostic boundaries and to clarify their overlapping and unique pathophysiologies. We contrasted untreated first episode patients with schizophrenia, bipolar disorder and psychotic depression, and matched controls, on a battery of neuropsychological, oculomotor and fMRI measures. Previously published data from the Pittsburgh first episode study will be presented together with data from our new sample from Chicago that now includes 40 schizophrenia patients, 22 bipolar patients and 15 unipolar depression patients. In both samples, neuropsychological data indicate similar profiles of deficit across cognitive domains across disorders that were more severe in schizophrenia patients. Profiles of oculomotor deficit were more variable. Measures most heavily dependent on prefrontal systems were impaired in all groups but showed greater deficit in schizophrenia. Preliminary analyses of fMRI data with oculomotor tasks also suggest greater deficits in prefrontal systems in schizophrenia. Some attention-dependent and sensorimotor tasks were equally or more impaired in one or both groups of patients with affective psychoses than in schizophrenia. Patients with psychotic depression generally had the least severe cognitive deficits, but uniquely manifested some specific motor system dysfunctions. These findings document neurobehavioral deficits in both affective and nonaffective psychotic disorders. The similarities and differences in their severity and profile suggest that the illnesses have somewhat different impacts across functional neural systems, and also suggest promising phenotypic approaches for characterizing unique and common neurocognitive deficits associated with schizophrenia and psychotic affective disorders.
ID: 550510

MAJOR DEPRESSIVE EPISODES IN FIRST EPISODE PSYCHOSIS

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There are clear indications that depressive symptoms contribute to increased morbidity and mortality in patients with schizophrenia spectrum disorders, but the actual rate of patients experiencing clinically significant depressive

symptoms in the early phases of the disorder (from before onset of psychotic symptoms until start of first treatment) is not known. The main aims of this study were to examine the prevalence of lifetime DSM-IV Major Depressive Episode in a sample of patients with first episode schizophrenia spectrum disorders, and to examine the demographic and clinical characteristics distinguishing this patient group (MDE) from patients that never had experienced a Major Depressive Episode (Non-MDE). A total of 123 patients (age 18–65) from the ongoing longitudinal Thematic Organized Psychosis research study (TOP) were included at the time of their first treatment. Diagnoses were set according to SCID-I for DSM-IV (schizophrenia, schizophreniform disorder, schizoaffective disorder and psychosis NOS). Present symptom level was assessed by the Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning scale (GAF). Premorbid functioning was measured by the Premorbid Adjustment Scale (PAS). The duration of untreated psychosis (DUP) was measured as weeks from first psychotic symptoms until start of first treatment. A total of 59 (48%) patients had experienced one or more MDE. Poor premorbid adjustment in childhood and adolescence was significantly associated with more depressive episodes. There were no significant differences between the MDE and Non-MDE group for age, gender and DUP. With the exception of the PANSS general score (which was higher in the MDE group), there were no differences between the groups concerning positive and negative symptom scores or GAF scores. This study shed more light on the frequency of MDE among patients with first episode psychosis. The fact that as many as 48% of the patients met the MDE criteria shows the importance of achieving more knowledge about depressive symptoms among patients with first episode psychosis.
ID: 550371

HEIGHTENED RATES OF SCHIZOAFFECTIVE DISORDER AMONG IMMIGRANTS? A CROSS-SECTIONAL STUDY

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Migration has been found to be a relevant risk factor in the development of schizophrenia and other psychotic disorders. The purpose of this study is to explore if migration is associated with particular symptoms among psychosis patients exposed to migration (IM) compared to non-immigrants (NI) patients. Our main hypothesis is that among an IM group we will find a higher rate of schizophrenia-like psychotic symptoms in connection with mood episodes, suggesting possible heightened rates of schizoaffective (SA) disorder compared to NI. We used naturalistic cross-sectional data from a cohort of patients being treated for schizophrenia- or bipolar-spectrum disorders in the greater Oslo region (Thematic Organized Psychosis research (TOP) study). Exclusion criteria was drug-induced psychosis, IQ < 70, or limited Scandinavian language skills. Participants (age 18–65) received a DSM-IV diagnosis on the basis of a SCID-I interview. Present symptom level was assessed by the Positive and Negative Syndrome Scale (PANSS). Immigration status was based on observed ethnicity, country of birth, mother tongue and immigrant status of parents. The sample consisted of 435 participants with lifetime psychosis symptoms, whereof 27 % were 1st. or 2nd. generation IM. We found more IM with a DSM-IV diagnosis of SA disorder ($\chi^2 = 8214$, $df = 1$; $P < .005$), and more NI with a diagnosis of Bipolar I (BPI) ($\chi^2 = 12,915$, $df = 1$; $P < .001$). Logistic regression was performed to explore main effects of diagnostic grouping for SA and BPI in the context of independent variables. Results indicated that IM had a 7,2 (CI = 2,4–21,6) times higher risk of receiving a SA disorder diagnosis (Wald = 12,609, $df = 1$, $P < .001$) than NI. ANOVA analyses of the three PANSS subscales (positive, negative and general) showed similar symptom patterns for IM and NI in the SA group, but significantly higher positive ($F = 18,848$, $df = 3$, $P < .001$), and general symptoms ($F = 9,396$, $df = 3$, $P < .001$) for the BPI-IM group compared to the BPI-NI group. In conclusion we found that immigrant status was a significant predictor of receiving a SA diagnosis in our sample. Comparisons of symptom patterns within diagnostic categories suggests that this finding was not due to misclassification of affective disorders as belonging to the schizophrenia spectrum in the IM group, but rather supports the hypothesis that aspects of the migration experience are associated with specific clinical symptom expression.
ID: 550226

IS SCREENING FOR PSYCHOSIS POSSIBLE IN GENERAL POPULATION SAMPLES?

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The criteria used to ascertain youth at high clinical risk for psychosis emphasize the recent onset of sub-psychotic intensity psychotic-like symptoms. We have developed a self-report screening instrument (the Prodromal Questionnaire or PQ) to provide an efficient screen for these symptoms. Adolescents and young adults referred to a prodromal psychosis research clinic completed the PQ and the Structured Interview for Prodromal Syndromes. PQ positive symptom scores predicted a concurrent prodromal or psychotic diagnosis with 92% sensitivity and 42% specificity. The PQ thus shows good preliminary validity in detecting individuals with an interview-based diagnosis of a prodromal or psychotic syndrome, but is not sensitive to the threshold between prodromal and full psychosis. We also assessed the rates of self-reported "prodromal" psychotic symptoms and related distress in a college population ($N = 1020$). Participants' responses to the PQ were highly similar to the responses of non-psychotic-spectrum patients in the original PQ validation sample, suggesting that the PQ may perform similarly with a variety of populations. Applying the cutoff proposed for screening treatment-seeking patients identified 43% of students, while comparatively fewer participants (25%) endorsed items at the frequency required for prodromal syndrome diagnosis by interview (ie, weekly), and only 2% endorsed the positive symptom items as distressing. Although attenuated psychotic experiences are commonly reported by "normal" young adults, frequent and distressing items identify a proportion of students more consistent with the prevalence of psychotic-spectrum disorders in the general population, which suggests a potential for future screening of unselected samples.
ID: 550092

IMPRESSION-MANAGEMENT EFFECTS IN PARANOIA ASSESSMENT

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It is challenging to objectively measure undesirable personal characteristics (eg, racism) due to participants' tendency to portray a positive impression. However, impression-management effects can be overcome with the use of non-obvious measures. In schizophrenia, there is evidence linking paranoia with an Externalizing-Personalizing Bias (EPB), a tendency to blame negative experiences on the hostile intentions of others. However, this finding is inconsistent, possibly due to participants' efforts to appear non-paranoid. The Social Cognition Screening Questionnaire (SCSQ) uses non-obvious measurement to assess both EPB and efforts to under-endorse EPB. The SCSQ is presented as a memory task consisting of ten verbally-presented, second-person vignettes describing unpleasant

social interactions. Each is followed by three Yes-or-No "memory" questions, one of which tacitly elicits a judgment about whether story characters had negative intentionality toward the participant (eg, "Was the manager trying to be rude to you?"). Five of the vignettes include explicit evidence of negative intentionality toward the participant, while five include no such evidence. The SCSQ yields two scores: 1) An EPB score reflects endorsement of negative intentionality in vignettes in which it is *not present*; 2) A Disavowal of Negative Intentionality (DNI) score reflects non-endorsement of negative intentionality in vignettes in which it *is present*. Outpatients with schizophrenia completed the SCSQ and PANSS ($n = 38$), and two established measures of paranoid attributional bias ($n = 19$). Convergent validity of the EPB score was supported by its correlations with existing measures of paranoid attributional bias ($r = .598$; $P = .011$; and $r = .574$; $P = .010$). The DNI score correlated significantly with the PANSS suspiciousness item ($r = .357$; $P = .033$), whereas the EPB score did not ($r = .257$; NS). Additionally, the DNI score discriminated between schizophrenia subgroups that were high (> 3; $n = 14$) versus low (< 3; $n = 12$) on the PANSS suspiciousness item ($t = 2.15$; $P = .042$), whereas the EPB score did not ($t = 1.61$; NS). This study provides preliminary evidence that individuals with paranoia may under-report inferences of negative intentionality, and that objective measurement of this effect may add incremental validity to paranoia assessment in schizophrenia.
ID: 549924

ANTIDEPRESSANT EFFECT OF ANTIPSYCHOTICS IN SCHIZOPHRENIA: COMPARISON OF TYPICAL AND ATYPICAL ANTIPSYCHOTIC DRUGS

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Objective: Despite progress in the treatment of schizophrenia the efficacy of atypical antipsychotics on depressive symptoms in schizophrenia is not well established and for clarify this question we examined the effects of atypical versus typical antipsychotics on depressive symptoms in a cohort study in patients with schizophrenia. Methods: The data were drawn from a cohort, naturalistic, observational study with 96 subjects diagnosed as being affected by schizophrenia during a re-exacerbation phase. The patients were taking typical or atypical antipsychotics. All subjects completed the Calgary Depression Scale for Schizophrenia (CDSS) to rate the severity of the depressive symptoms. The severity of schizophrenic symptoms was rated by the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) severity and improvement scales. Assessments of scales above were undertaken at baseline, 8 weeks, 16 weeks and 24 weeks. Results: The PANSS total score higher than 70 and female gender were significantly associated with the presence of depressive symptoms. Global improvement of depressive symptoms was associated with use of antipsychotics in general, however atypical antipsychotics showed a statistically significant effect when compared to typical antipsychotics. Conclusion: This observational study provides evidence that atypical antipsychotics are more effective than typical antipsychotics on the depressive symptoms in patients with schizophrenia.
ID: 549525

AFFECT IN SCHIZOPHRENIA: IMPLICATIONS FOR DSM V AND RESEARCH

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A flat or inappropriate facial affect has been a consistent finding among a portion of people with schizophrenia from the earliest descriptions of the disease. Flat affect (restricted, blunted) describes a lack of observable emotional reactivity and inappropriate affect is the term for an incongruous facial emotional expression. Kraepelin viewed flat affect as indicative of a lack of emotional experience. Bleuler also observed incongruence between emotional expression and self-reported experience in his schizophrenia patients. Both Kraepelin and Bleuler agreed that abnormalities in affect denoted a defective or diminished emotional expression. As such, anchored ratings of the magnitude of affect abnormalities may be important indicators of the success of new treatments for the core emotional deficits in the disease. Additionally, as the truly heterogeneous nature of the schizophrenia syndrome has been better appreciated, the possibility of using stable flat affect as a categorical tool for subtyping schizophrenia has been supported in numerous studies.
ID: 549399

ANTI-GAD65, NMDAR AND VGKC ANTIBODIES DETECTED IN FIRST EPISODE PSYCHOSIS

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There are many lines of evidence to suggest that schizophrenia may be an autoimmune disorder. To date there have been no reports of pathogenic antibodies in cases of pure psychosis. However in cases of limbic encephalitis, where psychosis is often present, there have been new serum autoantibodies identified, which have been responsive to immunotherapy. Our aim was to screen serum from cases of first episode psychosis for these antibodies. Methods: 16 patients under the care of Cameo (www.cameo.nhs.uk). Serum collected within six months of symptoms (range 2–26 weeks, mean 8 weeks). Serum was also collected from 22 patients with chronic schizophrenia (length illness >2 years) and 23 healthy controls. Voltage gated potassium channel (VGKC)-Ab titres were measured by radioimmunoassay (Vincent et al. 2004), and anti GAD65 antibodies measured by radio-immunoprecipitation assay using 125I (RSR Cardiff). Anti-NMDAR antibodies were measured:HEK cells were transfected with NR1 and NR2B subunits and incubated with patient serum and a fluorescent antihuman secondary to detect cell surface binding. Results: One case with raised NMDAR antibodies, one with raised VGKC antibodies and three with raised GAD antibodies were identified in the first episode group. No antibodies were found in the chronic patients, or controls. Discussion: These cases were all under the care of a first episode psychosis service. None had any signs of organic illness. None had features suggestive of limbic encephalitis. No antibodies were identified in chronic group, in keeping with other studies of autoimmune mediated neurological disorders. Each of these antibodies identified has validity in having an aetiological role in schizophrenia. If the incidence found in this group is replicated, 31% of schizophrenia may be autoimmune, and amenable to immunotherapy. We should now aim to establish the frequency of these antibodies in all cases of first episode psychosis, and introduce early recognition and treatment.
ID: 549060

NEUROPSYCHOLOGICAL TESTING AND STRUCTURAL MAGNETIC RESONANCE IMAGING IN THE DIAGNOSIS OF SCHIZOPHRENIA AFTER A FIRST PSYCHOTIC EPISODE

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Introduction: Making an accurate diagnosis after a first psychotic episode is important for initiating treatment and counseling patients and families. Previous work by our group demonstrated the potential of applying linear discriminant analysis (LDA) to structural magnetic resonance imaging (sMRI) and neuropsychological (NP) testing in adolescents (Pardo et al. 2006). In this study, we developed sMRI and NP models for disease diagnosis and, additionally, cross-validated the accuracy of our modeling algorithms. The analysis was made on a subject subsample characterized by a first psychotic episode from the larger MIND Clinical Imaging Consortium (MCIC) sample. Methods: Prospective first-episode schizophrenic patients (47 controls; 28 patients) underwent structured interview evaluations, sMRI scanning and NP testing. In the ensuing analysis 75 NP and 95 sMRI variables were used. We developed diagnostic models based on the following algorithms. First, a stepwise-LDA was performed, where subsets of the original variables were used in the final models. Second, an LDA was performed on latent variables, which were in turn created by Principal Component Analysis (PCA) and selected according to Humphrey-Ilgen parallel analysis. Error estimation of the modeling algorithms was evaluated by leave-one-out external-cross-validation. The described analyses were performed on NP and sMRI variables both in combination and separately. Results: The following cross-validation results were obtained.

Table.

sex/age	antibody	assay level (normal range)	clinical features	other diagnostic tests	outcome
F/20	GAD65	3904cpm (<2500)	3/7 elated mood, paranoid psychosis	repeat GAD after 18/12 < 3u/l	remitting course for 6 months, treated with Risperidone. well since
M/20	GAD65	5581cpm (<2500)	2/12 paranoid psychosis, catatonia		5/12 admission, continued negative symptoms
M/25	GAD65	21622cpm (<2500)	2/52 paranoid psychosis		improved after 2/12 on Olanzapine disengaged from follow up gradual improvement over 3/12 on Risperidone
F/22	VGKC	2300 at 1ul cpm (<100)	2/52 paranoid psychosis, insomnia, overactivity	MRI normal, Na+ normal, no evidence paraneoplastic syndrome	
M/21	NMDAR	+ve	2/52 insomnia, elated mood, paranoid and grandiose delusions	No evidence teratoma	Improved after 3/12 Olanzapine

sMRI only. a) Stepwise-LDA: 53.6% sensitivity and 74.5% specificity, b) PCA-LDA: 67.9% sensitivity and 72.3% specificity. NP only. a) Stepwise-LDA: 78.5% sensitivity and 85.1% specificity, b) PCA-LDA: 78.5% sensitivity and 91.5% specificity. Combined sMRI-NP. a) Stepwise-LDA: 60.7% sensitivity and 72.3% specificity, b) PCA-LDA: 89.3% sensitivity and 93.6% specificity. Conclusions: These results reveal that a) the combination of sMRI and NP variables can significantly improve diagnostic accuracy, b) the PCA-LDA approach accounting for more of the variance in the data is more robust than Stepwise-LDA, c) NP variables are more informative than sMRI indicating that cognitive deficits precede structural anomalies. This work verifies the accuracy of the applied modeling algorithms and, by extension, any of the models produced in the process. To obtain an error estimate for a specific model to be used in clinical practice, that model will have to be tested on a separate test sample.
ID: 548502

A PARADIGM SHIFT: CRITICAL CHANGES ANTICIPATED IN THE CLASSIFICATION OF PSYCHOTIC DISORDERS

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DSM-V, when published in 2012, will shape the clinical care, education, and research agendas for psychotic illnesses for the following decade. It was previously hoped that classification would be reorganized based on etiological and pathophysiological evidence that would move diagnoses from syndromes to disease entities. In the absence of sufficient evidence, critical issues related to a more modest modification of DSM-IV are addressed. These issues, briefly stated, are: 1) Criteria emphasize reality distortion and neglect avolition, psychomotor and cognitive pathology; 2) Schizoaffective schizophrenia is weak on validity and reliability, but is clinically useful; 3) Psychosis NOS is over-utilized, and there is inadequate data on psychotic disorders other than schizophrenia; 4) Data from early detection studies has not been integrated with classification; 5) Similarities between cases of schizophrenia and cases on the diagnostic borders raise questions regarding bipolar disorders and schizophrenia spectrum personality disorders; and 6) The role of affect pathology in classification of psychotic disorders. Addressing these issues is an important challenge, but a more substantial basis for advancing classification relates to a proposed paradigm shift. A dimensional system may augment diagnostic classes. This presentation will outline psychopathological dimensions based on evidence that domains of pathology represent critical issues for clinical care and education, and provide a more heuristic framework for research. Individual cases within a class vary in which domains of pathology are manifest, and domains of pathology may better explain across boundary similarities. Dimensions include some diagnostic criteria (eg, negative symptoms) and some additional features (eg, depression, cognition). A tentative model for diagnostic criteria and pathological dimensions for schizophrenia will be presented for audience critique.
ID: 548047

THE AUSTRALIAN SCHIZOPHRENIA RESEARCH BANK (ASRB): THE DEVELOPMENT OF AN ELECTRONICALLY DELIVERED CLINICAL ASSESSMENT BATTERY

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The Australian Schizophrenia Research Bank (ASRB) was established in 2007 to collect cross referenced diagnostic, neuropsychological, anatomical (MRI) and genetic data from 2000 people with schizophrenia and 2000 healthy age and gender matched controls. A clinical assessment battery (CAB), administered over 3 hours, was developed and consists of a structured diagnostic interview, clinical and family history, measures of neuropsychological and cognitive performance (WTAR, WASI, RBANS, COWAT), symptom (SANS) and general functioning (GAF) ratings. This large scale data collection across multiple Australian sites necessitated a quality-controlled, time and cost effective data collection strategy. To this end, the ASRB has developed an electronic version of the assessment battery called eCAB. The eCAB was developed using SQL programming. Data is entered directly into the software by assessment officers using a lap top computer. Each assessment item is presented in a question and answer format, and the program allows navigation through questions with comment boxes for note taking. Quality control parameters for data input and a checking mechanism at the end of the assessment ensure all questions are answered. Scoring formulae embedded into the program calculate raw scores, standard scores and factor scores for the neuropsychological evaluations and rating scales, reducing scoring time and error. The OPCRIT algorithm (Craddock et al., 2006) is used to derive diagnostic confirmation based on DIP answers. Completed assessments are uploaded to the ASRB central server in encrypted format for access by researchers. The eCAB is a time and cost efficient method for collecting research data, and significantly reduces data handling errors through automatic score calculations. It is well tolerated by patients and controls alike, and eliminates the need for paper assessment storage in large scale projects such as the ASRB. ID: 550847

A NEW DIAGNOSTIC CLASS: THE PRODROMAL RISK SYNDROME FOR FIRST PSYCHOSIS

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Since Falloon's seminal pilot study in 1992 (1), research on early detection and intervention in psychotic disorders has demonstrated that reliably identifiable clinical syndromes can be identified in help-seeking persons which are also ''prodromal'', meaning they signal a very high risk for developing (converting to) psychosis in the near future, ie, within 2–3 years (2). A Scale of Prodromal Symptoms (SOPS) embedded within a Structured Interview for Prodromal Syndromes (SIPS) has been developed by the presenter and colleagues and used in ''prodromal'' clinics nationally, and internationally in studies of the natural course and treatment of these clinical high risk syndromes (3). This presentation will include: 1) a review of prodromal assessment from Falloon (1) to Yung and McGorry (4) to Miller and McGlashan (3), 2) reliability studies of the SIPS and SOPS prodromal syndromes (5), 3) early longitudinal studies validating high risk for psychosis in these syndromes (4), 4) a later study of 372 patients meeting SIPS/SOPS prodromal criteria (6) showing predictive accuracy for psychosis comparable to

other areas of preventive medicine and (7) an unpublished study comparing the NAPLS prodromal sample with a) 195 natural subjects, b) 200 help-seeking persons who do not develop psychosis, c) 40 familial (genetic) high risk subjects, and d) 53 persons with Schizotypal personality disorder. The groups are compared across the symptoms, functioning, comorbidity, family history, and course of illness domains originally identified by Robins and Guze as validating psychiatric syndromes. The data from these studies collectively support the inclusion of the Prodromal Risk Syndromes for First Psychosis in DSM-IV alongside traditional diagnoses in the Psychotic Disorders spectrum. Specific criteria have been formulated. The clinical, therapeutic, scientific, ethical, and political issues involved in adding a reliably identifiable and potentially treatable risk syndrome to the DSM-V psychotic disorders will also be discussed (8).

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ID: 551923

A TAXOMETRIC ANALYSIS OF NEGATIVE SYMPTOMS IN THE WHO TEN-COUNTRY STUDY OF SCHIZOPHRENIA

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It has been proposed that enduring primary negative symptoms, or deficit symptoms, reflect a distinct subtype of schizophrenia—the deficit syndrome (Carpenter et al., 1988). Although differences between deficit and nondeficit schizophrenics are suggestive of a distinct and separate disease process (Buchanan and Carpenter, 1994), these findings are also consistent with a dimensional-only model where the deficit syndrome merely reflects an extreme on a continuum of severity. Taxometric statistical methods (Waller and Meehl, 1998) allow for a quantitative examination of whether a taxonic or latent class model best describes negative symptoms in schizophrenia. Using such methods Blanchard et al. (2005) have shown that negative symptoms are taxonic. In this study we sought to replicate these findings in a larger and more diverse sample. The current investigation is a taxometric analysis of the World Health Organization Ten-Country Study of Schizophrenia (Jablensky, et al., 1992). Negative symptom data from a subset of 694 schizophrenia participants within the WHO study were analyzed using the taxometric methods of maximum covariance analysis (MAXCOV) and mean above minus below a cut (MAMBAC). Results from MAXCOV and MAMBAC indicated a latent class with base rates of 16% and 18%, respectively. These results are consistent with a categorical view of negative symptoms in schizophrenia. ID: 551893

SCHIZOPHRENIA COLLABORATIVE RESOURCE (SCORE) TOOL: TRACKING PATIENT PROGRESS

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Unlike many other chronic disorders, stages of illness and disease progression for patients with schizophrenia are not well characterized. This gap in

understanding the course and stages of the illness impacts expectations, goal setting, recognition of clinically relevant change, and ultimately overall patient management. We describe software, entitled the Schizophrenia Collaborative Resource Tool (SCoRe), that identifies the stage of illness, creates a personalized patient profile, and tracks patient progress over time. A group of clinicians who are experts in the treatment of patients with schizophrenia were involved in the development of this tool. Literature reviews were conducted and data from clinical trials were analyzed to guide the clinicians in describing stages of illness and associated symptom severity and level of functioning. A software tool designed to capture information about the status of patients with schizophrenia was then developed for use in clinical practice. This interactive program captures information (from both clinician and patient) on current interventions, symptom severity, social functioning, stress tolerance, cognition, and physical health. The patient's illness is staged according to an algorithm that considers the type of clinical intervention needed and the severity of core symptoms of schizophrenia. Four stages of illness were defined based on both clinician input and data analysis: 1) acute, 2) stabilization, 3) stable, and 4) remission. These stages are reassessed at each subsequent visit. This information can then be used to develop treatment goals and to track patient progress over time. The program can also provide graphical outputs of an individual patient's clinical profile over time. SCoRe may help in the management of patients with schizophrenia. It can identify milestones for improvement throughout the course of illness toward which both the patient and clinician can strive to achieve. Additionally, this software provides physicians with a mechanism to record and track patient progress and assist with the development of treatment goals. Supported by funding from Ortho-McNeil Janssen Scientific Affairs, LLC.
ID: 551850

DEVELOPMENT AND INITIAL PSYCHOMETRIC EXPLORATION OF A CLINICAL GLOBAL IMPRESSION SCALE FOR SCHIZOAFFECTIVE DISORDER (CGI-SCA)

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Currently, there is no rating scale specific to schizoaffective disorder (SCA). This study tests the psychometric properties of a new scale, the Clinical Global Impression for Schizoaffective Disorder (CGI-SCA), using the familiar 7-point format to measure positive, negative, manic, depressive and global severity and change. Experts adapted the CGI and developed a manual for evaluation of patients with SCA. Data for psychometric exploration of the CGI-SCA were gathered during training for an international multicenter drug trial using the CGI, PANSS, HAM-D-21 and YMRS. Exploratory data were obtained using 132 investigators from the United States ($N = 41$), India ($N = 35$) and Eastern Europe ($N = 56$) rating 2 videotapes. Inter-rater reliability was initially evaluated using intra-class correlation (ICC) and convergent and divergent validity using Cramer's V. Effect sizes were calculated for sensitivity to change. A questionnaire examined content validity. Power analysis using the training data suggested that with sufficient variability among subjects, inter-rater reliability could be demonstrated with 2 raters and 12 subjects. This formal assessment was accomplished using 12 sets of videotaped interviews and 2 additional raters. Test-retest reliability was assessed with 10 randomly selected raters from each region rating the same tapes on 2 occasions separated by a minimum of 2 weeks and maximum of 4 weeks. Inter-rater reliability varied across the 3 geographic regions. ICC ranges: CGI-Manic, 0.829–0.948; CGI-Depressive, 0.916–0.972; CGI-Positive, 0.245–0.759; CGI-Negative, 0.464–0.624; CGI-Global, −0.005–0.428. Pairs of ratings, eg, YMRS and CGI-Manic, converged in 5 of 6 cases (Cramer's V 0.44–0.82) and diverged in 3 of 5, eg, CGI-Positive vs CGI-Manic (Cramer's V 0.64–0.76). Sensitivity to change ranged in effect size from 2.7 to 12.7. Overall, raters in each region concurred that the CGI-SCA was useful, with 90% or more agreeing that the CGI-SCA captured a large fraction of the variance. Formal testing of inter-rater reliability found ICCs of 0.5–0.883. Test-retest reliability ranged from 0.444 to 0.888. Initial psychometric examination indicates at least moderate inter-rater and test-retest reliability for these symptom domains and good sensitivity to change. Content validity was high in the United States, India and Europe. These results suggest that the CGI-SCA may be useful in clinical trials. Supported by Ortho-McNeil Janssen Scientific Affairs, LLC. ID: 551816

DIMENSIONAL CLASSIFICATION OF SCHIZO-PHRENIA

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Introduction: The objective of this research is to propose a simple, dimensional classification of schizophrenia, based on the concept of endophenotypes (Gottesman, 2003). Methods: A total of 1200 participants were the subjects. Neuropsychological tests were applied . We operationalized two neurocognitive endophenotypes: sensorial gating and cognitive performance. Results: A: Dimensional Classification of Schizophrenia: Structural dimensions. A1: Genetically-defined Dimensions, as a Working Group 1. Negative Schizophrenia and 2. Positive Schizophrenia. B. The Longitudinal Diagnosis of the Disease: Longitudinal Dimensions. B1. The Continuous Dimensions: The dimensions as phases of a continuum from a pre-clinical state to a more chronic, pathological state. 1) the schizophrenia prodrome. 2) first episode of illness. 3) The Spontaneous Amileoration Syndrome: typically active phase or positive symptoms. 4) A progressive neurodegeneration and neurodeterioration phase. 5) Deficit Syndrome. Conclusions: The classification allows full inclusion of the neurocognitive endophenotypes in the classification of schizophrenia, defining the genotypes to benefit the understanding and treatment of schizophrenia. The full explanation of this categorization will be presented along with the results of this pilot sample.

Reference

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ID: 551775

SCHIZOPHRENIA AT THE BORDERS WITH BIPOLAR DISORDER AND SCHIZOTYPAL PERSONALITY

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In order to delineate similarities and differences between schizophrenia (SCZ) and schizophrenia spectrum personality pathology, on the one hand, and SCZ and bipolar disorder (BD), on the other for the purposes of defining the relationship between these disorders in DSM-V, external validators, evaluated by imaging methodology including functional

imaging and measurement of D_1 binding and raclopride displacement, biomarkers, physiologic measures, cognitive status, genetic data, environmental risk factors, course, and treatment response will be compared between schizotypal personality disorder (SPD) and SCZ and between BP and SCZ incorporating new data from our and other laboratories. These studies suggest that SCZ and SPD share structural and functional imaging characteristics, cognitive profile, and asociality but are distinguished by the neurobiology of dopaminergic activity, course of illness, comorbidity, and treatment response. SPD and schizophrenic patients both show volume decreases, with sparing of frontal lobe in SPD. SPD patients, in contrast to schizophrenia patients overactivate instead of underactivate prefrontal cortex, recruit compensatory regions (eg, BA10) doing cognitive tasks, are more vigilance on a startle-blink task, and evidence lesser activation of the dopamine system on provocation than SCZ patients. In contrast, SCZ and BD, both of which may be characterized by psychosis, appear to share dopaminergic hyperactivity and reduced gabaminergic markers as measured in imaging and neurochemical studies, treatment response to dopamine antagonists, genetic antecedents such as neuroregulin 1, and altered physiology. BP and SCZ patients both share decreases in grey matter, greater in SCZ patients, reduced NAA on MRS, abnormal PPI, P300, and pursuit maintenance, while BP patients have better preserved cognitive function and intact MMN. SPD thus appears to be related to schizophrenia as reflected as part of the schizophrenia spectrum while bipolar disorder and schizophrenia share complementary characteristics reflecting a diathesis to psychosis, reflected in neurotransmitter (DA, GABA) abnormalities.
ID: 551702

STRESS REACTIVITY IN ULTRA-HIGH RISK PATIENTS: THE INFLUENCE OF CLINICAL SYMPTOM LEVELS, LIFE STRESS, SOCIAL SUPPORT AND OTHER PSYCHOSOCIAL FACTORS

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From the perspective of the diathesis-stress model of schizophrenia, life stress is likely a critical factor in the development of psychosis. It has been suggested that the hypothalamic-pituitary-adrenal (HPA) axis may serve as a biological pathway underlying the relationship between stress and illness expression (eg, Corcoran et al., 2003). The present study sought to elucidate this relationship in individuals at ultra-high risk (UHR) for psychosis by examining HPA activity at rest and in response to a psychosocial stressor. Previous studies investigating the stress response in schizophrenia have shown that patients display higher resting cortisol relative to healthy individuals and a blunted response to stress (eg, Jansen et al., 2000). Heightened resting cortisol levels also have been observed in schizotypal personality disorder, possibly reflecting vulnerability to schizophrenia (Walker et al., 1996). Although prior research has examined cortisol reactivity in patients with schizophrenia-spectrum disorders, less is known about the relationship between risk status for psychosis and the stress response. In the present study, the Trier Social Stress Test (TSST) was administered to 33 UHR individuals, as determined by the Structured Interview for Prodromal States (Miller et al., 2002), and 20 healthy comparison subjects. Salivary cortisol was sampled before and immediately after the TSST. UHR participants were later subdivided into those who subsequently developed a psychotic disorder ($n = 10$) and those who did not ($n = 23$) over the following 12–24 months. Initial results suggest that among the UHR individuals, those who converted to

psychosis had higher resting cortisol relative to non-converters and healthy participants. Both UHR groups showed blunted cortisol reactivity to the TSST as compared to healthy individuals, who exhibited a robust response to the stressor. These findings support the view that the stress response may be a marker of evolving psychosis. It is unclear, however, if the distinct patterns of HPA reactivity among UHR patients who converted might be due to their vulnerability for psychosis, the acuity of their illness and related increases in life stress, or a combination of these factors. Behavioral ratings of life stress, clinical symptom levels and their relevance to this hypothesis are examined, as well as relationships between cortisol reactivity and self-report measures of coping style, social support, and early life adversity.
ID: 551667

PERSONALITY TRAITS PREDICT PSYCHOTIC TRANSITION IN ULTRA HIGH RISK

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This is the first study to deal with personality traits in the transition of Ultra High Risk Subjects. In a Ultra High Risk group for psychosis (Dutch Prediction Study for Psychosis: subjects ($n = 77$) rated the Schizotypal Personality Questionnaire (SPQ) and a DSM-IV screener (PDQ-R)for personality disorders at the start of the study. After a median follow up time of 24 months transitioners were compared with non-transitioners on the SPC en SCID-II subscales with regard to transition (yes/no) and time to transition (multivariate survival with correction; two sided $P = .10$). SPQ-factors 2 (negative schizotypy) and factor 3 (desorganization)turned out to be the best predictors for transition (yes versus no) and speed of transition. Conclusion is that: 1) personality traits influence transition into psychosis; 2) schizotypy concept is applicable to UHR, 3) SPQ is a better predictor for transition than PDQ-R.
ID: 551291

AN INNOVATING TOOL FOR THE EARLY DIAGNOSIS OF SCHIZOPHRENIA AND OTHER PSYCHIATRIC DISORDERS

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The phase before the emergence of a first episode psychosis is today attract a widespread interest in the field of clinical research of schizophrenia. Indeed, it has been shown that the earlier patients are treated, the better their outcome. It is also important from a preventive perspective. However, the prodromal phase is difficult to detect as it is characterised by many none specific behavioural and cognitive deficits. The most widely used approach is an interview for the detection of ultra-high risk (UHR) patients (McGorry, Yung 1996). This test combines symptoms and signs with other risk factors, eg, age, family history, personality disorder. This approach has revealed to be promising but its time consuming. The aim of our work was to see if non-verbal motor tasks could be as efficient in dissociating UHR, first episode and chronic patients with schizophrenia. A load cell was used to quantify those motor disorders and agency impairments that are known to be affected in schizophrenia (Bulot et al. 2007; Delevoye-Turrell et al. 2003). The CAARMS (Comprehensive Assessment of At Risk Mental State—Yung et al., 2003) was used

to divided the young patients into two distinct groups: UHR patients ($n =$ 10) and patients after the onset of fully fledged psychosis ($n = 10$). Control subjects included healthy and schizophrenic adults. The subjects' task was to use an object to hit (task 1) or resist (task 2) impacts produced by a collision between the hand held object and a pendulum. The results of the hit task provided the means to quantify motor preparation, motor prediction and motor coordination. For the resist task, we further contrasted the case when the pendulum was self released and released by the experimenter in order to evaluate agency. The two groups of patients were impaired in the execution of motor control. However, the pattern of the deficit was different compared to both healthy and chronic schizophrenic adults. A deficit of agency was observed only in the group of patients after the onset of fully fledged psychosis. This deficit was similar to that observed in the chronic schizophrenic; the UHR had similar results than that observed in the healthy controls. Motor deficits are present very early in the evolution of psychosis development while the agency deficit seems to be the result of a first episode psychosis. These first results suggest that non-verbal motor tasks may reveal an efficient tool to help for an early diagnosis of schizophrenia.
ID: 551186

KRAEPELIN'S INFLUENCE ON THE SCHIZOPHRENIA CONCEPT IN DSM

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Emil Kraepelin has shaped diagnostic systems and research strategies in psychiatry with the introduction of the diagnoses dementia praecox and manic-depressive illness. He conjectured that clinical observation, experimental studies of patients, and basic studies of disease mechanisms will identify psychiatric disorders, with clearly delineated etiology, mechanisms, and outcome. However, his separation of diagnostic classes and the reliance on disease course and outcome for diagnostic classification have been challenged repeatedly. Despite these concerns, DSM-III and DSM-IV have continued a categorical classification of psychotic disorders in the tradition of Kraepelin, emphasizing outcome and affective symptoms for the subtyping of psychotic disorders and minimizing the importance of psychomotor changes and avolition. The presentation will review in detail how Kraepelin's dementia praecox concept: 1) evolved over several decades, 2) emphasized avolition and cognitive deficits and deemphasized psychotic symptoms, and 3) continues to fuel schizophrenia research even today. The presentation will review the implications of Kraepelin's scientific biases for the current DSM and will outline options for DSM-V.
ID: 551175

VALIDATION OF "PRODROMAL" CRITERIA TO DETECT INDIVIDUALS AT ULTRA HIGH RISK OF PSYCHOSIS: 2 YEAR FOLLOW UP

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Background: Identification of individuals "prodromal" for schizophrenia and other psychotic disorders relies on criteria that predict onset within a brief period. Previous trials and biological research have been predicated on the view that certain "ultra high risk" (UHR) criteria detect "the prodrome", but there is a need to test the validity of these criteria. Also, it may be the fact of seeking help from a UHR service, rather than the UHR criteria per se, which predicts onset of psychosis. Aim: To assess the predictive validity of the UHR criteria in a clinical population. A secondary aim was to assess clinicians' ability to detect UHR criteria. Method: Presence of UHR criteria was determined in 292 individuals at baseline. At 2 year follow up the number of new cases of psychotic disorder was assessed in those meeting and not meeting the UHR criteria. Results: Help-seeking per se was not a risk factor for development of psychotic disorder, rather it was the UHR+ status at baseline that predicted psychosis onset within 2 years. The transition rate of 16% was much lower than in initial cohorts (over 40%). Clinicians frequently missed UHR+ve individuals and failed to diagnose the UHR criteria in others. Conclusions: Although young help-seekers meeting UHR criteria are at greater risk of psychotic disorder than those who do not meet them, caution is needed in their management, since a high transition rate can no longer be assumed. Training with a structured assessment tool may aid clinicians in detecting the UHR criteria.
ID: 550971

IS LATE-ONSET SCHIZOPHRENIA A DISTINCT SUBTYPE OF SCHIZOPHRENIA?

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Introduction: Onset of schizophrenia in later life has been a controversial topic. Different versions of DSM have taken varying positions on this issue, usually without adequate data. An International Consensus Statement by researchers in late-life schizophrenia recommended that age 40 be used as the lower age cutoff for defining late-onset schizophrenia (LOS). Yet, whether LOS is a distinct subtype of schizophrenia remains unsettled. Methods: We analyzed data from over 800 community-dwelling patients age > 40 years with DSM-III-R or DSM-IV diagnosis of schizophrenia or schizoaffective disorder, studied at our NIMH-funded research center at UCSD over a 12-year period. These included more than 700 patients with EOS, and about 100 with LOS, using age of 40 at first manifestation of prodromal symptoms as the cutoff. Baseline assessments included standardized instruments for psychopathology (Positive And Negative Syndrome Scale, Hamilton's Depression scale), motor abnormalities (Abnormal Involuntary Movement Scale), cognition (including Wechsler Adult Intelligence Scale—Revised, California Verbal Learning Test, Wisconsin Card Sorting Test), and health-related quality of life (Quality of Well-Being scale). The patients were followed annually. Results: Compared to EOS, the LOS patients were older, had a greater proportion of women, shorter duration of illness, less severe positive symptoms, better performance on abstraction/cognitive flexibility and psychomotor speed, and better health-related quality of life. Most of these differences remained significant after controlling for age, gender, and severity of negative symptoms. The EOS and LOS groups did not differ in education, ethnicity, severity of depressive, negative, or motor symptoms, proportion of patients with deficit syndrome, or in crystallized verbal knowledge and perceptual-organization/visual construction. The diagnosis of most of the patients followed longitudinally did not change. Discussion: Our results support the notion that LOS may be a distinct subtype of schizophrenia. Limitations of our study will be discussed. The implications of the results are clinical as well as theoretical in that they may relate to pathophysiologic factors present at menopausal or post-menopausal age of onset of LOS. Biological research on identifying factors responsible for a delayed onset of schizophrenia could be useful in opening possible new leads in prevention and intervention strategies for schizophrenia.
ID: 552223

2. 2. Phenomenology

BILINGUAL LANGUAGE UNDERSTANDING IN SCHIZOPHRENIA

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Investigations of language in people with schizophrenia date back to the first scientific accounts of the disorder. Virtually all of this work has focussed on language in monolingual people despite the fact that bilingualism is more prevalent globally than monolingualism. Basic studies of bilingualism are relevant to theories of language and neurocognitive dysfunction in schizophrenia, and to both the clinical assessment and treatment of bilingual individuals with schizophrenia. We present preliminary data from a study of language in four French-English bilingual people diagnosed with schizophrenia and four matched bilingual non-psychiatric controls. Participants read short English sentences that were literally plausible ("She kept her desk"), idiomatic ("He had a lark"), or anomalous ("He hired the debt"), and they made speeded decisions about the sensibility of each sentence. These sentences also varied in the contextual constraint of the final word of literal and idiomatic sentences (eg, "She drove the car" vs. "He bought the knife"). Further, a common feature of bilingual communicative interaction, code-mixing, was experimentally simulated by replacing the final word of each sentence with its French translation equivalent (eg, "He used his comb" vs. "He used his peigne"). Mixed design analysis of variance revealed that bilingual people with schizophrenia were slower to make sensibility judgments overall, less able to comprehend idiomatic language, and were less likely to capitalize on high contextual constraint than bilingual non-psychiatric controls (all relevant group interactions, $P < .05$). Thus, several of the most replicated findings observed for monolingual people with schizophrenia were evident in this preliminary bilingual sample. Moreover, comprehension of code-mixed sentences was less accurate and slower for bilingual people with schizophrenia than for non-psychiatric controls, especially for contextually constrained sentences (all relevant group interactions, $P < .05$). This novel finding suggests that language impairment in schizophrenia may be especially pronounced under conditions that simulate normal bilingual communicative interaction. Whether bilingual people with schizophrenia engage in less cross-language interaction than normal, or experience more difficulty resolving cross-language interaction is a topic of future investigation.
ID: 539076

SELF-ESTEEM, ANXIETY, AND DEFEATIST PERFORMANCE BELIEFS AS RISK FACTORS FOR PARANOIA

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Paranoid delusions are one of the most prevalent psychiatric symptoms in individuals suffering from psychosis. Psychological theories have implicated a number of variables in the formation and maintenance of paranoid beliefs, including self-esteem, anxiety, and negative beliefs about the self. Empirical studies evaluating the relationship between paranoia and self-esteem in clinical samples have yielded inconsistent findings. This may be due to differential mechanisms in various symptomatic subgroups. The current cross-sectional study examined the interrelationships between predictors of persecutory ideation in people with psychosis who range across the continuum of paranoid symptom intensity. One hundred and ninety-nine community-dwelling people with schizophrenia ($n = 140$) or schizoaffective disorder ($n = 59$) completed measures of psychotic symptoms (PANSS), paranoia (Paranoia Scale-PS), anxiety (Beck Anxiety Inventory- BAI), self-esteem (Self-Esteem Rating Scale, Sort Version-SERS-SF), and defeatist performance beliefs (Performance Evaluation factor from the Dysfunctional Attitudes Scale-DPAS). Participants were divided in to 3 groups: Paranoid (PANSS "suspiciousness" score of 4 or more), Non Paranoid (PANSS "Suspiciousness" score of 3 or less, and a score of 4 or more on one of the PANSS items "delusions", "hallucinatory behavior", "grandiosity", and "unusual thought content"), and Remitted (score of 3 or less on all described PANNS items). Multiple regression analyses showed that in all three groups self-esteem predicted paranoia. In the paranoid group the relationship between self-esteem and paranoia was mediated by anxiety and not defeatist performance beliefs, whereas in the other two groups this relationship was mediated by defeatist performance beliefs but not anxiety. Participants from the paranoid group were significantly more anxious than non paranoid and remitted participants. Defeatist performance beliefs did not differ significantly across groups. The findings suggest different treatment strategies for different groups, and highlight the importance of anxiety reduction as a potential treatment target for patients with more severe paranoia.
ID: 550695

EMOTION RECOGNITION AND SCHIZOPHRENIA

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Schizophrenia is associated with deficits in the processing of affective information from facial expressions and other social cues. The purpose of the present study was to explore whether schizophrenia patients show deficits in recognition of specific facial expressions. Healthy comparison subjects, unaffected siblings of schizophrenia patients, and schizophrenia patients were tested with a computerized test of degraded facial affect recognition. Patients demonstrated a worse recognition of facial expressions. Specifically with greater impairments of matched positive (happy) and negative (angry) whereas healthy subjects and unaffected siblings recognized negative and positive expressions at an equal level of accuracy. These results suggest that deficits in the processing of facial emotion recognition from social cues may contribute to poor social functioning in schizophrenia patients and must be identified as an important target for clinical intervention.
ID: 550494

SENSE OF HUMOR IN PATIENTS WITH SCHIZOPHRENIA

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Introduction: Sense of humor is an important social skill. It can facilitate social interaction and can help to cope with adverse situations. So far, it has not been studied systematically in patients with schizophrenia. Methods: 18 patients with schizophrenia and 18 healthy controls were examined with standardized self-assessment questionnaires to study potential group differences in humor type preferences, state and trait cheerfulness, seriousness and bad mood as well as the use of humour as a coping strategy. Results: The patients had more difficulties in understanding the test joke items but patients and controls did not differ in their humor type preferences and their use of humor as a coping strategy. The patients' readiness to react to funny stimuli with exhilaration was negatively correlated with the

severity of accompanying depressive symptoms. Conclusion: If understood and if no additional depression is present, patients with schizophrenia can enjoy humorous stimuli as controls do. This indicates a close connection between exhilaration and hedonia. The ability to use humour as a coping strategy is unaffected by the disorder.
ID: 550463

FEWER NEUROLOGICAL SOFT SIGNS AMONG FIRST EPISODE PSYCHOSIS PATIENTS WITH HEAVY CANNABIS USE

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Background: Although neurological soft signs (NSS) have been consistently associated with schizophrenia and a variety of risk factors, few studies have focused on the association between NSS and environmental factors such as cannabis use, particularly in first episode patients. Methods: We administered the Neurological Evaluation Scale (NES) to 92 patients during their first episode of functional psychosis. Psychopathology was assessed with the Positive And Negative Syndrome Scale (PANSS) and the family history of psychotic disorder was established on the basis of the Family Interview for Genetic Studies (FIGS). We also assessed lifetime cannabis and cocaine use utilizing that specific section of the Composite International 28 Diagnostic Interview. The outcome variable was the presence of high NSS, defined by a score above the median split of the NES score (N21). Results: Most patients (80/92, 87%) presented a non-affective psychosis. The presence of high NSS showed a significant independent association with not having been a heavy cannabis user (OR = 8.3; 95% CI = 2.4–33.3), family history of psychosis (OR = 4.3; 95% CI = 1.2–14.9), male sex 33 (OR = 4.0; 95% CI = 1.2–14.0), lower score in verbal fluency and higher score in negative symptoms (both $P < .01$). Conclusion: Our cross-sectional results support the hypothesis that potentially different pathways associated with the emergence of first episode psychosis may exist, including neurological premorbid alteration and environmental cannabis abuse.
ID: 550355

INITIAL RELIABILITY AND VALIDITY OF THE NEW NIMH-MATRICS NEGATIVE SYMPTOM RATING SCALE

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Negative symptoms in schizophrenia are a major determinant of the functional impairments that characterize the disorder as well as a significant source of distress for caregivers. Unfortunately, negative symptoms represent an unmet therapeutic need as no medications have shown to be effective in their treatment. One outcome of an NIMH consensus development conference on negative symptoms (Kirkpatrick et al., 2006) was the recommendation for the development of a new negative symptom assessment instrument that addresses conceptual and psychometric limitations of existing instruments. The NIMH-MATRICS negative symptom workgroup has developed a new instrument, the Negative Symptom Rating Scale (NSRS), which represents a substantial step forward in the assessment of this critical symptom domain. The current study is the first assessment of the newly developed NSRS. Forty individuals diagnosed with schizophrenia or schizoaffective disorder completed assessments of current symptoms and social functioning. To examine convergent validity of the NSRS, independent assessments of negative symptoms were obtained with the Scale for the Assessment of Negative Symptoms (SANS). Discriminant validity was examined by assessing the independence of the NSRS ratings from psychotic and depressed symptoms. Finally, it was expected that the NSRS ratings would be related to assessments of social functioning in the community. Analyses indicated that the NSRS has high internal consistency reliability (total scale alpha = .86) and high convergent correlations with SANS scales (median $r = .52$, $P < .01$). The NSRS ratings were uncorrelated with either psychotic or affective symptoms (all ps > .05). The NSRS demonstrated significant correlations with social functioning in the community. These initial findings indicate that the NSRS holds promise as a next-generation negative symptom scale.
ID: 550319

INSTRUMENTAL ASSESSMENT OF MOVEMENT DISORDERS IN PATIENTS WITH SCHIZOPHRENIA, THEIR HEALTHY SIBLINGS AND CONTROLS

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Background: Movement disorders as dyskinesia and parkinsonism are regarded as core features of schizophrenia and highly related to the dopamine system. Several studies suggested that the presence of these movement disorders in siblings of patients would constitute (genetic) markers of vulnerability. However, most individual studies on first degree-relatives failed to find this association, possibly due to insufficient sensitivity of the applied clinical rating scales. Quantitative instrumental measurements can be more sensitive to detect subclinical movement disorders (Cortese 2005). This study compares prevalences of dyskinesia and parkinsonism in patients with schizophrenia, healthy siblings and matched controls using instrumental assessments. Methods: Instrumental measurements of tongue and finger instability as a measure of dyskinesia and resting tremor of the finger as a measure of parkinsonism were carried out in 44 medicated patients with a non-affective psychosis (70% schizophrenia), 44 healthy siblings and 32 controls. Dyskinesia and parkinsonism were quantified using instrumental force variability, a method to measure the percentage of motor instability and tremor (Caligiuri 1994). All subjects were screened for Axis-1 pathology using CASH-interviews. Siblings and controls were matched according to age, sex and years of education. Results: Siblings displayed significantly more finger instability and resting tremor than controls (2.35% vs.1.97%; $P = .02$ and 0.30% vs. 0.25%; $P = .01$ respectively). There was no difference in tongue instability (16.7% vs 16.9%; $P = .88$). In addition, patients not only demonstrated more finger instability and resting tremor than siblings (2.80% vs. 2.35%; $P = .03$ and 0.43% vs 0.30% $P < .01$ respectively), but also more tongue instability (21.2% vs. 16.7%; $P < .01$). Demographic information of patients, siblings and controls are given for age, years of education and percentage of males (27.2, 27.7 and 25.7 years), (12.1, 14.2 and 14.7 years) and (82%, 55% and 50%). Conclusion: This is the first study that used instrumental assessments to compare prevalences of motor disorders between patients with schizophrenia, healthy siblings and controls. It clearly shows that siblings have more dyskinetic and parkinsonian movements of the fingers than controls suggesting a (genetic) risk of developing schizophrenia. Instrumental measurement

can be used for detecting subclinical movement disorders in high risk populations.
ID: 550265

ASSESSING AUDITORY VOCAL HALLUCINATIONS: THE PSYCHOMETRIC EVALUATION OF THE AUDITORY VOCAL HALLUCINATION RATING SCALE (AVHRS)

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Introduction: Assessing auditory vocal hallucinations (AVH) is important, both for clinical practice and research purposes. Questioning patients thoroughly about different dimensions of their voices may offer a solid base for therapeutic interventions, whereas reliable instruments are useful for outcome assessment and research. Our aim is to examine the inter-rater reliability and concurrent validity of the Auditory Vocal Hallucination Rating Scale (AVHRS), a more extensive version of an existing scale to assess voices. Methods: To examine the inter-rater reliability (IRR) 23 patients of the Voices Outpatient Department (VOPD) of the University Medical Center Groningen (the Netherlands) were assessed with the AVHRS, both about the past month and about lifetime. AVHRS total scores were compared with available PANSS scores—of all patients from September 2006 till September 2008—to investigate concurrent validity. Results: The IRR of the AVHRS was good (lifetime) to excellent (past month). Correlations with the PANSS will be presented at the conference. Face validity was excellent. Conclusions: So far, we consider the AVHRS to be a very comprehensive scale with favourable psychometric properties. The instrument is useful for both clinical therapy and research.

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ID: 550238

SOCIAL ANXIETY AND IDEAS OF REFERENCE IN EARLY PSYCHOSIS

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An increased prevalence of social anxiety disorder is observed in patients with psychosis (16%–38%, compared with 13% in the general population). Despite important treatment implications, previous attempts in understanding the comorbidity have been inconclusive. This study aims to explore the relationship between social anxiety and other psychopathological characteristics in psychotic disorders, with a conceptually driven focus on the possible linkage between social anxiety and the sub-threshold symptom ideas of reference. A consecutive sample of 137 outpatients with early psychosis was assessed for social anxiety using the Liebowitz Social Anxiety Scale (LSAS), and for ideas of reference using a new instrument Ideas of Reference Interview Schedule (IRIS). Positive symptoms, negative symptoms, depression and insight were measured using the Scale for the Assessment of Positive Symptoms in Schizophrenia (SAPS), the Scale for the Assessment of Negative Symptoms in Schizophrenia (SANS), Calgary Depression Scale for Schizophrenia (CDSS) and the Scale to Assess Unawareness of Illness (SUMD). To identify potential explanatory variables for social anxiety, univariate analyses were first carried out between LSAS and age, sex and all symptom subscales. Variables that displayed simple correlation with LSAS (based on a lax criterion of $P < .1$) were then entered as independent variables into a stepwise multiple regression analysis to determine the symptoms specifically correlated with LSAS. Results suggested a three-factor model, with IRIS included as the strongest explanatory factor, while avolition and blunting were also related (adjust R2 = 0.18; $P = .00$). The association observed between social anxiety and negative symptoms is consistent with previous findings. This is the first study to demonstrate that a proportion of social anxiety covaries with ideas of reference. The nature of their relationship and the extent to which ideas of reference may explain for the excess of social anxiety prevalence in early psychosis need to be further investigated.
ID: 550218

CHARACTERISTICS OF HIGH FUNCTIONING INDIVIDUALS WITH SCHIZOPHRENIA

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Recent attention has focused on individuals who live remarkably productive lives with rich interpersonal relationships despite active symptoms. We know very little about how these "high functioning" individuals with schizophrenia successfully cope with their illness to achieve occupational and social success. Therefore, we initiated a qualitative study of high functioning individuals with schizophrenia who are living in Los Angeles. For this study, "high functioning" was defined as employment in a professional, technical, or managerial occupation or high-level functionality as a stay-at-home caretaker or full-time student. Method: Subjects who responded to flyers were evaluated according to entry criteria. Following informed consent, subjects were evaluated using the SCID, the PANSS, a background survey, and the BASIS-24. This was followed by a Person-centered Interview. This interview uses a method that is used in psychological anthropology to obtain in-depth, phenomenological perspectives. Results: Fourteen subjects qualified for the study and were interviewed. Subjects included 1 MD, 2 PhD's, 2 MA's as well as 4 BA's. The majority had managerial or supervisory responsibilities in their current job. Nearly all of the subjects had active symptoms that affected their everyday life. The majority could point to cognitive or behavioral techniques used to manage symptoms in the face of these responsibilities. Participants tended to be very familiar with mental health recovery concepts and articulated the ways in which these concepts interfaced with their ideas about their own mental health experiences.
ID: 549746

AN EXPERIENCE SAMPLING STUDY OF THE EXPRESSION OF POSITIVE AND NEGATIVE SCHIZOTYPY IN DAILY LIFE

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Psychometrically identified positive and negative schizotypy are differentially related to psychopathology, personality, and social functioning. However, little is known about the experience and expression of schizotypy in daily life. The present study employed the experience sampling method (ESM) to assess positive and negative schizotypy in daily life in a nonclinical sample of 412 young adults. ESM is a structured diary technique in which participants are prompted at random times during the day to complete an assessment of their current experiences. As hypothesized, positive schizotypy was associated with increased negative affect, thought impairment, suspiciousness, negative beliefs about current activities, and feelings of rejection, but not with social disinterest or decreased positive affect. Negative schizotypy, on the other hand, was associated with decreased positive affect and pleasure in daily life, increased negative affect, and marked decreases in social contact and interest. Both positive and negative schizotypy were associated with the desire to be alone when with others. However, this desire appeared to be moderated by anxiety in positive schizotypy and by diminished positive affect in negative schizotypy. The findings support the construct validity of a multidimensional model of schizotypy and the use of psychometric inventories for assessing these dimensions. ESM appears to be a promising method for examining the daily life experiences of schizotypic individuals.
ID: 549731

EFFECTS OF PRE-ONSET CANNABIS USE ON EARLY-COURSE FEATURES OF FIRST-EPISODE NONAFFECTIVE PSYCHOSIS: PREMORBID FUNCTIONING, THE PRODROME, AND ONSET OF PSYCHOSIS

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Background: Several studies suggest that pre-onset cannabis use results in an earlier age at onset of psychosis, independent of effects of gender and use of other drugs. However, little is known about the influence of prior cannabis use on other early-course epochs, including the premorbid and prodromal phases. We examined the effects of prior cannabis use on: (1) early adolescent (12–15 years) premorbid functioning, (2) late adolescent (16–18 years) premorbid functioning, (3) four features of the prodrome, and (4) mode of onset and age at onset of psychosis. Methods: Participants included urban, low-income, predominantly African American, first-episode patients (n = 109) in a public-sector hospital. The assessment included the Premorbid Adjustment Scale (PAS) and the Symptom Onset in Schizophrenia inventory, along with other measures. Potential confounders, including gender, family history of psychosis, and prior nicotine and alcohol use, were considered. Results: Those having used cannabis before or at age 15 years had a mean PAS early adolescence social score of 1.21 ± 0.85, compared to 1.75 ± 1.27 in those who had not ($t = 2.46$, $P = .02$), indicating better social functioning among those having used cannabis. On the other hand, those having used cannabis before or at age 18 had a mean PAS late adolescence academic score of 3.59 ± 1.46, compared to 2.00 ± 1.33 ($t = -4.52$, $P < .001$), indicating poorer academic functioning among those having used cannabis. Cannabis use prior to onset of psychotic symptoms was not associated with having had a prodrome, duration of prodrome, or number of prodromal features experienced. Whereas 16 (42.1%) of those having used cannabis daily had an acute mode of onset of psychosis, only 12 (20.0%) of those without past daily use had an acute mode ($\chi^2 = 6.53$, $P = .04$).

Conversely, 9 (23.7%) of those who had used daily had a subacute mode, compared to 26 (43.3%) of those who had not used daily. Pre-onset cannabis use was associated with an earlier age at onset of psychotic as well as prodromal symptoms. Conclusions: We replicated the finding that pre-onset cannabis use is associated with an earlier age at onset. Further, these findings suggest that cannabis use is associated with poorer premorbid social and academic functioning and an acute mode of onset of psychosis. Further research is warranted to further elucidate the complex associations between early-course features and cannabis use.
ID: 549715

THE RELATIONSHIP BETWEEN AWARENESS OF TARDIVE DYSKINESIA AND INSIGHT INTO MENTAL ILLNESS IN SCHIZOPHRENIA

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Background: A striking feature of tardive dyskinesia TD is that a large percentage of patients display an unawareness or lack of concern for the movement disorder, with reported rates ranging between 44% and 95%.5;6 Poor insight into their mental illness is also a common and often striking symptom in schizophrenia, with an estimated 50% to 80% of such individuals not being convinced that they have a disorder.12 Both phenomena have been likened to anosognosia, a neurological deficit characterised by unawareness or denial of an impairment, and associated with damage to specific brain areas.6 We investigated whether poor awareness of TD is related to poor insight into mental illness and examined their clinical correlates. Methods: The sample comprised 84 men and 46 women aged 45 ± 11.4 yrs with schizophrenia and TD. Motor disorders were assessed by means of the Extrapyramidal Symptom Rating Scale (ESRS)18 and schizophrenia psychopathology by means of the Positive and Negative Syndrome Scale (PANSS)19. The level of awareness of TD was calculated by the sum of two items on the ESRS scale that rate the patient's subjective evaluation of the intensity of dyskinesia of extremities. For assessing insight into mental illness we used a single item on the PANSS scale (item G 12). Results: We found high rates of poor awareness of TD (52%) and poor insight into their mental illness (72%). Poor of awareness of TD and impairment of insight into mental illness were significantly related, although regression analysis indicated that relatively little variance is shared between them. In fact, correlation profiles for level of awareness of TD and the level of impairment of insight into the mental illness were very different, suggesting that the two phenomena are not related. Discussion: Insight into mental illness was related to the presence and severity of core psychosis symptoms, while awareness of TD was related to severity of TD and the presence of parkinsonism.
ID: 549413

SCHIZOTYPY: PSYCHOMETRIC PROPERTIES AND FACTORIAL STRUCTURE OF THREE SELF-REPORT RATING SCALES, DEMOGRAPHIC CORRELATES, AND ASSOCIATIONS WITH NICOTINE, ALCOHOL, AND CANNABIS USE

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Introduction: Schizotypy and schizotypal personality disorder are thought to be genetically related to schizophrenia given that relatives of people with schizophrenia are more likely to exhibit schizotypal traits than individuals without a family history of schizophrenia. This presentation gives an overview of a recent survey of undergraduate students, focusing on: (1) measurement issues regarding self-report rating scales of schizotypy, (2) demographic correlates of schizotypy scores, and (3) associations between self-reported schizotypy and reports of nicotine, alcohol, and cannabis use. Methods: A survey was conducted with 825 undergraduate college students. Measures included the Schizotypal Personality Questionnaire (SPQ), the Perceptual Aberration Scale (PAS), and the Social Anhedonia Scale (SAS). Demographic characteristics and substance use variables also were assessed. Results: Confirmatory factor analysis (CFA) supported a 4-factor structure of the SPQ in this sample. Correlations between scores on the three schizotypy measures were relatively modest, though intercorrelations among the four SPQ subscales were fairly high. Internal consistency reliability coefficients were acceptable for all instruments. A CFA of an abbreviated version of the SPQ (SPQ-B) revealed that the standard 3-factor solution may not fit the data better than a 1-factor solution. Male gender was significantly associated with higher SAS scores, and race was associated with several schizotypy measures. Students reporting past use of cigarettes, alcohol, or cannabis generally had higher schizotypy scores than those without past use of these substances. Specifically, higher levels of disorganized schizotypy were associated with greater indices of use of all three substances. Furthermore, lower negative schizotypy and higher cognitive-perceptual schizotypy were selectively associated with nicotine and cannabis use, respectively. Discussion: These findings indicate that commonly used measures of schizotypy have adequate psychometric properties in this sample; that scores on some dimensions of schizotypy may differ by gender and race; and that the use of nicotine, alcohol, and cannabis are associated with schizotypal features. Greater elucidation of these associations, ideally using longitudinal research designs, could provide crucial information not only on the connection between substance use and schizotypy, but also between substance use and schizophrenia.
ID: 549144

PARANOIA AND HALLUCINATIONS IN THE CONTEXT OF DAILY LIFE: THE ROLE OF EMOTIONAL EXPERIENCES AND SELF-ESTEEM

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Emotional experiences—anxiety in particular—and self-esteem are considered to play an important role in the generation and maintenance of paranoia. The goal of current study was to explore the dynamic association between emotional experiences (anxiety, anger, depression) and self-esteem on the one hand and paranoia on the other. In addition, it was investigated whether the association is symptom-specific by looking at hallucinations as well. The Experience Sampling Method, a structured self-assessment diary technique, was used to examine the alleged association in the daily life of 158 individuals who ranged across the paranoia continuum. Multilevel regression analyses were performed to investigate the association between self-esteem and emotional experiences and paranoia / hallucinatory episodes (= uninterrupted series of occurrence of paranoia / hallucination). Results showed that self-esteem plays a significant role in the onset of both paranoia and hallucinatory episodes. In addition, level of self-esteem is significantly lower during both paranoia and hallucinatory episodes.

However, self-esteem only plays a significant maintaining role in the duration of a paranoia episode. Paranoia and hallucinatory episodes are both characterised by higher levels of anxiety and depression. However, anxiety is most strongly associated with paranoia. Only paranoia episodes are characterised by higher levels of anger. It can be concluded that emotional experiences and self-esteem are associated with both paranoia and hallucinations. The findings give support to the postulation that especially anxiety is important in the relationship with paranoia, probably because both anxiety and paranoia can be seen as treat beliefs.
ID: 549120

PHENOMENOLOGY OF SCHIZOPHRENIA AND AFFECTIVE FIRST EPISODE PSYCHOSIS

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Objective: This study compares the phenomenological dimensions of psychotic disorders at initial presentation of first episode psychosis in both schizophrenia and affective psychotic disorders. Method: Patients were recruited from the University of Illinois Medical Center. Lifetime exposure to psychotropics in all patients was less than 16 weeks, and patients were evaluated free of pharmacological treatment. Diagnosis was determined using the DSM-IVtr and consensus procedure including treating clinicians. All patients were assessed on standardized research instruments evaluating symptoms and global functioning prior to starting drug treatment. 5-factor scoring of PANNS dimensions included positive, negative, cognitive, excitement, and depression. A composite Cluster score for PANNS dimensions assessed anergia, thought disturbance, activation, paranoia and depression. Results: Of the 110 first episode psychosis subjects who participated, 56 were diagnosed with schizophrenia, 30 with bipolar disorder, and 24 with unipolar depression. PANSS 5-factor scores at baseline demonstrated that schizophrenia and bipolar patients showed significantly more positive symptoms than depressed patients ($P < .001$) while schizophrenia and depressed patients demonstrated significantly more negative symptoms than bipolar patients ($P < .001$). Additionally, patients with schizophrenia reported greater cognitive symptoms than patients with either bipolar or depression ($P < .001$). Lastly, PANSS cluster scores showed that schizophrenia and bipolar patients exhibited significantly more thought disturbance ($P = .007$), activation ($P < .05$), and paranoia ($P = .02$) than patients with depression. Schizophrenia and depressed patients exhibited greater anergia ($P < .001$) than bipolar patients. Conclusions: This study compared patients with schizophrenia, bipolar disorder and unipolar depression at the time of their initial clinical presentation of psychosis. Data emerging from this study suggests that phenomenology of these disorders is overlapping with a broad co-occurrence of psychopathological symptom dimensions. However, differences across groups were observed with acute psychosis severity being greater in schizophrenia and bipolar disorder than depression. The similarities of psychotic symptoms in schizophrenia and bipolar disorder may suggest some common mechanisms underlying psychosis in these disorders.
ID: 548869

A PHENOMENOLOGICAL STUDY OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: AMOTIVATION AND ITS RELATIONSHIP TO FUNCTIONING

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The negative symptoms of schizophrenia are comprised of two key symptom subdomains: 1) diminished expression (affective flattening and

poverty of speech); and 2) amotivation (apathy and anhedonia), and contribute to functional impairment in this illness. Of note, there is evidence that individuals with schizophrenia do not, in fact, experience anhedonia (ie. a consummatory pleasure deficit), but rather deficits in anticipating pleasure. To date we are unaware of any investigation that has concurrently examined amotivation and these different facets of the experience of pleasure, and their relationship with functioning in schizophrenia. This study aims to specifically examine these relationships, with the hypothesis that amotivation bears the strongest relationship to functional outcomes. Outpatients between the ages of 18 and 55 with a diagnosis of schizophrenia, on stable doses of antipsychotic medication, were evaluated with the Scales for the Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS). Amotivation was assessed with the Apathy Evaluation Scale—Clinician version (AES-C), anticipatory/consummatory pleasure with the Temporal Experience of Pleasure Scale (TEPS), and cognition with the Brief Assessment of Cognition in Schizophrenia (BACS). The Quality of Life Scale (QLS) was used to evaluate current functioning. Analysis of data from 11 subjects (mean age of 38, mean duration of illness of 13 years) revealed significant relationships between QLS scores and total SANS ($r = -.645$, $P = .032$), Amotivation subdomain ($r = -.704$, $P = .016$), and AES-C ($r = -.771$, $P = .005$). Other measures including SAPS total score, Diminished Expression subdomain score, TEPS anticipatory/consummatory pleasure scores, and BACS composite score did not exhibit any significant association with functional status. Negative symptoms have been implicated in poor functional outcome, reflected here as well with total SANS and QLS scores. The present data, albeit preliminary, take this issue a step further though, examining different aspects of the negative symptom domain. Amotivation was strongly correlated with current functioning, whereas this was not the case for the expressive component of negative symptoms, or for anticipatory or consummatory pleasure. These preliminary findings suggest that it is loss of drive, rather than pleasure, that links negative symptoms to poor functional outcome.
ID: 546949

A META-ANALYSIS AND QUALITATIVE REVIEW OF THE IMPACT OF FAMILY HISTORY OF PSYCHOSIS ON PRESENTATION AND COURSE OF ILLNESS IN SCHIZOPHRENIA

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Research on the influence of a positive family history of psychosis on presentation and course of illness in schizophrenia has been mixed, and to date, there have been no comprehensive reviews that have attempted to bring together this large area of research and determine the exact impact of this potentially important etiologic factor. Therefore, the current review qualitatively and quantitatively reviews four areas of research relative to positive family history: age at onset, presentation of positive and negative symptoms, course of positive and negative symptoms, and treatment response. Results showed that positive family history of psychosis has a small but significant impact on several of these areas, including age at onset and its relationship with gender, negative symptoms, course, and treatment response. While only one moderator analysis was significant, there were several interesting trends. The findings of the current review are discussed in light of an extension of the diathesis-stress model for the development of schizophrenia. Theoretical assumptions and empirical research are reviewed to support the notion that family history operates to influence presentation and course through the same mechanisms it operates through to influence susceptibility. Finally, implications of the current findings, limitations of the review, and directions for future research are highlighted.
ID: 546059

AN ALTERNATE EXPLANATION TO "COGNITIVE DYSMETRIA" IN SCHIZOPHRENIA

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Background: Schizophrenia is considered to be an illness in which there is a generalized "cognitive dysmetria" in which cortical-cerebelar-thalmic-cortical circuitry shows impairments when compared with individuals without mental illness. Method: We reviewed the literature pertinent to circuitry abnormalities in schizophrenia. Also, we looked for correlates with severity of illness. Further we focused on described impairments in various domains of insight in schizophrenia. Results: Form the data gathered we observed that insight into the symptoms is less often impaired than insight into the illness and the consequences of illness. Experiential aspect of perception is obtained from processing primitive awareness through working memory and referenced through the association areas. The reported difficulties for schizophrenia in processing and encoding would lead in time to incremental deteriorations in reality testing. Thinking can be understood as related to perception (impure cognition) and not related to experience (pure cognition, eg, close systems such as matematics). We propose that even though are severe dysfunction in each of the presented domains, they occur at different degree of severity. The cognitive dysmetria can be explained as a "schism" in the interplay of impaired perception and faulty cognition. Discussion: Despite the fact that is a vast literature discussing neurological abnormalities in schizophrenia, very limited integrative work was done. Our hypothesis suggests a different way of assessing and understanding each individual affected with this illness and ultimately proposes to correct the specific dysfunctions to reduce the decalage between levels of cognition and perception.
ID: 543795

IMPULSIVITY IN CO-OCCURING SCHIZOPHRENIA AND SUBSTANCE USE

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Impulsivity is a risk factor associated with substance use disorders. On paper-and-pencil measures, people with schizophrenia and substance use disorders have been shown to be more impulsive than their non-using counterparts. However, there has been little research elucidating the various behavioral components which often define the concept of impulsivity. These components include: temporal discounting, risk taking, underestimating time and failure to inhibit extraneous responding. Specifically, the study compared people with schizophrenia who did and did not use cocaine on these behavioral impulsivity measures. One group had a positive urine drug screen (UDS) for cocaine ($N = 20$). A second group had a negative UDS, but a positive cocaine history ($N = 20$). Finally, the third group had no history of cocaine use ($N = 20$). Participants were assessed using computer-based tasks. Those with a current or past history of cocaine use had greater means on the Balloon Analogue Risk Task and engaged in more risk-taking behaviors. People with schizophrenia with a current or drug use history seemed to be less affected by loss and more attuned to monetary gains. Contrary to our hypothesis, the study found that patients with a positive UDS for cocaine selected larger, delayed rewards over the smaller, immediate rewards. Performances on the immediate/delay task also suggest greater attentiveness to magnitude of the monetary reward. On the GoStop computer task, a trend was found toward significant differences between the means for inhibited responses and total number of

responses. However, no significant differences were found between groups for time estimation. These data indicate that depending on the conditions, people with comorbid schizophrenia and cocaine abuse may demonstrate more or less impulsivity than people with either disorder alone. Implications for understanding the interaction between the CNS effects of cocaine and psychosis will be discussed.
ID: 541250

INSIGHT INTO DEFICITS? THE DEFICIT SYNDROME IN FIRST-EPISODE SCHIZOPHRENIA

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Schizophrenia as it is currently conceptualized is a markedly heterogeneous disorder. Researchers have long attempted to decrease this variability to allow greater predictive power regarding illness course and treatment response. The aim of the current research is to examine the deficit syndrome, a category gaining increasing support in the literature. Studies of deficit syndrome patients have indicated a history of poor functioning (Tiryaki et al., 2003), but decreased clinical distress (Kirkpatrick et al., 1994, Fenton and McGlashan et al., 1994) compared to nondeficit patients. Poor insight in patients with deficit schizophrenia may be one explanation for these findings. One study in a sample of patients with chronic illness found that deficit patients had poor insight compared to nondeficit patients (Kirkpatrick et al., 2000). We hypothesized that poor insight would be present early in the course of illness in deficit patients. Selected clinical correlates of the deficit syndrome were also examined. We used the Proxy for the Deficit Syndrome (PDS) to categorize 109 newly diagnosed patients with nonaffective psychosis into deficit ($N = 31$) and nondeficit ($N = 78$) groups (Kirkpatrick et al., 1993) based on Positive and Negative Syndrome Scale scores. Results indicate that first-episode deficit patients have poorer insight than first-episode nondeficit patients after accounting for age, gender, hallucinatory behavior, and delusional thinking. Deficit patients exhibited greater negative symptoms, less severe positive symptoms, and less distress. Deficit patients also demonstrated greater impairments in global indicators of functioning (education, marital/relationship status, employment status). These results were not confounded by greater substance abuse in the deficit group. Results from the current study further validate the deficit syndrome as a useful subcategory of schizophrenia in a sample of first-episode patients. Results also suggest that the treatment of deficit patients may be complicated by poor insight. Understanding heterogeneity in the early course of schizophrenia may hasten treatment interventions and enhance the development of new treatment targets.
ID: 550901

TRAUMA EXPOSURE AND POSITIVE SYMPTOM SEVERITY IN PRODROMAL PATIENTS

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Introduction: Although traumatic childhood experiences are commonly endorsed by individuals with schizophrenia, and associated with psychotic symptoms, little is known about childhood trauma in prodromal or clinical high risk samples. Methods: We examined the prevalence of childhood trauma and its symptom correlates in 30 clinical high risk patients, including prodromal and depressive symptoms. Results: All forms of childhood abuse were prevalent, particularly among ethnic minority participants, among whom trauma was associated with subthreshold psychotic symptoms, in particular grandiosity. By contrast, childhood trauma was associated with depression only in Caucasian participants at heightened risk for psychosis. Discussion: This exploratory study suggests childhood trauma is common among prodromal patients and related to symptoms. Further studies will entail the predictive value of traumatic experiences and their neuroendocrine correlates.
ID: 551921

THE WINTER BLUES: SEASON OF BIRTH PATTERNS IN SCHIZOTYPY

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The season of birth effect, defined in terms of an elevated incidence of birth during certain months, is one of the most replicated findings in schizophrenia research. The majority of research has reported elevated rates of winter births for individuals with schizophrenia dating back to 1929. Many theories have attempted to explain this effect by including risk factors such as maternal stress and influenza exposure during pregnancy. Although this effect has been extensively studied in individuals with schizophrenia, it has not been examined on individuals with schizotypy—those with a putative genetic vulnerability who don't manifest symptomatology. In the current study, we examined individuals with schizotypy to see whether a pattern of birth rates is exhibited. The schizotypal personality questionnaire (SPQ) was administered to 1135 undergraduates and computed dimensional positive, negative, and disorganization scores for each individual, We examined 2 issues: 1) whether schizotypal features were associated with season of birth and 2) how gender differences might moderate this relationship. We found that those with higher positive schizotypy scores showed a higher incidence of winter birth, however only within males. This study has replicated in schizotypy what has been found in schizophrenia—that winter births are associated with positive symptomotology. However, this relationship was only present for males.
ID: 551862

THEORY OF MIND ABILITIES AND SELF-CONFIDENCE IN SCHIZOTYPY

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Social cognitive deficits have been well established in schizophrenia. However, there have been mixed results in research on social cognition in individuals with schizotypy, those with the underlying genetic vulnerability that do not exhibit full-blown symptomology. The current study investigated theory of mind, one component of social cognition involving the ability to infer mental states. Participants included 81 psychometrically-identified schizotypes and 35 controls who completed a computerized theory of mind task (TOM). This task was designed to be more sensitive than those used in previous research, and was composed of items from an existing published hinting task with a true/false response format. We also has participants rate how confident they were that their answers were correct. Schizotypes performed similarly to controls on TOM, although they were significantly less confident. Confidence ratings were not related to overall performance but were positively correlated with performance on true/false items in which a correct social inference was made. Results suggest that although schizotypes may have intact theory of mind, they are less confident in their abilities. Among possible interpretations are that: 1) social cognitive deficits seen in patients with schizophrenia stem from later decline in general cognition in conjunction with lower confidence in social abilities, 2) social cognitive abilities serve as a resilience factor buffering against the eventual

decline into psychosis, and that 3) schizotypes may be employing a compensatory strategy leading them to the correct responses.
ID: 551824

EVALUATION OF SPEECH MISATTRIBUTION BIAS IN SCHIZOPHRENIA

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Background: Attributing self-generated speech to others could explain the experience of verbal hallucinations. This theory was based on experiments that used non-linguistic, or speech perception paradigms. Speech generation paradigms compared self-other to other-self misattribution errors. Impairment in the self-other distinction could cause both types of errors. In this study we compare both self-other and other-self misattribution errors to errors that are not related to the self-other distinction. Methods: 39 schizophrenia patients and 26 matched healthy controls were required to distinguish between self-generated, other-generated, and non-generated (self or other) sentences. The sentences were in the first, second or third person and read in a male or female voice in equal proportion. Mixed multilevel logistic regression models were used to investigate the effect of group, sentence source, pronoun, and gender of the heard sentences on response accuracy. Results: Patients differed from controls in the recognition of self-generated and other- generated sentences, but not in general recognition ability. Pronoun was a significant predictor of response accuracy but without any significant interaction with group. The gender of heard sentences variable was not significant. Misattribution bias differentiated groups only in the self-other direction. Conclusions: These data support the theory that misattributing self-generated speech to other could result in verbal hallucinations. Syntactic (pronoun) but not acoustic (gender) manipulations affect the recognition of self and other generated speech. This indirectly implicates language, rather than sensory, disorder in the pathogenesis of AVH.
ID: 551803

THC ELICITS NEGATIVE SYMPTOMS IN HEALTHY CONTROLS: AN EXPERIMENTAL STUDY

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Background: It is well recognised that cannabis can induce transient positive psychotic symptoms in healthy subjects and in people with schizophrenia. The psychotogenic effects are attributable to the molecule delta-9-tetrahydrocannibinol (THC). Less well understood is the effect of cannabis/THC on the negative dimension. It has been suggested that patients who use cannabis experience less negative symptomatology compared to those who don't. In contrast, there is some experimental evidence that THC may actually induce schizophrenia-like negative symptoms. Here we report the effects of pure THC on the negative dimension in a sample of healthy male subjects. Method: A validated structured instrument, The Community Assessment of Psychic Experiences (CAPE-state version) was used to assess drug effects on the negative dimension in 22 participants. The CAPE distinguishes between positive, negative and depressive dimensions. Pharmaceuticals were administered by intravenous injection under randomised, double-blind placebo controlled conditions. The dose of THC (2.5 mg) was chosen on the basis of previous studies. Ratings were made at baseline and at 30, 80 and 120 minutes post-injection. Plasma levels of THC and its

major metabolites were measured over the course of the experiment. Results: Nineteen participants completed the paradigm. Overall, subject-rated scores on the CAPE negative dimension were increased from baseline following THC but not placebo administration (Friedman's $\chi^2 = 25.3$, $df = 7$, $P = .001$). At 30 minutes post THC, CAPE negative scores had increased by a mean of 4 points, returning to baseline levels by 120 minutes post-injection. There was wide inter-individual variation in responses to THC. Overall, 70% of subjects reported an increase in the CAPE negative dimension following THC whilst 15% showed no change and 15% reported a decrease. Plasma levels of THC were similar to those observed following inhalational use of cannabis. Conclusion: In a majority of healthy subjects, pure THC elicits negative symptoms. Further work to explore the underlying mechanism is underway in our lab.
ID: 551761

PERSISTENCE OF RATER TRAINING EFFECTS IN SCHIZOPHRENIA CLINICAL TRIALS

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Background: We report a retrospective assessment of rater drift in 9 CNS trials involving the Positive and Negative Syndrome Scale (PANSS) and Negative Symptom Assessment Scale (NSA-16) in schizophrenia. We hypothesized that measures of rater adherence to scoring would be significantly lower at study mid-point than at initiation. Method: All trials included had at least one post-investigator meeting recertification or refresher procedure at least 6 months (range approximately 6–19 months) after the initial approval. For each scale, raters were trained to rate these scales by viewing at least one training lecture and viewing and rating at least one videotaped practice subject interview using the scale, followed by detailed feedback on proper scoring from an expert trainer utilizing an audience response system and expert panel consensus scoring explanations. Subsequently, in order to be approved to rate, investigators were evaluated on their ratings of an additional videotaped subject interview. Approximately 9–16 months later, raters were required to complete a self-instructional review of rater scoring technique using internet based training or instructional CD and retested on their ability to properly score a videotaped interview. For purposes of this analysis, rater performance was evaluated as passing if 80% of the scale items were scored within one point of the modal score or within 1 point of the expert consensus. The proportion of all raters who scored within one point of the modal score or panel expert consensus on at least 80% of the scale items was compared at study initiation and mid-study using the chi-square statistic. Results: For schizophrenia (PANSS and NSA-16), rater performance at mid-study compared to study initiation was not statistically significant ($\chi^2 = 2.66$; P NS; $df = 1$). At initial testing 85.9% ($n = 1198$) of raters met criteria considered acceptable for passing and 14.1 % ($n = 197$) did not. At retesting 88.6% ($n = 528$) of raters met criteria considered acceptable for passing and 11.4% ($n = 68$) did not. Discussion: A retrospective analysis of 9 CNS clinical trials in schizophrenia suggests relatively high levels of rater agreement may be sustainable 6–19 months after initial training with an instructional review at mid-study.
ID: 551757

EXPLORING THE INTERPLAY BETWEEN MARIJUANA USE, MEDICATION ADHERENCE, AND PSYCHOTIC SYMPTOMS IN FIRST-EPISODE PSYCHOSIS

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Marijuana use is a frequently present co-morbidity among people with a first episode of psychosis (FEP), and has an impact on symptoms and on outcome. The objective of this study was to examine, in the context of a FEP program, the proportion of marijuana users who persist in using during the first year in treatment. The study also examined the interaction between drug use, medication compliance, and symptomatology. The study was conducted at PEPP-Montreal, a specialized integrated treatment service for all incident FEP cases within a defined area. Subjects were 192 consecutive admissions, aged between 14 and 30, suffering from at least two weeks of psychotic symptoms meeting DSM-IV syndromal criteria, and with no history of antipsychotic treatment. Diagnoses, including co-morbid substance use diagnoses, were determined using the Structured Clinical Interview for DSM-IV (SCID-I), administered shortly after program admission, and again at one year. Symptoms were evaluated at regular intervals through one year of follow-up using the Positive and Negative Symptom Scale (PANSS). Antipsychotic medication compliance was also evaluated regularly based on patient report and corroborated by collateral report and clinical notes. 56 subjects (29.2%) had a current cannabis use disorder at baseline. Of the cannabis-using subjects for whom information was available at one year (50), 29 (58.0%) had continued to use marijuana, while 21 (42.0%) had stopped. PANSS total score did not differ between stable users compared to those who abstained, either at baseline (75.1 vs. 77.6, $t = -0.47$, $P = .64$) or at one year (56.2 vs. 50.3, $t = 1.40$, $P = .17$). The groups did not differ in their rate of compliance at baseline (85.2% vs. 90.5%, Fisher's $P = .68$). However, at month 12 stable users were significantly more compliant than cannabis users who had stopped (92.3% vs. 60.0%, Fisher's $P = .01$). An ANCOVA revealed that PANSS total at 12 months was associated with compliance at 12 months, $F_{1,39} = 5.28$, $P = .03$, but that the effect of stability of marijuana consumption remained significant after controlling for this covariance, $F_{2,39} = 17.16$, $P < .001$. These results suggest that FEP patients who continue to use marijuana are more adherent to medications than abstaining users, and that this effect is not explained by patients who, having stopped marijuana, felt they no longer need medications to control symptoms.
ID: 551746

DEFINING THE RELATIONSHIP BETWEEN CLINICAL RATINGS OF BLUNTED AFFECT AND BEHAVIORAL CODING OF FACIAL AFFECT: FREQUENCY, INTENSITY, OR DURATION?

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Negative symptoms within schizophrenia include profound changes in the expression of emotion as reflected in the symptom domain of flat or blunted affect. Despite the importance of this domain it remains unclear how expression is altered. Specifically, it is not yet known whether diminished expression reflects changes in the frequency, duration, or intensity of emotional expression. In order to better understand the nature of blunted affect, the present study conducted a detailed assessment of facial affect using the Facial Affect Coding System (FACES; Kring and Sloan, 2007). A further refinement in this study was the use of the newly developed NIMH-MATRICS Negative Symptom Rating Scale (NSRS) for the assessment of negative symptoms. 40 outpatient schizophrenics were assessed with diagnostic and symptom interviews including the NSRS and BPRS. Videotaped interviews were subsequently rated for facial affective displays using the FACES. Data analyses will examine the relationship between clinical ratings of blunted affect and behavioral coding of the frequency, duration, and intensity of facial affective displays. Further, the association between other negative, psychotic, and affective symptoms will be examined.
ID: 551706

CANNABIS USE AND CLINICAL AND FUNCTIONAL OUTCOME IN PRODROMAL ADOLESCENTS AND YOUNG ADULTS

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The Recognition and Prevention Program has recently found that cannabis use is not related to worsening of positive symptoms or to conversion to psychosis. However, the North American Prodromal Longitudinal Study (NAPLS), a consortium of eight longitudinal prodromal programs, has found that drug use in general is related to conversion (Cannon et al. 2008). This poster will involve a more intensive evaluation of the relationship between cannabis use and prodromal symptoms, social and role functioning, and conversion to psychosis utilizing the NAPLS retrospective database. Subjects include 330 prodromal individuals who met criteria for Attenuated Positive Symptom Syndrome according to the Scale of Prodromal Symptoms. Level of cannabis use was divided into those with no or low use and those with abuse or dependence. Social and role functioning was assessed with rating scales developed for NAPLS. Baseline and 12 month follow up data were utilized. Of the 330 participants, 64 (19.4%) met the criteria for cannabis abuse or dependence and the remainder reported no or low levels of cannabis use. Cannabis misusers were older at baseline but did not differ from no/low users on other demographic variables. In terms of prodromal symptoms, there were no significant differences between cannabis misusers and no/low users on attenuated positive or negative symptoms at baseline. However, cannabis misusers were significantly more likely to convert to psychosis over follow up (38.2% vs. 24.9%; $P = .038$). 33% of participants with follow up cannabis data (68/205) changed their level of cannabis use over the follow up period. In terms of functioning, subjects with cannabis misuse at baseline had significantly better social functioning than those who had no/low use ($P = .021$), but there were no differences on role functioning. These results indicate that cannabis misuse is related to conversion to psychosis in the NAPLS retrospective sample, although cannabis misusers could not be distinguished from no/low users on attenuated symptoms at baseline. Cannabis misusers were older and had better social functioning. Further analyses will examine whether prodromal symptoms and cannabis use fluctuate in relation to each other.
ID: 551705

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ASSESSMENT OF NEUROLOGICAL SOFT SIGNS IN POSITIVE AND NEGATIVE SCHIZOTYPY

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Patients with schizophrenia often exhibit structural brain abnormalities, as well as neurological soft signs, consistent with the conceptualization of schizophrenia as a neurodevelopmental disorder. Neurological soft signs are mild, presumably nonlocalizing, neurological impairments that are inferred from performance deficits in domains such as sensory integration, motor coordination, and motor sequencing. The vulnerability for schizophrenia is presumed to be expressed across a broad continuum of impairment referred to as schizotypy. It is hypothesized that nonpsychotic people along the schizotypy continuum should exhibit elevated rates of neurological soft signs. The present study examined the relation between psychometrically identified positive and negative schizotypy and neurological soft signs in a nonclinically ascertained sample of young adults ($n = 177$). Positive and negative schizotypy dimensional scores were derived from the Perceptual Aberration, Magical Ideation, Physical Anhedonia and Revised Social Anhedonia Scales. The neurological assessment was conducted using the Neurological Evaluation Scale (NES). The battery consists of 26 tasks that tap three neurological soft sign domains including sensory integration, motor coordination, and motor sequencing. As hypothesized, negative, but not positive, schizotypy was related to increased neurological soft signs associated with deficits in tasks related to fine and gross motor coordination, motor sequencing, eye movement abnormalities, and memory recall. However, positive schizotypy was associated with deficits in a few tasks related to sensory integration dysfunction. In general, the positive x negative schizotypy interaction term was unrelated to soft signs. Recommendations are offered to strengthen the utility of the NES for use with nonclinical samples, including using a modified version of the battery and a continuous scoring system. The findings support: a) the theory that the vulnerability for schizophrenia is expressed across a broad continuum of subclinical and clinical impairment referred to as schizotypy; b) the multidimensional structure of schizotypy; and c) the notion that schizotypy may be a more appropriate construct for understanding the etiology and development of spectrum psychopathology than full-blown schizophrenia.
ID: 551536

ASSESSING SUICIDIDAL BEHAVIOR IN SCHIZO-PHRENIA: PSYCHOMETRIC PROPERTIES OF A BRIEF SELF-REPORT MEASURE

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Individuals with schizophrenia are at risk for suicidal behavior. Careful and ongoing assessment is important for detecting risk. The HASS is a 21-item self-report measure of suicidal behavior assessing suicidal behavior over the past 2 weeks (HASS I) and the patient's whole life except the past 2 weeks (HASS II). The strong psychometric properties and the application of this measure will be presented. Data will be presented demonstrating the efficacy of the HASS at identifying suicidal behavior and measuring change with treatment. Over 140 individuals with Sz/SA disorder completed the HASS. Three factors accounting for 59% of the variance were identified for the HASS I: 1) thoughts of life, death and suicide; 2) suicidal behaviors including attempts; 3) substance use. Four factors were identified for the HASS II accounting for almost 67% of the variance: 1) Thoughts of suicide; 2) suicidal plans and actions; 3) substance use; and 4) thoughts of impulsive suicidal behavior. Data will be presented regarding relationships with depression, psychotic symptoms, impulsivity, aggression and the Beck Scale for Suicidal Ideation. The findings will be compared with a sample of adolescent high school students and with a sample of adolescents hospitalized for suicidal behavior in order to demonstrate the external validity of the

instrument. Sixty-five individuals were administered the HASS I on admission and discharge to the Schizophrenia Research Unit at New York State Psychiatric Institute and the HASS II was administered on admission. The HASS I detected attempts during the 2 weeks prior to admission and coupled with the HASS II identified 100% of documented attempters in the sample. There was a significant decrease in suicidal behavior from admission to discharge ($P < .001$). The relationship between change in suicidal behavior and change in other symptoms will be presented. The ability to assess suicidal behavior in Sz regularly and thoroughly is important. The HASS is the only self-report measure in the literature available at this time. The reliability is excellent and a significant amount of validity data has been accrued. The hope is that the availability of this measure will increase the likelihood of the assessment of suicidal behavior in research as well as clinically. Supported by NIMH RO1 MH 56422-O1A, 2 P30 MH4674.

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ID: 551535

THE PSYCHOTIC BRAIN-MIND BEYOND THE KRAEPELINIAN DICHOTOMY: SIMILAR LEVELS OF COGNITIVE BIZARRENESS FOUND IN THE DREAM AND WAKING MENTATION OF PATIENTS DIAGNOSED WITH BIPOLAR DISORDER AND SCHIZOPHRENIA

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Similarities and differences were evaluated in terms of structural organization of thought across two diagnostically distinct groups of actively psychotic subjects, by measuring cognitive bizarreness in their dream and waking mentation. Dreams reported upon awakening and narrative responses to a standardized projective stimulus, the Thematic Apperception Test (TAT), were collected from 20 acutely manic inpatients with psychotic symptoms, 20 actively psychotic schizophrenic inpatients and 20 subjects with no present or past history of mental illness, all adequately matched in terms of age and education. The material was scored by two highly-trained judges who evaluated the degree of bizarre elements referred to the formal architecture of verbalized thoughts according to the dream bizarreness scale (Scarone et al., 2008). A mean Bizarreness Density Index (BDI) was then elaborated for each of the three experimental groups' sets of dream and TAT reports; analysis of the data indicated a substantial similarity in terms of cognitive bizarreness in all reports, with the only statistically significant outlier being the control group's waking mentation (see Table). Cognitive bizarreness can be interpreted as the phenomenological correlate of the specific activation pattern occurring in the brain during REM sleep, where dream imagery is more vivid and storylines more articulated and incongruous. Similar experimentally measurable and clinically objectivable departures from the physiological functioning of the brain-mind have been shown to underlie dreaming and schizophrenia (Scarone et al., 2008). The results found in this study support the view of psychotic mentation as a correlate of the same type of neurobiological activation underlying dream sleep. Moreover, waking levels of cognitive bizarreness appear to be shared amongst acutely manic bipolar patients and actively psychotic schizophrenic subjects, linking psychosis to a specific shift in brain-mind functioning independent of diagnostic categories.

Reference

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Table. Descriptive statistics (Mean BDI Standard Deviation)

	DREAM BDI	TAT BDI
Control subjects	0.29 ± 0.20	0.11 ± 0.11
Schizophrenic subjects	0.32 ± 0.13	0.32 ± 0.19
Manic bipolar subjects	0.33 ± 0.11	0.29 ± 0.15

ID: 551484

HIGH FREQUENCY BAND ACTIVITY IN RESTING EEG AND THE RELATIONSHIP WITH SMOKING IN SCHIZOPHRENIA

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Evidence suggests that high nicotine dependence observed in schizophrenia is related to its core neuronal deficits such as abnormalities in neural synchronization and sensory gating deficits. Some of these neuronal deficits are shown to mark schizophrenia liability, raising the possibility that the increased nicotine dependence in schizophrenia is related to its etiological factors. In an ongoing study, we are examining the rates of nicotine dependence in families of schizophrenia probands using the Fagerstrom Test for Nicotine Dependence, and the relationships between nicotine dependence and schizophrenia endophenotypes in these subjects. Rates of nicotine use were significantly greater in patients ($n = 103$) than controls ($n = 77$) with respect to a history of ever smoking (69.9% vs 46.8%) and current smoking (58.3% vs 23.4%) with patients reporting greater levels of nicotine dependence (FTND; $F_{1,103} = 20.33$, $P < .001$). The two phenotypes, ie, ever smoking and current smoking, were associated with moderate to high heritability among schizophrenia families (heritability estimates > 0.9) and control families (> 0.5). We are in the process of examining their relationships with schizophrenia endophenotypes; at present data are available only in schizophrenia probands and control subjects on resting EEG measures and P50 gating. Resting EEG (5 min. sample) were analyzed to yield absolute power averages in alpha (8–10Hz), beta (12–28Hz) and gamma (30–50Hz) frequency bands examined at electrode sites Cz and Fz with repeated measures ANOVA to test for diagnostic differences and interactions with smoking status. No main effect of diagnosis was found for power in the alpha, beta, or gamma bands (all p values > 0.20), but classification by never, former, or current smoker yielded a significant main effect in the gamma band ($F_{2,173} = 3.34$, $P = .038$) and a trend towards significance for the beta band ($F_{2,174} = 2.62$, $P = .076$); post-hoc tests demonstrated significantly lower gamma band activity in current smokers than former smokers ($P = .037$). There was a significant group by smoking status interaction for P50 ratio ($F_{1,81} = 9.12$, $P = .003$) whereby sensory gating deficits were normalized in patient but not control smokers. We are in the process of analyzing data in the relatives. These results suggest that further analysis of high frequency bandpower in resting EEG may provide important links between neurophysiological deficits associated with schizophrenia and smoking.
ID: 551482

SELF-DISORDERS IN THE PRODROME: A PILOT STUDY AMONG HELP-SEEKING ADOLESCENTS

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The overarching objective of this pilot study was to lay the ground for a large-scale, community-based, prospective study that will examine the potential of anomalous self-experiences as an early, pre-psychotic phenotype of emerging schizophrenia. More specifically, the present study had two interrelated goals: 1) to demonstrate the feasibility of identification of anomalous self-experiences among non-psychotic help-seeking adolescents, and 2) to examine the potential of these experiences to serve as an early risk marker by examining their relationship with level of worry for a future psychotic illness as rated by an experienced child psychiatrist, presence and severity of prodromal symptoms, and decline in level of functioning. The study was motivated by the view that present research is not guided by a comprehensive psychopathological theory regarding the nature of the pre-psychotic phase. To accomplish these goals we administered the Examination of Anomalous Self-Experience (EASE: Parnas et al. 2005) to a group of 30 adolescents seeking help for emotional and behavioral problems. In addition, all participants were assessed with an extensive battery measuring conventional genetic and clinical risk factors such as familial predisposition, prodromal symptoms, emotional distress, psychosocial functioning, and (meta-)cognitive functioning. All assessments were carried out in complete blindness to the level of worry for future psychotic illness as assessed by the intake psychiatrist. A wide range of anomalous self experiences has been observed in about two thirds of the sample. The prevalence and level of severity of these experiences were significantly correlated with level of worry as assessed by the child psychiatrist, as well as with level of prodromal symptoms, emotional distress, and depth of cognitive and metacognitive deficits. If further validated, these preliminary findings suggest that anomalous self-experiences can enrich current early detection models by expanding the focus to the subjective experiences that may antecede the more descriptive-observational at-risk phenomena.
ID: 551427

RATES AND CORRELATES OF PAST INCARCERATION AMONG PATIENTS HOSPITALIZED FOR A FIRST-EPISODE OF NONAFFECTIVE PSYCHOSIS

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Background: Population-based and clinical studies attest to the fact that individuals with schizophrenia have high rates of arrest and incarceration. However, little is known about the prevalence of arrest and incarceration in first-episode psychosis samples, or social and clinical correlates of such legal system involvement occurring prior to initial treatment seeking. This study examined prevalence of arrest/incarceration and associations between incarceration and demographic, premorbid functioning, and clinical variables in a first-episode sample. Methods: The sample consisted of 109 urban, predominantly African American patients with first-episode nonaffective psychosis, hospitalized in a public-sector setting. Assessments included the Premorbid Adjustment Scale and the Positive and Negative Syndrome Scale (PANSS), along with a number of other measures. Results: Rates of past arrest and incarceration were very high in this sample (77% and 63%, respectively). Patients with a history of incarceration had completed fewer years of education (10.9 ± 2.1) compared to those who had not been incarcerated (12.6 ± 2.4; $t = 3.9$, $P < .001$). Past incarceration was associated with poorer academic functioning in early ($P = .020$) and late adolescence ($P = .007$), though no association was found with academic functioning before the age of 11 years or social functioning during any premorbid period. Past incarceration was significantly associated with the presence of alcohol ($P = .017$) and cannabis ($P = .003$) abuse or dependence. Of those having ever used cannabis, patients who had been previously incarcerated had a mean age at first reported cannabis use of 15.2 ± 4.1, compared to those who had not been arrested (17.0 ± 3.6; $t = 2.0$, $P = .049$).

There was a significant association between past incarceration and the total number of Axis IV psychosocial and environmental stressors (P = .002), PANSS positive symptoms, and PANSS general symptoms, each indicating poorer functioning among those having been previously incarcerated. Discussion: Although criminalization of individuals with serious mental illnesses is a widely recognized problem, it is typically conceptualized as a function of chronicity of illness. These data indicate that even prior to the first treatment contact, this sample had already accumulated substantial psychosocial consequences in terms of arrest/incarceration. Each significant correlate of past incarceration suggested grave implications for symptomatic and social functioning.

ID: 551399

DIFFERENTIAL HEDONIC CAPACITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER.

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Emotional abnormalities characterize both affective and non-affective psychosis, and both schizophrenia and bipolar disorder have poor functional outcomes. However, socio-emotional and volitional impairment are central to the Kraepelinian distinction between the groups, suggesting that emotional measures should differentiate them. To investigate this question, we administered several emotion function scales to patients with affective and non-affective psychosis in order to differentiate hedonic capacity. Stable outpatients (43 with schizophrenia/schizoaffective disorder [SCZ]; 27 with bipolar disorder I/II [BP]) and 36 matched healthy subjects (HC) were administered tests of hedonic capacity (Physical and revised Social Anhedonia scales[PAS, RSAS]), basic drive and inhibition (Behavioral Inhibition and Activation Scales [BIS-BAS]), and consummatory/anticipatory hedonic capacity (Temporal Experience of Pleasure Scale –TEPS). Subjects also completed a measure of anxiety/negative affect (State-trait anxiety, STAI) and the Social Adjustment Scale (SAS). Twelve-month follow-up data is reported from 33 SCZ and 18 BP subjects. Internal reliability of the self-rating scales was favorable for both groups (alpha > 0.75). Both patient groups exhibited significant negative affect (STAI: F = 26.7, $P <$ .000, SCZ = BP > HC), and significant functional social impairment (SAS: F = 20.9, $P <$ .000; SCZ = B, $P <$ HC). On traditional anhedonia measures, both groups were impaired (PAS: F = 14.7, $P <$ .000, SCZ = BP > HC; RSAS: F = 9.7, $P <$ .000, SCZ = BP > HC). However, the TEPS differentiated the groups (F = 5.8, P = .004, SCZ<B, $P <$ HC), as did BAS reward reinforcement (F = 6.8, P = .002, SCZ < BP = HC) and BAS drive (F = 4.7, P = .01, SCZ < BP = HC). The BP group exhibited greater inhibition than the HC group (F = 6.2, P = .003, BP > HC). The TEPS did not show differential impairment according to anticipatory or consummatory pleasure, i. e. no group by subscale interaction ($P >$ .5). However, in SCZ only the TEPS anticipatory subscale correlated with clinician-rated anhedonia (r = −.33, $P <$ .05), predicted current social adjustment (r = −.35, $P <$ .05), and predicted social adjustment at 12 months (r = −.45, $P <$ .01). Negative affect (STAI) predicted social adjustment in SCZ (r = .58, $P <$ .01) and BP (r = .56, $P <$ .05). The findings illustrate the phenotypic overlap of the two groups, but also support the Kraepelinian poles of affective and non-affective psychosis by way of hedonic capacity and emotional drive.

ID: 551292

AN INVESTIGATION OF NEGATIVE AFFECT AND POSITIVE SYMPTOMS OF PSYCHOSIS

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Disturbances of negative affect, such as depression and anxiety, are consistently identified as core features of both psychotic and psychosis-prone (at-risk) individuals and represent important treatment considerations for individuals with psychotic disorders. Vulnerability-stress models suggest that individuals with a predisposition to psychosis may have heightened emotional reactivity to environmental, biological, and psychosocial stressors – and therefore may be more susceptible to negative affective states (Asarnaw, Cromwell, and Rennick, 1978; Meehl, 1962; Walker and Diforio, 1997). Additionally, emerging evidence suggests a cross-sectional association between negative affect and positive symptoms of psychosis, such as hallucinations, delusions, and thought disorder; however, few longitudinal studies have examined these relationships (eg, Docherty, Grosh, and Wexler, 1996; Docherty, Rhinewine, Nienow, and Cohen, 2001). The current study examined cross-sectional and longitudinal associations between disturbances in negative affect (depression and anxiety) and positive symptoms of psychosis (hallucinations, delusions, and thought disorder). Specifically, we hypothesized synchronous (cross-sectional) associations between negative affect and positive psychosis and believed these associations would remain stable over time after accounting for baseline levels. It was also hypothesized that negative affective traits at baseline would predict an increase in severity of positive symptoms of psychosis among those individuals with a diagnosis of psychotic disorder at subsequent time frames (10 and 20 weeks). Data were drawn from the MacArthur Violence Risk Assessment study and included individuals (N = 245) with a diagnosis of psychotic disorder and scores of individual items on the Brief Psychiatric Rating Scale. Results of Confirmatory Factor Analysis and Structural Equation Modeling suggested good fit to the data (CFI = .94, RMSEA = .05, SRMR = .05, BIC = 12023). Analyses revealed moderately strong, statistically significant cross-sectional associations between negative affect (Depression-Anxiety) and positive symptoms of psychosis. These correlations remained stable over time after accounting for baseline and previous effects of the latent variables. Contrary to hypotheses, no significant cross-lagged effect was identified, suggesting no directional relationship between negative affect and positive psychotic symptoms.

ID: 551278

22Q11DELETION SYNDROME AND SCHIZOTYPAL PERSONALITY DISORDER: BEHAVIORAL AND PRODROMAL SYMPTOMS IN INDIVIDUALS AT HIGH RISK FOR PSYCHOSIS

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Adolescents with 22q11 Deletion Syndrome (22q11DS) and Schizotypal Personality Disorder (SPD) are at increased risk for the development of psychosis. This is evidenced by rates of illness much higher than those in the general population, as well as by the presence, in both, of subthreshold psychotic symptoms. The current study compares the behavioral and prodromal symptom profiles of adolescents in genetic (22q11DS) and behavioral (SPD) high risk groups. While many studies have investigated the behavioral and symptom profiles in each of these groups, no published report has directly compared them with each other. Doing so can potentially shed light on the relevance of etiological subtypes for understanding the pathogenesis of schizophrenia. The current study used two measures: the Achenbach Child Behavior Checklist (CBCL; SPD: n = 13, 22q11DS: n = 13), and the Structured Interview for Prodromal Syndromes (SIPS; SPD: n = 23, 22q11DS: n = 23). The two risk groups

were matched on age, gender, and where possible, ethnicity. PRELIM-INARY RESULTS: CBCL—Individuals in the SPD group had scores that were in the clinically significant range, and higher than those in the 22q11DS group on the anxious/depressed, social problems, thought problems, attention problems, internalizing problems, and total problems scales. The 22q11DS group did not have any scores in the clinically significant range. SIPS—individuals in the SPD group had more positive symptoms and attenuated ideational richness, as well as fewer motor problems. Both groups also showed heightened attention problems and elevated anhedonia scores. Thus, results show both similarities and differences between these two high risk groups, suggesting that individuals with 22q11DS and those with SPD may share some of the same risk factors for the development of schizophrenia. Results are consistent with the notion that genes mapping the 22q11 chromosomal region are involved in the pathogenesis of schizophrenia and spectrum disorders.
ID: 551246

THE PATTERN OF CANNABIS USE AND WITH-DRAWAL SYMPTOMS IN PEOPLE WITH SCHIZO-PHRENIA

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Chronic users of cannabis often report withdrawal symptoms after abstinence from use (1), but it is unknown whether this occurs in people with schizophrenia. This study used a structured questionnaire (Marijuana Quit Questionnaire (1)) to examine behavioral patterns of cannabis use and withdrawal symptoms. Fifty-four people in treatment for schizophrenia or schizoaffective disorder who were > 18 years old and reported at least one serious cannabis quit attempt participated in the study. Volunteers were 40.1 ± 10.9 years old (mean $\pm$ SD), 66.76% male, 54% Caucasian, and 37% African-American. First reported age of cannabis use was 16.5 ± 6.1 yrs, and reported age of onset of psychotic symptoms ($n = 50$) was 21.0 ± 5.6 yrs. Ninety-two percent (46/50) reported using cannabis before the onset of psychotic symptoms. The number of lifetime uses of cannabis ranged from 1 to > 10 000 (63% reported at least 500 uses). Seventeen percent met criteria for cannabis abuse; 74% met surrogate criteria for cannabis dependence. Cannabis use had a negative effect on quality of life: 87% (46/53) reported experiencing psychological or emotional problems and 60% (32/54) reported physical health problems related to cannabis use. Withdrawal symptoms were reported by 93%; 52% reported between 1–5 withdrawal symptoms, 28% reported 6–10 symptoms, and 20% reported > 10 symptoms. The most common reported withdrawal symptoms were: anxiety (50%), depression (46%), craving for cannabis (44%), and boredom (39%), similar to the symptoms reported by users without psychiatric comorbidity (1). Ten percent reported using cannabis to relieve withdrawal symptoms. This suggests that withdrawal is a negative reinforcer for relapse. We conclude that most people with schizophrenia who use cannabis begin before the onset of psychosis and that withdrawal symptoms are common in those who have attempted to quit. Withdrawal symptoms are important in the clinical treatment of schizophrenia and comorbid cannabis use disorders. Supported by the Intramural Research Program, NIH, National Institute on Drug Abuse and the NIDA Residential Research Support Services Contract HHSN271200599091CADB.

Reference
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ID: 551198

SOCIAL WORLD INTERACTIONS: HOW COMPANY CONNECTS TO PARANOIA

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Background: Many surveys and experimental studies have indicated that social contact, even when it is neutral, triggers paranoid thinking in people who score high on clinical or sub-clinical paranoia. However, little is known about the relationship between paranoia and social environmental effects in the context of daily life reality. The current study aims to investigate whether contextual variables are predictive of momentary increases in the intensity of paranoid thinking in a sample of subjects with clinical and non-clinical paranoia. Methods: A sample of 37 control subjects, 37 high-schizotypy participants, and 33 paranoid patients were assessed with the Experience Sampling Method (a structured diary technique) assessing momentary social context, appraisal of social company, perceived social threat and paranoia in daily life. Results: Multilevel analyses revealed a significant interaction effect between group and being alone in the model of momentary paranoia ($\chi^2 (2) = 20.22$, $P < .00$). Patients reported lower levels of paranoia when in company than when alone ($\chi^2 (1) = 13.84$, $P < .000$), whereas no such difference was found in the high-schizotypy group or controls. With regard to the type of social company, differential associations were found for momentary paranoia ($\chi^2 (2) = 28.83$, $P < .000$), and perceived social threat ($\chi^2 (2) = 41.88$, $P < .000$) in the three groups. Controls and high-schizotypy individuals reported higher levels of perceived social threat when with non-familiar compared to familiar individuals. Moreover, the high-schizotypy group reported more paranoia in non-familiar company. The patients, on the other hand, reported no difference in the perception of social threat between familiar and non-familiar contacts. They even reported less paranoia when in non-familiar compared to familiar company. Discussion: The data suggest that the development of sub-clinical momentary paranoia is context-dependent. However, once in a full-blown paranoid episode, momentary paranoia seems to become more autonomous and independent of the social reality. Being with other people, especially with non-familiar individuals, may then even serve as a protective factor.
ID: 551181

DEVELOPMENT OF AN INTERVIEW-BASED "CO-PRIMARY" MEASURE OF COGNITION

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Background: The MATRICS initiative has reached a consensus that practical, reliable "co-primary" measures of cognition are needed to evaluate change in cognitive functioning after new drug interventions (Green

et al., 2008). However, for data to be meaningful there should be evidence that the co-primary instrument effectively measures the appropriate concept. Method: Data were collected as part of the MATRICS initiative ($n = 176$) with the (SCoRS and CGI-CogS; total of 41 items), two interview-based measures of cognition. Sources of information included a patient, a caregiver, and the rater. The aim of these analyses was to develop a valid but brief co-primary measure of cognition. The study investigators used classical test theory (CTT) including factor analysis and modern test theory approaches, such as Item Response Theory (IRT) and developed a 10-item Cognitive Assessment Interview (CAI). The validity analysis focused on the relationship between the CAI and objective measures of cognitive functioning (MCCB), functional outcome (Birchwood Social Functioning Scale), and psychiatric symptoms (BPRS). Results: For the CAI, both the patient ($r = .82$) and the caregiver ($r = .95$) ratings were highly correlated with the rater's composite. The 10-item CAI correlates highly ($r = .87$) with the combined set of parent instruments (CGI-CogS and SCoRS; 41 items). In addition, the CAI is moderately correlated with objectively measured cognition ($r = -.32$) and with functional outcomes ($r = -.31$) at levels that are comparable the parent instruments. The CAI was correlated with positive symptoms ($r = .28$), but not with depression ($r = .06$) or negative symptoms ($r = .09$). Conclusions: The CAI allows a rater to use expert judgment to evaluate the patient's or the caregiver's report of cognitive functioning. The CAI is experience-near, and given the moderate correlation with neurocognition and functional outcome, shows indications of being valid. Although the CAI is correlated with positive symptoms, the ratings are not unduly influenced by all types of symptoms. The CAI is brief and repeatable, and therefore might be a valuable tool for assessing cognitive functioning for schizophrenia patients who are participating in clinical trials.
ID: 551133

THE ECOLOGICAL VALIDITY OF NEGATIVE SYMPTOMS

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Flat affect and social anhedonia are assumed to be key characteristics of negative symptomatology in psychotic disorders. However, the ecological validity of these concepts remains unclear. This study compared flat affect and social anhedonia as measured by a structured interview to emotional experience and social behavior in the realm of daily life. In the current study, emotional experience and social behavior of 178 patients diagnosed with psychotic spectrum disorders and 164 controls were explored using the Experience Sampling Method (a structured diary method). Social anhedonic and blunted patients were identified using the Positive and Negative Symptom Scale. Flat affect in daily life was defined as diminished emotional intensity. Social anhedonia in daily life was conceptualized using 1) frequency of being in company, 2) preference of being alone while in company and 3) emotional reward of being in company. Multilevel regression analyses revealed that the patient group as a whole experienced more intense negative and less intense positive emotions than controls. Blunted patients, however, did not differ from non-blunted patients in emotional intensity. Compared to controls, patients were more often alone and showed a higher preference of being alone when in company. However, social company was associated with more positive and less negative emotions in both patients and controls. No differences between social anhedonic and non-anhedonic patients were found on all three indicators of social anhe-

donia. These results suggest that patients may experience problems with positive emotions and social isolation in normal reality of daily life. However, these problems were not validly captured using a structured interview, since no differences on social anhedonia and flat affect in daily life were found between patients scoring high or low on the negative symptom items of the structured interview.
ID: 551083

PRODROMAL SYMPTOMS IN CANNABIS, KETAMINE AND COCAINE USERS

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Three classes of drugs have been repeatedly associated with psychotic phenomena: cannabis, the stimulants (cocaine and amphetamine), and the dissociative anaesthetics (PCP and ketamine) but their users have never been directly compared on psychotic symptoms. We used a pre-clinical or prodromal measure of symptoms to compare non-psychotic users of these three groups of drugs. 130 volunteers were rated on the Schizophrenia Proneness Instrument-Adult (Schulz-Lutter et al. 2008; SPI-A): 29 dependent 'skunk' (high potency cannabis) users, 22 dependent cocaine users, 21 dependent ketamine users, along with 28 'recreational' poly-drug (ketamine, cannabis and cocaine) users, and 30 drug-naïve controls. Group membership was verified by hair and urine analysis. The SPI-A yields 6 basic symptom 'factors': affective symptoms, attentional symptoms, cognitive disturbances, perception of self and surroundings, body perception and general perceptual changes. SPI-A data were also compared with existing data on prodromal individuals (Kloster-Kotter et al., 2007). Ketamine users showed the greatest number of affective and perceptual symptoms. Both ketamine and cannabis users manifested the greatest levels of attentional problems and cognitive disturbances. Cocaine users showed greater perceptual disturbances than the cannabis group but fewer than ketamine users. Overall dependent drug users exhibited more symptoms than recreational users on every factor except disturbances in body perception. Recreational drug users did not differ from non-drug users in affective symptoms and other perceptual disturbances. Of the dependent groups, ketamine users presented with basic symptoms which were the most similar to prodromal individuals; 'cognitive' basic symptoms were also prominent in dependent cannabis users; the symptom profile of cocaine users was the most subtle. The drug-related elevation in symptoms was restricted largely to dependent drug users, with much lower levels of symptoms in recreational drug users. Few of these drug-dependent individuals will likely transition to psychosis but these drug induced increases in basic symptoms may represent mechanism of risk in people with a predisposition to the disorder. In addition, clinicians should be aware of the similarity of symptoms observed in drug users who will likely not transition to psychosis and genuinely prodromal individuals.
ID: 550978

CHILDHOOD TRAUMA, CORTISOL LEVELS AND HPA AXIS FUNCTION IN DRUG-NAÏVE FIRST EPISODE PSYCHOSIS PATIENTS

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Early life trauma is associated with increased vulnerability for psychiatric disorders, possibly mediated by alterations in the hypothalamic-pituitary-adrenal (HPA) axis. This study examined the relationship between childhood trauma and HPA axis function in 17 first-episode psychosis (FEP) patients and 19 healthy controls using the low dose (0.25mg) Dexamethasone Suppression Test (DST). Blood samples were obtained at 9am before and after administration of 0.25mg oral dexamethasone at 11pm. Suppression was defined as a cortisol level <5ug/dL. Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ). FEP patients had significantly higher CTQ scores for emotional abuse ($P < .001$), sexual abuse ($P = .043$) and physical neglect ($P = .01$) compared to controls. Baseline cortisol levels tended to be lower in FEP patients compared to controls (mean (SEM): FEP = 16.4 (1.4) ug/dL; controls = 20.6 (1.4) ug/dL; $P = .054$). Six out of 17 FEP patients (35.3%) suppressed cortisol following ingestion of dexamethasone compared to 2 out of 19 (10.5%) control participants ($x^2 = 3.18$; $P = .07$). In the entire sample, there was a non-significant negative correlation between baseline cortisol levels and total CTQ scores (-0.2; $P = .2$). In the low dose DST, percent cortisol suppression was significantly correlated with emotional abuse in FEP patients ($r = .58$, $P = .038$), but not in control participants ($r = -.05$; $P = .8$). No significant correlations were observed for the other CTQ dimension scores. These preliminary findings show for the first time that a subset of FEP patients have enhanced feedback inhibition of the HPA axis, which might be linked to prior exposure to childhood trauma. Further studies with larger sample sizes are needed. Examination of the relationship between childhood trauma, HPA function and the development of PTSD symptoms following the first psychotic episode is currently underway.
ID: 550972

SEPARABLE DEVELOPMENTAL TRAJECTORIES IN SCHIZOPHRENIA FROM WOMB TO GRAVE. RESULTS FROM THE NORTHERN FINLAND 1966 BIRTH COHORT

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Subtle developmental (motor, emotional, structural, cognitive and behavioural) abnormalities are often present in individuals who later develop psychosis suggesting that some aspects of causation are established before overt psychosis. However, their effect size and predictive power are small, and the longitudinal trajectory of developmental factors can be difficult to tease apart. The Northern Finland 1966 Birth Cohort Study examines the pre- and postmorbid life-span developmental trajectory for schizophrenia in a population-based cohort. We studied developmental pathways across diagnostic groups using developmental markers at birth, at ages 1, 16, and at ages 31, 34 and (in progress) 43 (genetics, brain morphology, cognitive capacity, clinical status). The main results were: the schizophrenia group had excess of achieved developmental milestones later and showed altered patterns of development over time when compared with non-psychotic controls. The associations between early development and post-onset cognition/brain morphology differed in various diagnostic groups. Furthermore, we have identified evidence of progressive dysfunction in a distributed network involving a fronto-striatal-cerebellar circuit ("developmental dysmetria") in schizophrenia. This is akin to the system underpinning the cognitive dysmetria of schizophrenia and provides a mechanistic link between the developmental dysmetria prior to schizophrenia. Schizophrenic persons experience different trails also after the illness onset: separable outcomes in terms of psychiatric symptomatology, somatic health and mortality. We conclude that the developmental trajectories in schizophrenia from womb to grave are distinctly different compared to controls and also within the schizophrenia group. These findings emphasize both neurodevelopmental and neurodegenerative aspects of schizophrenia and the scientific value of pathway variables collected in longitudinal birth cohort studies.
ID: 550963

THE RELATIONSHIP AMONG CHILDHOOD TRAUMA, STRESS AND COPING IN THE FIRST EPISODE PSYCHOTIC POPULATION: PRELIMINARY RESULTS FROM SHARP STUDY

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SHARP (Stress, HPA function And Related Psychosis) is a project to investigate the relationship among childhood trauma, stress, coping, psychopathology, HPA function, neuro-cognition, brain structure and medical compliance in the first episode psychotic (FEP) population. This abstract is the results about childhood trauma, stress, coping, medical compliance and psychopathology. 50 first episode psychosis drug naïve or early treated (less than 7 days of antipsychotic or antidepressant) patients and 40 matched healthy controls were recruited from the ORYGEN Youth Health in Melbourne, Australia. Their psychopathology (BPRS, SANS, HAMA and HAMD), social function (GAF and SOFAS), medical compliance (Clinical rating scale, Drug attitude Inventory), NEO personality inventory, trauma (Childhood Trauma Questionnaire and List of Threatening Experiences) and Stress and coping (Coping Inventory for Stressful Situations, Daily Hassles Scale, Perceived Stress Scale and Connor-Davidson Resilience Scale) were measured at baseline and after 12 weeks follow up. The prevalence of childhood trauma in FEP group is higher than in the control group. In the FEP group, the level of daily hassle is positively correlated to perceived distress at baseline. The bigger change of hassle total score and severity of hassle is linked to the more severe negative symptoms at 12 week follow up. Perceived stress at baseline is correlated to less severe negative symptom, higher hassle and hassle severity and poor clinical rating score. Also higher CTQ is linked to higher baseline hassle total score, severity of hassle and higher perceived stress. It also related to lower mood symptom in the FEP group. FEP with childhood traumatic history might experiences more hassle, more severe hassles and perceived more stress when they were suffering from the psychosis, also might report less mood symptom.
ID: 550957

DISORGANIZATION IN SCHIZOPHRENIA: POSITIVE SYMPTOM OR NEUROCOGNITIVE DEFICIT?

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Background: Several factor analytic studies have shown that in schizophrenia patients, disorganization is a separate dimension from positive (non-disorganizing) symptoms termed, reality distortion. A prior meta-analysis found that the strength of the relationship between positive symptoms and neurocognition can vary depending on whether researchers were examining "reality distortion" or "disorganization" (Nieuwenstein et al., 2001). Several studies on this topic have now been added to the literature. Methods: Meta-analysis of 58 studies published in the English language (combined $n = 5,029$) was conducted to determine the magnitude of the relationship

between neurocognition and reality distortion, eg, delusions and hallucinations as compared to disorganization, eg, formal thought disorder. Additional analyses were conducted to determine whether the strength of these relationships differed depending on the neurocognitive domain under investigation. Results: The effect size of relationship between neurocognition and reality distortion was small ($r = -.16$) as compared to disorganization which was moderately associated with neurocognition ($r = -.26$). In four of five MATRICS domains that were examined, neurocognition was more closely related to disorganization (r's range from $-.20$ to $-.28$) than was reality distortion (r's = $-.08$ to $-.15$). For disorganization, moderate effects were found for reasoning and problem solving ($r = -.26$) and verbal memory ($r = -.28$). Conclusions: The effect size of the relationship between neurocognition and reality distortion was small compared to disorganization which was moderately related in several MATRICS domains. These findings support a dimensional view of positive symptoms indicating that the strongest relationship to neurocognitive deficits is shown by the category of disorganization. The cognitive domains of reasoning and problem solving, and verbal memory appear to be more conceptually linked to disorganization than to reality distortion.
ID: 550927

DECREASED BDNF IN PATIENTS WITH FIRST EPISODE TREATMENT NAÏVE PSYCHOSIS

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Objective: Brain-derived neurotrophic factor (BDNF) is a key factor that may mediate neuronal proliferation, differentiation, survival and response to stress. Several small studies show a decrease in BDNF levels in patients with psychosis. However, studies of effect of antipsychotic agents on BDNF have yielded conflicting results. Herein we report on BDNF levels in first-episode treatment naïve psychosis. Method: Fasting serum BDNF levels were measured in .43.patients with treatment naïve first episode psychosis and 42 age matched healthy controls. Baseline levels in the 9 patients were compared with their levels after 4–8 weeks of antipsychotic treatment with second generation antipsychotic agents. Data were square root transformed to ensure normality of distribution. Results: Serum BDNF levels (square root) were reduced in the patients ($9.95 + 1.5$) versus controls ($10.70 + 1.6$) (Mann Whitney $U = 670.5$; $P = .04$). The levels did not significantly differ after treatment (before treatment $9 + 1.43$) versus after treatment ($8.9 + 1.17$); Mann Whitney $U = 39.5$; $P = .93$) Conclusions: Low BDNF levels at the onset of psychosis suggest a possible role in the pathogenesis of schizophrenia. Our failure to detect treatment may either reflect inadequate statistical power, or a true lack of effect of the atypical antipsychotic agents on BDNF. The inadequacy of contemporary treatments in addressing the core pathology of schizophrenia highlights the need to examine alternative treatment targets. This publication was supported by funds received from AAGP SRI Alumni Award (P.I Ripu Jindal) and the NIH/NCRR/GCRC grant #M01 RR00056.The clinical core staff of the Center for the Neuroscience of Mental Disorders (MH45156) assisted in diagnostic assessments.
ID: 551937

CHILDHOOD BEHAVIOR AND SCHIZOPHRENIA SPECTRUM PSYCHOPATHOLOGY IN YOUNG GENETIC HIGH-RISK RELATIVES

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Introduction: High frequency of psychopathological disorders are seen among offsprings of schizophrenia and bipolar disorder. The Child Behavior Checklist (CBCL) is a reliable measure of the assessment of changes in behavior over a period of time as reported by parents and subjects. Schizotypy scores in high risk patients have been shown to be related to premorbid psychopathological traits and is a specific predictor of later development of schizophrenia spectrum disorder. We wanted to examine the relation between schizotypy and CBCL scores as reported by parents and subjects. Methods: Subjects for this study were recruited from the Pittsburgh Risk Evaluation Program (PREP) at the Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center , as well as Wayne State University, Detroit. The Chapman subscales evaluating magical ideation (MA), perceptual aberration (PA) and social anhedonia (SA) were used to evaluate schizotypy scores using the Chapman psychosis proneness scale. Internalizing and externalizing symptoms were evaluated using the parent and child version of the CBCL. Seventy-four young relatives, with a first-degree family history of schizophrenia or bipolar disorder, aged 10 to 24 years were evaluated. Results: Cross-sectional analyses revealed that child internalizing subscale correlated with Chapman subscales of magical ideation (Spearman $r = 0.31$, $P = .007$), perceptual aberration (Spearman $r = 0.29$, $P = .038$), and social anhedonia (Spearman $r = 0.438$, $P = .004$). Strong correlations were also seen the child externalizing subscales and Chapman subscales of magical ideation (Spearman $r = 0.41$, $P = .0004$), perceptual aberration (Spearman $r = 0.23$, $P = .052$), and social anhedonia (Spearman $r = 0.37$, $P = .005$). There was no correlation between the Parent version of CBCL and Chapman subscales. Conclusions: Child version of CBCL correlates better than parent version with schizotypy. Given that schizotypy scores may reliably predict progression towards future schizophrenia spectrum disorders, it is prudent to recognize and treat internalizing and externalizing symptoms early into the prodrome. High-risk offsprings may be better able to state and recognize their problems earlier on before their parents could recognize it. The CBCL may be used as an effective tool to screen these high risk children to aid early detection and predict progression of the illness. This work was supported by MH064023 (Keshavan).
ID: 555210

SCHIZOTYPAL INDIVIDUALS DISPLAY DEFICITS IN SOCIAL COGNITION

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Deficits in social information processing have been consistently observed in schizophrenia patients. Social cognition is a multifaceted construct that includes the ability to perceive others' mental states (Theory of Mind), recognize affect, and accurately identify and interpret emotional meanings from the environmental milieu. The extent to which these social cognition deficits are present in individuals at risk for schizophrenia is not clear. The purpose of the present study was to compare psychometrically-identified individuals at heightened risk for the later development of schizophrenia and spectrum disorders with controls in terms of their performance on two tasks tapping social cognition. Individuals with excessively high ($n = 33$) and normal ($n = 62$) scores on the revised Social Anhedonia Scale were administered the Reading the Mind in the Eyes Task (RMET) and the Facial Affect and Social Cue Test (FASC). The Social Anhedonia group showed significantly poorer performance on the RMET relative to the controls, $t(93) = -2.34$, $P < .05$. The two groups did not differ in terms of the FASC. We observed a small but significant association between the two measures of social cognition. These findings indicate that individuals at heightened risk for the later development of schizophrenia and schizophrenia-spectrum disorders display deficits in social cognition. It is possible, however, that the deficits in social information processing are more

circumscribed in at-risk samples. Our results will be considered in the larger context of social cognition and social functioning deficits in the premorbid and prodromal stages of schizophrenia.
ID: 553487

REEXAMINING THEORY OF MIND IMPAIRMENT AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: A ROLE FOR ATTENTIONAL DYSFUNCTION?

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Abstract: Patients with prominent negative symptoms consistently perform worse than other clinical groups on Theory of Mind (ToM) tasks. However, the nature of this relationship has not been closely examined. In this study, we investigated the relationship between ToM and the Scale for the Assessment of Negative Symptoms (SANS) components. We replicated our findings in two independent samples and at two timepoints. Methods: 227 patients with DSM-III-R diagnosis of schizophrenia or schizoaffective disorder in two independent samples were administered the Hinting Task and the SANS. One sample ($n = 137$) was reassessed at 6 months. Pearson's correlations were used to examine the relationships between the Hinting Task and the SANS subscales and total scores. Subscale scores that were significantly correlated with the Hinting task were entered into a stepwise multiple regression to determine how much of the variance they explained. Results: Results indicate a modest but significant relationship between negative symptoms and the Hinting Task. Examination of the components revealed that Attention is largely responsible. Alogia made a minor contribution. Conclusions: ToM deficits are associated with negative symptoms. A common mechanism may be the allocation of attention to social events and socially relevant stimuli. Disrupted processing at the level of implicit, ''on line'' representations may contribute to impairments in attentional function as assessed by the SANS as well as contributing to impaired ToM performance on the Hinting Task. The current findings indicate that we should reexamine ToM impairment in patients with negative symptoms and how it might be targeted in therapeutic interventions.
ID: 551995

TOWARD A COMPREHENSIVE MODEL OF NEUROLOGICAL SOFT-SIGNS AND PSYCHO-PATHOLOGY IN SCHIZOPHRENIA

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The goal of this study was to explore interrelations between core dimensions of schizophrenia, neurological soft-signs and age at onset, by using structural modeling. Two hundred and thirty four patients with a DSM-IV diagnosis of schizophrenia were included in the study. All subjects were administered a semi-structured interview (DIGS) for diagnosis and age at psychotic onset, the Positive and Negative Syndrome Scale (PANSS), and neurological signs were assessed with a standarized scaleSeveral structural equations analyses were performed. The best structural model in terms of fit indices incorporated two latent components of the disease and nine observed variables (TLI: 0.86; RMSEA:0.064). The first latent component, Neurological Loading (NL), was mostly related to abnormal motor coordination and motor integration scores (structural coefficients: respectively .81 and .72). The second latent component, Schizophrenic Psychopathology (SP), was strongly linked to the dimension of disorganisation (.99). NL and SP were significantly inter-correlated (.49; $P < .001$).Age at onset was significantly correlated to SP but not to NL. The close association of neurological abnormalities with core schizophrenic dimensions, particularly disorganisation, suggest common physiopathological pathways.
ID: 551957

3. 3. Drug Side Effects and Physical Illness

ANTIPSYCHOTIC STAY VS. SWITCH FOR METABOLIC BENEFIT: PSYCHIATRIC COST

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Background: Switching antipsychotics is one option for patients with antipsychotic-induced metabolic effects,[1] yet there is concern that switching stable patients carries a psychiatric cost, and may result in exacerbation.[2] Methods: Data were analyzed from a randomized, 6-month, open-label switch study for overweight or obese nondiabetic schizophrenia patients taking risperidone or olanzapine. Eligible subjects were randomized to usual care non-switch (UC) or open-label switch (S) to ziprasidone. Arms were balanced for gender and race/ethnicity. Imaging measures of adiposity and endocrine measures were obtained at baseline and 6 months. The primary psychiatric outcome measure was total hospital days in each arm, while secondary analyses examined change in total PANSS and PANSS subscale scores. Results: To date, 51 subjects have entered the randomization phase of the study: UC $n = 22$; S $n = 29$. Mean age of randomized subjects was 47.3, 78.4% were male, 66.7% white and 9.8% Hispanic. Mean BMI was 33.4 kg/m^2, 63% smoked, and 15.7% reported a 1st-degree family history of diabetes. Baseline total PANSS score was 64, positive subscale 18, and negative subscale 15. At baseline there were no significant between-group differences on any demographic, adiposity or laboratory variable, nor on total PANSS, positive or negative subscale symptom scores. There were no significant differences in total hospital days between the UC arm (26 days), and the S arm (25 days), or in proportion of subjects hospitalized: UC (14%) vs. S (21%) ($\chi^2 = .338$, $P = .561$). In a linear regression model with change in total PANSS score from baseline to week 26 as the dependent variable, neither treatment arm, nor baseline antipsychotic significantly predicted the outcome variable. Conclusions: Contrary to many assumptions, in this 6-month, open-label, randomized trial, the hospitalization rate and total hospital days in non-switchers did not significantly exceed that seen with careful antipsychotic switching. This inherent relapse rate among stable patients with schizophrenia must be factored into the stay vs. switch decision to change antipsychotic treatment for possible metabolic benefit.

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ID: 538155

REDUCED EPS RISK WITH LURASIDONE, A NOVEL PSYCHOTROPIC AGENT UNDER DEVELOPMENT FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Lurasidone is a novel psychotropic agent with affinity for dopamine D_2 and serotonin 5-HT$_{2A}$ receptors. Compared with other atypical antipsychotics, lurasidone has high affinity at serotonin 5-HT$_7$, 5-HT$_{1A}$, and noradrenaline α_{2c} receptors; minimal affinity for α_1 adrenocep-tors, dopamine D_1 and D_3 receptors, serotonin 5-HT$_{2C}$ receptors, and α_{2A} adrenoceptors; and no affinity for histamine H_1 and cholinergic M_1 receptors. The goal of the current series of studies was to evaluate the EPS-producing potential of lurasidone compared to other antipsychotics in standard animal models. Methods: The EPS potential of lurasidone was evaluated in animal models. The mouse pole-test was used to measure bradykinesia-inducing activity. The rat and mouse catalepsy was measured by duration of immobility induced by lurasidone in a catalepsy apparatus. The rat paw test was used to measure forepaw retraction time. Results: As summarized in Table 1, below, lurasidone was much weaker than other antipsychotic drugs in inducing catalepsy in both rats and mice. In the mouse pole test, lurasidone was also far weaker than other antipsychotics in inducing bradykinesia, and failed to cause a significant motor impairment (delay in turning and pole-descending behaviors) even at 1000 mg/kg (Table 1). Finally, in the rat paw test, even high doses of lurasidone did not increase the forepaw retraction time. In contrast, other antipsychotic drugs were associated with increased retraction times even at relatively low doses (Table 1). Conclusion: The results of these pre-clinical studies suggest that lurasidone has a low potential for causing clinically significant EPS.

Table 1. Comparative ED50 (mg/kg) for induction of extrapyramidal side effects across 4 animal models

Drug	Rat Catalepsy	Mouse Catalepsy	Mouse Pole Test Bradykinesia	Rat Paw Test
Lurasidone	>1000	>1000	>1000	>1000
Risperidone	20	0.85	3	30
Olanzapine	28	>10	10	30
Sertindole	>300	>30	10	>1000
Quetiapine	NT	>300	NT	NT
Ziprasidone	97	63	30	100
Clozapine	>300	>30	>30	300
Haloperidol	12	2.0	1	1
Chlorpromazine	25	7.3	10	30
Thioridazine	890	42	30	>1000

ID: 550540

PREDICTORS OF CARDIOVASCULAR MORTALITY IN HOSPITALIZED PATIENTS WITH SEVERE MENTAL ILLNESS

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People with mental illness have an increased risk of comorbid medical conditions (Sokal, et al., 2004) and premature death (Harris and Barraclough, 1998). Cardiovascular (CV) disease is the second leading cause of death in patients with schizophrenia (Osbey et al., 2000). The present study investigated predictors of CV mortality in hospitalized people with severe mental illness: psychosis (predominantly schizophrenia (SZ)), bipolar disorder (BD), or other mental illness (predominantly depression and anxiety disorders ([OTH]). Clinical chart data was

abstracted and available on 1828 patients (n_{SZ} = 1443, n_{BD} = 165, n_{OTH} = 220) from inpatient State psychiatric hospitals between 1994 and 2000 in order to assess risk factors for cardiovascular (CV) mortality. Deaths were identified from the Social Security Death Index and death records were collected for all decedents. Males (n = 1065) and females (n = 762) between the ages of 35–65 were included. Groups were similar in age, smoking status, and sex, however, the SZ group had more non-whites (41%) than BD (29%) or OTH (22%). There were 60 (n_{male} = 30, n_{female} = 30) deaths in this sample. A Cox proportional hazards model, including age>55, race (white vs. non-white), sex, smoking status, and diagnosis, was used for multivariate survival analysis. Increased CV mortality was associated with age>55 (hazard ratio (HR) = 4.1, χ^2 = 15.76, $P < 0.001$), white race (HR = 2.4, χ^2 = 4.07, $P < 0.05$), and smoking (HR = 2.0, χ^2 = 3.63, $P = .057$). Compared with patients with SZ, increase in CV mortality was not significant in patients with bipolar disorder (HR = 1.7, χ^2 = 0.71, $P = .399$), and was marginally elevated in the OTH group (HR = 2.7 χ^2 = 3.30, $P = .069$). Sex was not significantly associated with CV mortality, $P = .25$. These findings are consistent with numerous studies that suggest that older age and smoking are risk factors for heart disease (Hennekens, 2007). Previous studies have also indicated greater CV mortality risks for patients with anxiety and depressive disorders than patients with schizophrenia (Harris and Barraclough, 1998). Racial differences in CV mortality in patients with severe mental illness require further investigation. This project was funded by the National Institutes of Mental Health (NIMH R03 MH069871-01; Kelly, PI) and the Advanced Centers for Intervention and Services Research (NIMH P50 MH40279; Carpenter, PI).
ID: 550530

THE RELATIONSHIP OF BRAIN WEIGHT TO BODY MASS INDEX (BMI) UPON AUTOPSY IN PEOPLE WITH SEVERE MENTAL ILLNESS

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Weight gain and other metabolic adverse effects of antipsychotic medications have been of concern in maintaining the physical health of patients with schizophrenia. However, the potential effects of possible brain changes during weight gain have received less attention. In the non-schizophrenia population, it has been observed that an association exists between high body mass index (BMI) and reduced gray matter, and BMI has also been found to be inversely related to brain volume measured by MRI. This association has not been reported thus far in patients with schizophrenia. Also, people with first episode schizophrenia have been shown to undergo changes in gray matter and ventricular volume over time and some evidence suggests that brain volume changes may occur with some antipsychotic medications. This study examined the relationship between BMI and brain weight upon autopsy in 60 patients with severe mental illness treated with antipsychotics. The population was 67% Caucasian, 70% male, with a mean age of 38.2 ± 9.6 years. The mean BMI and brain weights were 29.64 ± 8.71 kg/m^2 and 1322.58 ± 162.23 gm, respectively. Mean brain weight was significantly higher in men as compared to women, despite no gender differences in BMI (Kruskal-Wallis test, χ^2=12.28, df = 1, P = .0005). No racial differences were evident. Normal

weight subjects (BMI = 18.5–24.9 kg/m^2; n = 19) had a significantly greater mean brain weight (1357.4 ± 141.7 gm) as compared to those who were considered obese (BMI ≥ 30 kg/m^2) (1299.0 ± 194.0 gm; n = 29) (Kruskal-Wallis test, χ^2 = 33.8, df = 1, $P < .0001$). Further characterization found that in those with morbid obesity (Obesity class III BMI ≥ 40 kg/m^2; n = 5), the mean brain weight was the smallest among all obese categories (1186.0 ± 286.2 gm). There were no differences in brain weight by antipsychotic treatment and no correlations between brain weight and body weight were found by race, gender or drug treatment. The results of this study suggest that further research is needed regarding the effects of obesity on brain changes in people with severe mental illness. This project was funded by the National Institutes of Mental Health (NIMH R03 MH069871-01; Kelly, PI) and the Advanced Centers for Intervention and Services Research (NIMH P50 MH40279; Carpenter, PI).
ID: 550511

METHODS USED TO ASSESS ADVERSE EFFECTS IN A SAMPLE OF REPORTS OF CLINICAL STUDIES OF ANTIPSYCHOTIC MEDICATION

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Evidence-based decisions regarding the selection of antipsychotics (APs) for the long-term treatment of schizophrenia are influenced by existing knowledge regarding the relative safety and tolerability profiles of different agents. However, collecting information about AP safety is methodologically challenging because there is no single assessment approach capable of capturing the full range of adverse effects. Different methods for collecting information about adverse effects have been shown to result in different prevalence figures, which may represent a source of bias in reports of AP safety and tolerability. To identify how investigators typically collect and report information about AP safety, we surveyed eligible journal articles. To generate a representative sample, we searched the Cochrane Schizophrenia Group's register. Reports on 103 eligible clinical studies of antipsychotic drug treatment (90 of which were double-blind) were identified. The findings revealed that published rating scales were frequently used to evaluate drug-induced extrapyramidal symptoms (EPS), although relatively few studies employed several measures to assess the full range of EPS. In contrast, published scales were rarely used to assess general treatment emergent adverse effects and a large number of reports failed to specify how such information had been collected. Despite broad uniformity in the choice of measures used to evaluate EPS, findings from different studies remain difficult to interpret due to variations in reporting. Scores derived from rating scales tended to be presented as statistics such as mean change, which do not provide clinicians with meaningful information about the clinical or functional impact of the movement abnormalities observed. After EPS, weight gain was the second most frequently reported adverse effect. Despite increasing concerns about other metabolic risks associated with APs, relatively few studies explicitly referred to collecting data regarding markers of the metabolic syndrome. Only a small minority of studies reported assessing adverse effects that may be of particular concern to patients, eg, sexual dysfunction and aversive subjective experiences. These findings highlight the need for more consistent approaches to collecting and reporting information about the adverse effects of APs. Such information is vital if meaningful comparisons are to be made between the safety and tolerability profiles of different APs.
ID: 550476

GENE PROFILING REVEALS MAJOR DIFFERENCES IN THE EFFECT OF ANTI-PSYCHOTICS ON LIPID METABOLISM

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Background: Some anti-psychotics (APs) are associated with metabolic side effects. We investigated the effect of aripiprazole and other APs on gene expression in human hepatoma cells (HepG2) and primary human adipocytes. Methods: Cultured HepG2 and differentiated human adipocytes were exposed to Cmax and 10-fold Cmax of aripiprazole (ARI), olanzapine (OLZ), quetiapine (QUE), risperidone (RIS), 9-OH risperidone (9-OH-RIS) or ziprasidone (ZIP) for 6 or 24 hrs. Total RNA was isolated and used to evaluate expression levels for the treated vs vehicle control. GeneChip hybridization Array technology (Affymetrix) ($P \leq 0.01$) was used. Statistical comparisons were made by ANOVA with Dunnet's correction. Results: In adipocytes, OLZ and QUE induced genes involved in cholesterol transport and lipid synthesis. These genes are unchanged by other APs and down-regulated by ARI. In HepG2, PCA analysis grouped OLZ/QUE together but only QUE treatment resulted in the up-regulation of squalene epoxidase, an enzyme converting cholesterol to oxysterols. ARI treatment led to the down-regulation of this gene. Furthermore, in lipid synthesis studies, QUE treatment shifted the cholesterol band to a higher molecular weight product corresponding to an oxysterol. Conclusions: AP treatment of both HepG2 and adipocytes resulted in changes in expression levels of genes involved in lipid metabolism and cholesterol reverse transport. In addition, in HepG2 QUE led to the shunt of cholesterol pathway to oxysterols, known LXR ligands. The possible activation of the transcription factor LXR by oxysterols could be the reason for the observed gene up-regulation, contributing potentially to an increase in plasma lipids levels and cardiovascular risks.
ID: 550415

PHARMACOGENETICS OF FOLIC ACID METABOLISM AND METABOLIC DISTURBANCES IN SCHIZOPHRENIA

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Purpose: To examine the relationship between the methylenetetrahydrofolate reductase (MTHFR) 677C/T variant and metabolic syndrome in schizophrenia subjects receiving antipsychotics for ≥ 12 months. This variant is associated with aberrant folic acid metabolism and cardiovascular disease risk due to alterations in the Aldomet cycle associated with homocysteine and folic acid metabolism. Methods: 121 subjects were recruited from the Universities of Iowa and Michigan for this cross-sectional analysis. They were screened for the metabolic syndrome (NCEP ATP-III criteria) and genotyped for MTHFR 677C/T. Additionally serum folate, vitamin B12, leptin, and homocysteine were measured in some subjects. Results: 49 subjects (40%) met metabolic syndrome criteria. The groups mean age ($\pm$ s.d.) was 41.05 ± 11.17 years, 78% ($n = 94$) were Caucasian, 61% ($n = 74$) were male, and 71% ($n = 84$) were receiving clozapine, olanzapine, risperidone or quetiapine. There were no differences in age, gender, race, or antipsychotic exposure, between the genotype groups. The genotypes were CC (53%), CT (395), TT (8%) and are in Hardy Weinberg ($\chi^2 = 0.11$, $P = .74$) Overall, for those receiving an atypical antipsychotic (AAP)

a significant relationship was found between metabolic syndrome and the MTHFR TT genotype ($\chi^2 = 6.81$, $P = .009$). Specifically, subjects with this genotype receiving an AAP had a relative risk of 2.42 (95% CI: 1.87–3.14) for meeting metabolic syndrome criteria compared to those without this genotype receiving AAPs. For subjects not receiving AAPs no relationship between MTHFR genotype and metabolic syndrome was found ($\chi^2 = 0.47$, $P = .49$). No statistically significant relationship between MTHFR genotype and homocysteine was found, however subjects with the TT genotype did have higher levels (9.6 vs 10.3, $P = .7$). Conclusion: Overall, these results confirm our group's previous data. Aberrant function in MTHFR related to poor folic acid metabolism and hyperhomocysteinemia may be associated with antipsychotic associated metabolic complications. However, these results should be taken cautiously due to the small sample size included in this study.
ID: 550377

SUBJECTIVE WELL-BEING AND D_2 RECEPTOR OCCUPANCY IN PSYCHOTIC PATIENTS TREATED WITH ANTIPSYCHOTICS: AN EXPERIENCE SAMPLING STUDY

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Background: Blockade of dopamine D_2 receptors is a key element in the therapeutic activity of antipsychotic medication, but may also reduce motivation and subjective well-being. Previous laboratory studies have related D_2 receptor occupancy to subjective well-being measured with questionnaires. The current study aims to extend these findings to a broader domain of well-being assessed in the realm of daily life. In addition, antipsychotic agents differ in how tightly they bind to the D_2 receptor, possibly resulting in different effects on subjective well-being. The differential effect of 'tight' and 'loose' binding drugs will be investigated. Methods: The Experience Sampling Method (a structured diary technique) was used to assess subjective experience in daily life in 111 patients with a diagnosis of psychotic disorder. Patients were on current antipsychotic medication and were divided into a loose (olanzapine; $n = 41$) and tight (haloperidol,-risperidone; $n = 70$) binding agent user group based on the agents' dissociation constants at the D_2 receptor. D_2 occupancy values were estimated using occupancy formulas extracted from previous literature. Based on the tertiles, a three level D_2 occupancy variable was defined. Results: Multilevel analyses showed a significant interaction between binding group and D_2 receptor occupancy (positive affect (PA):$\beta = .05$ (SE = .02), $P < .009$; negative affect (NA):$\beta = -.04$(SE = .02), $P < .03$). For tight binding agent users, a significant effect was found of D_2 receptor binding on PA and NA (PA: $\chi^2(2) = 6.41$, $P < .042$; NA:$\chi^2(2) = 29.73$, $P < .0001$). There was a decrease in PA in the middle group and an even larger decrease in the group with the most D_2 receptor occupancy. A significant increase in NA was found in the group with the most D_2 receptor occupancy. For loose binding agent users, no main effect of D_2 occupancy on PA or NA was found. Although related to symptom severity, effects could not be entirely explained in terms of clinical symptom scores. Conclusions: These findings add ecological validity to previous laboratory findings showing an association between D_2 receptor

occupancy and subjective well-being, particularly pertaining to the tight binding agents. Furthermore, given that tight and loose binding agents showed overlap in terms of overall receptor occupancy estimates, our results suggest that the mechanism of dissociation from the D_2 receptor rather than mere occupancy levels of the drug may determine a drug's impact on subjective well-being.

ID: 550288

THE NATIONAL REGISTER OF ANTIPSYCHOTIC MEDICATION IN PREGNANCY (NRAMP)

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Current data on the use of antipsychotic medication in pregnancy is limited. Establishment of The National Register of Antipsychotic Medication in Pregnancy (NRAMP) will provide evidence-based clinical guidelines for the safest use of antipsychotic medication during pregnancy and for one year postnatally. NRAMP is an Australia-wide observational, non-interventional study involving female participants with a history of mental illness, who take antipsychotic medication and who become pregnant or have had a baby in the last 12 months. Information is collected via telephone or face to face interviews during the pregnancy and for the first year postpartum and includes demographic, social, family, medical, psychiatric, medication and obstetric history, as well as information on general health and wellbeing for both mother and baby. This observational study is current and ongoing, with 66 consented participants at different stages on the study timeline; that is, either antenatal or postnatal. This is reflected in the results to date, with regard to consenting data, pregnancy outcomes and maternal and neonatal complications. Preliminary interpretation of these results will therefore be spread across various time points: the antenatal period, post-delivery and for one year postnatally. The resultant evidence-based guidelines arising from The National Register of Antipsychotic Medication in Pregnancy (NRAMP) have the potential to provide regular, contemporary updates to clinical treating teams for the management of women in this vulnerable population group. We plan to fill a void in mental health services where currently there is a distinct lack of information available to treating clinicians, with regard to providing safe and timely care of women who take antipsychotic medication and become pregnant. This study is supported by AstraZeneca, Janssen-Cilag, Mayne Pharmaceuticals and the Australian Rotary Health Research Fund.

ID: 550183

THE INCIDENCE OF OBESITY AND DIABETES IN PATIENTS TREATED WITH CLOZAPINE

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This is a 15 year retrospective study to determine the correlation between Clozapine treatment and the development of diabetes and obesity . The study cohort consisted of all 136 patients (77M;59F) registered at the Clozapine outpatients clinic of the Blacktown Hospital in Sydney. All patients were suffering from drug resistant Schizophrenia and were on Clozapine. The data was collected from patient records, which included demographic details, duration of Clozapine treatment, vital signs including weight, Blood levels for Glucose, Cholesterol and Triglycerides. Patients were on Clozapine treatment for between 1–15 years(mean 5.6 years) of which 24 patients were on Clozapine for 10 years or more. As per the protocol, all patients had routine investigations including blood levels for glucose, cholesterol and triglycerides. Their weight was also recorded at least once a month. Of this cohort, 10(5M:5F) had consistently elevated blood glucose levels, 34 (19M:15F) had high cholesterol and 55(39M:16F) had high triglycerides. All the patients who had high glucose levels also had high cholesterol and triglycerides and were overweight. These figures were compared to the prevalence of obesity and Type II diabetes in the general population of Australia. These figures support the fact that there is a higher incidence of obesity and diabetes in patients treated with Clozapine even after adjusting for age and gender.

ID: 550161

EFFECTS OF CLOZAPINE AND HALOPERIDOL ON EXPRESSION OF DOWNSTREAM EFFECTORS OF INSULINE SIGNALING: FOCUS ON Ped/Pea-15

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Schizophrenia is a major highly debilitating psychiatric disorder with a prevalence of about 1% (Mueser and McGurk, 2004). Several lines of evidence have indicated that schizophrenic patients have an higher prevalence of impaired glucose tolerance, insulin-resistance, and type-2 diabetes mellitus than general population (Citrome et al., 2005). Clinical and experimental evidence indicates that first and second generation antipsychotic drugs may contribute to impair glucose metabolism (Haupt and Kane 2007). In our study we have shown, by *in vitro* (PC12 transplantable rat pheochromocytoma cells and L6 skeletal muscle cells) paradigm, that both haloperidol and clozapine reduced insulin-stimulated glucose uptake in PC12 neuronal cells and in L6 skeletal muscle cells. Pre-treatment with clozapine, but not with haloperidol, also prevented insulin effect on insulin receptor and IRS-1/2 tyrosine phosphorylation. Furthermore in neurons and skeletal muscle cells, both haloperidol and clozapine led to the activation of Akt and to increased expression of the Ped/Pea-15 protein, an Akt substrate. This is paralleled by decreased PKC-ζ activity and deranged insulin-stimulated glucose uptake. Similarly increased Akt activity and Ped/Pea-15 levels, as well as reduced PKC-ς activity, were detected in caudate-putamen and in skeletal muscle of mice (3-months-old male C57/BL/KsJ mice) treated with either haloperidol or clozapine. Our data suggest that first and second generation antipsychotics may contribute to the impairment of glucose metabolism by reducing insulin-mediated glucose uptake in insulin-targeted tissues. The molecular mechanism implicated in this effect involves intracellular effectors of the insulin signaling cascade. For instance, the increase of phosphorilated Akt enhances Ped/Pea-15 levels by increasing its phosphorylation on Ser-116; as a consequence, Ped/Pea-15 inhibits the activation of atypical PKC-ζ and prevents insulin-stimulated glucose uptake.

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ID: 549990

PHARMACOGENETICS OF THE METABOLIC CONSEQUENCES OF ANTIPSYCHOTIC TREATMENT - PREDICTION AND MECHANISM

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There are substantial differences between individuals in the effects of antipsychotic drugs. This is particularly true in the weight gain apparent following treatment with many of the second generation, as well as some of the first generation, antipsychotics; equivalent treatment regimes can cause profound fat deposition in some patients but minimal effects in others. Such weight gain can lead to further morbidity as indicated by the development of metabolic syndrome, identifying a set of risk factors for cardiovascular disease and diabetes. The pharmacology of antipsychotic-induced weight gain is not fully defined, but antagonist action at 5-HT2C receptors, as well as at histamine H1 and some other receptors, is strongly implicated. The underlying mechanisms too are unclear but may involve hypothalamic receptor antagonism interfering with the signalling of circulating hormones such as leptin. These receptors and hormonal hypotheses provide good candidate genes for pharmacogenetic study of antipsychotic drug-induced weight gain. In two pharmacogenetic studies of antipsychotic-induced weight gain in initially drug-naive patients, we demonstrated a strong association with weight gain of a promoter region polymorphism of the 5-HT2C receptor, which we have also shown to influence gene expression in neuronal cells in culture. The leptin gene also shows a functional promoter polymorphism and this too is associated with antipsychotic-induced weight gain, particularly in the longer term. Findings in a population of chronically-treated patients with schizophrenia have revealed interacting effects of the two polymorphisms on measures of obesity, and particularly association of the leptin gene polymorphism with the incidence of metabolic syndrome. This supports the interpretation that the leptin polymorphism may have longer-term effects on these metabolic consequences of antipsychotic treatment. Interestingly, not only the leptin polymorphism but also that of the 5-HT2C receptor gene was associated with blood leptin concentrations prior to treatment. These findings point towards underlying mechanisms, as well as indicating the potential for genetic testing for the propensity to develop weight gain and its severe metabolic consequences. ID: 549828

COMPARISON OF LEPTIN LEVELS AND OBESITY BETWEEN DRUG-NAÏVE FIRST-EPISODE SCHIZOPHRENIA PATIENTS AND CHRONICALLY MEDICATED PATIENTS

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Weight gain and metabolic disturbances now predominate the psychopharmacology of schizophrenia. In this study, plasma levels of leptin were evaluated in relation to weight and psychopathology measures in never-medicated first episode of psychosis patients (FEP; N = 23), patients with chronic schizophrenia who were receiving clozapine, (N = 21), and normal subjects (N = 11). Patients were clinically assessed using the PANSS and BPRS. Plasma leptin levels were determined by commercially available Enzyme Linked ImmunoSorbent (ELISA) kits. Plasma leptin levels were not significantly different between never-medicated FEP and matched normal controls. However leptin levels were significantly higher in patients treated with clozapine than in either control subjects or FEP patients (P = .065 and .016, respectively). While not surprisingly, clozapine-treated patients had significantly higher BMI than FEP patients or controls (29.86 ± 3.6 vs

25.1 ± 2.61 and 23.2 ± 2.14, respectively), higher leptin levels in these chronic schizophrenia patients did not correlate with higher BMI but did correlate with psychopathology measures. In some contrast, leptin levels in FEP patients were inversely related to psychopathology measures. Consistent with the emergent literature, leptin levels may be a useful measure for examining energy metabolism and relationships to antipsychotic-induced weight and metabolic disturbances in schizophrenia. ID: 549709

PROLACTIN LEVELS AND SEXUAL SIDE EFFECTS IN SCHIZOPHRENIA PATIENTS DURING ANTIPSYCHOTIC TREATMENT

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Introduction: Sexual dysfunction occurs frequently in schizophrenia patients treated with antipsychotic drugs. Prolactin levels can be elevated under antipsychotic treatment and have been suggested to impair sexual functioning through an action on the hypothalamic-pituitary-gonadal axis altering sex hormone release. As there is limited evidence about the association between prolactin levels and sexual dysfunction in schizophrenia patients receiving antipsychotic treatment we have prospectively investigated patients during treatment with second generation antipsychotics. Methods: Thirty-nine schizophrenia patients (diagnosed according to ICD 10) treated with amisulpride, clozapine, quetiapine, olazapine, risperidone or ziprasidone were included in a 4 week study. To quantify antipsychotic side effects we used the Udyalg for Klinske Undersogelser (UKU) Side Effect Scale. Prolactin levels were determined weekly. Results: Prolactin levels in males rose significantly while no significant changes in prolactin levels were observed in female patients from baseline to week 4. Men reported diminished sexual desire most frequently followed by orgastic dysfunction and ejaculatory dysfunction. Women most often complained about diminished sexual desire, amenorrhea or orgastic dysfunction. The incidence of sexual adverse events did not change significantly from baseline to week 4. At baseline a significant association was found between diminished sexual desire and prolactin levels in men. At week 4 orgastic dysfunction and higher prolactin levels showed a correlation in male and female patients. In addition a relationship between changes of prolactin concentration and diminished sexual desire was detected in female patients. Conclusion: Further studies, including more Patients, which need to be studied over a larger observation period, will be necessary to shed more light on sexual functioning in schizophrenia patients and to differentiate between antipsychotics, which was not the aim of this study. ID: 549658

PROSPECTIVE LONG-TERM EVALUATION OF SERUM CREATINE KINASE LEVELS AND NEUROMUSCULAR DYSFUNCTION IN SCHIZOPHRENIA PATIENTS: NEW RESULTS OF FOLLOW-UP STUDY

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Background: There are multiple causes of hyper-CKemia (HCK)—the elevation of serum creatine kinase (SCK) activity above upper limits. These increases may be related to underlying trait-like biological abnormalities in psychosis, phasic episodes related biological abnormalities, or the effect of drug treatment. Previously we found, that among HCKemic patients, the majority was treated with atypical antipsychotic drug (AAPD) and some of them had neuromuscular complaints. The purposes of this study were to follow-up prospectively and to estimate the incidence and severity of probable neuromuscular dysfunction in HCKemic schizophrenia and schizoaffective patients. Methods: For this study, we selected 39 HCK-emic patients suffering from schizophrenia or schizoaffective disorder. Eleven patients, treated either with clozapine, olanzapine or perphenazine had persistent/recurrent hyper-CKemia (PHCK). 25 patients had occasional HCKemia (OHCK). Blood samples for CK determinations were collected up to three years of follow-up. Each year, all patients were assessed neurologically for possible muscular and peripheral nervous systems involvement. Results: During the study, SCK activity in PHCK patients was found to be persistently elevated: 400 ± 200 (mean $\pm$ SD) in range 250–950 IU/L. Five of these patients had complaints of muscular weakness, early fatigue on exercise, some muscular pains and cramps. In two of them clinical assessment revealed mild general muscular weakness, especially in the proximal parts of the limbs. This pattern was diagnosed as probable mild myopathy. In majority of OHCK patients SCK activity was reduced to the normal levels range. Some patients remained with occasional HCK without any kind of neuromuscular pathology. Conclusions: The results of this first long-term large-scale prospective comparative study indicate that among HCK-emic schizophrenia and schizoaffective patients, only PHCK pattern may consider to be a biochemical marker of the neuromuscular dysfunction. Meanwhile, OHCK is likely to be a benign phenomenon, has no clinical manifestations, and does not need to be followed-up routinely. Further investigation of neuromuscular dysfunction, its mechanisms, pathophysiological significance and possible pharmacogenetics associations in schizophrenia patients is certainly indicated. The relationship of HCK to mutations in neuregulin, dysbindin or reelin—the genes related both to schizophrenia and to muscle, is also of interest.
ID: 549626

CHANGES IN BODY MASS INDEX (BMI) DURING TREATMENT WITH OLANZAPINE VERSUS AMISULPRIDE: A PROSPECTIVE STUDY

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Adiposity (body mass index [BMI] ≥ 30), hyperlipidemia, hypertension and increased blood glucose levels, which define the metabolic syndrome, are common side effects of atypical antipsychotic treatment. The aim of this prospective study was to examine changes in BMI during treatment with olanzapine versus amisulpride over a twelve-week period (day 0, week 4, week 8, week 12). 46 patients with schizophrenia (ICD-10) were included into the study (olanzapine: $n = 25$, amisulpride: $n = 21$), 32 patients (olanzapine: $n = 14$, amisulpride: $n = 18$) completed the trial. BMI increased by 1.81 ± 1.0 in the olanzapine group (baseline-BMI = 23.7 ± 4.8), whereas BMI decreased by 0.21 ± 1.6 in the amisulpride group (baseline-BMI = 28.5 ± 8.0). Analysis of covariance (adjustment for baseline differences) showed a significant difference ($P = .01$) in BMI change to the disadvantage of Olanzapine. These results support differences in metabolic side effects of olanzapine and amisulpride and further emphasize the need for a risk-benefit analysis regarding the choice of antipsychotics in schizophrenia.
ID: 549363

RELATIONSHIP BETWEEN THE ADIPONECTIN (*APM1*) 276G/T VARIANT AND METABOLIC DISTURBANCES IN A SCHIZOPHRENIA POPULATION RECEIVING ANTIPSYCHOTICS

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Purpose: To explore the relationship between the adiponectin (*APM1*) 276G>T (rs1501299) variant and metabolic abnormalities in schizophrenia subjects receiving antipsychotics. Methods: Subjects with schizophrenia, receiving antipsychotic treatment for ≥ 12 months were screened for the metabolic syndrome (NCEP ATP-III criteria), including blood pressure, height, weight, and fasting laboratory measures (cholesterol panel, glucose, insulin, hemoglobin A1C), and a DNA sample. From these measures, body mass index (BMI) and a Homeostasis Model Assessment Insulin Resistance (HOMA-IR) value was calculated. Results: A total of 110 schizophrenia spectrum disorder subjects were recruited. The sample contained 68 men (62%), with a mean age of 41 ± 11.17 years, and 40% meeting metabolic syndrome criteria. Eight-one percent of subjects were Caucasian and 75% were receiving olanzapine, clozapine, risperidone or quetiapine at the time of evaluation. Eight subjects with a known diabetes diagnosis were excluded from the analysis. The T allele was present in 51% of subjects and 49% had the GG genotype, which was in Hardy Weinberg ($\chi^2 = 0.68$, $P = .41$). There were no differences in demographic or laboratory values between genotype groups and no relationship between *APM1* and a metabolic syndrome diagnosis ($\chi^2 = 1.086$, $P = .29$). However, subjects with a T allele had lower BMIs compared to the GG genotype group ($P = .007$). Overall, a significant interaction between the *APM1* 276 G>T genotype and BMI was found, where those with the T allele had higher levels of insulin resistance (HOMA-IR) at similar BMIs compared to the GG genotype group ($F = 9.94$, $df = 3,104$, $P < .0001$). After controlling for BMI differences, this interaction remained significant ($P = .0035$). Conclusions: Schizophrenia subjects are at increased risk for type II diabetes and insulin resistance. New data suggests *APM1* variation may play a role. We found the *APM1* 276T allele may increase insulin resistance risk at similar BMIs compared to the GG genotype. These results should be interpreted cautiously due to the small sample size, lack of adiponectin levels, and the need for replication.
ID: 549235

EPIDEMIOLOGICAL STUDY FOR THE EVALUATION OF METABOLIC DISORDERS IN PATIENTS WITH SCHIZOPHRENIA: THE METEOR STUDY

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A large, observational, multinational cross-sectional pharmacoepidemiological study was initiated in 2006 in order to determine the prevalence of diabetes and other metabolic disorders in patients with schizophrenia receiving atypical antipsychotic drugs in Europe. Secondary objectives included identification of risk factors for metabolic disorders. The study included adult outpatients with schizophrenia (DSM IV TR) treated for at least 3 months by an antipsychotic drug. In each country, patients treated with classical or atypical antipsychotic drugs were recruited into two parallel strata (ratio of 1:3). The study consisted of a single visit at which a fasting blood sample was taken and height, weight, waist and hip circumference and blood pressure measured. Information was collected on socio-demographic variables, lifestyle, comorbidities and co-medications, metabolic and cardiovascular risk factors, psychiatric history and antipsychotic drug history. Biochemical parameters assessed included glucose, insulin, HbA1c, triglycerides, total cholesterol, HDL cholesterol and apolipoprotein B. 2463 patients were included in 12 countries (Bulgaria, Czech Republic, Estonia, Germany, Greece, Italy, Latvia, Lithuania, Romania, Russian Federation, Slovenia and Turkey). Median age of included patients was 41.0 years and 54.6% were male. Medical history revealed that 10.9% of patients were treated for arterial hypertension, 7.1% of patients for a lipid disorder, 0.3% for type I diabetes and 3.5% for type II diabetes. In addition, 26% of untreated patients presented biochemical evidence of dysglycemia, 67.7% of dyslipidemia and 38% had hypertension. A metabolic syndrome was identified in 34% of the patients. No overall difference was observed in the proportion of patients with glycemic and lipid disorders between the two strata of antipsychotic treatment (classical or atypical). Mean weight and weight gain, abdominal obesity and the proportion of patients with BMI $\geq$ 25 kg/m2 were slightly higher in the atypical stratum compared to the classical stratum. Hypertension was more frequent in the classical stratum (47.3%) than in the atypical stratum (42.2%). The results observed in this large epidemiological study emphasize the need for careful follow-up of patients with schizophrenia treated with antipsychotic drugs to detect metabolic disorders. The rate of patients with glycemic or lipid disorders was very high and as such largely underdiagnosed. Funding: Sanofi-Aventis.
ID: 549033

BONE MINERAL DENSITY AND OSTEOPOROSIS RISK IN OLDER PATIENTS WITH SCHIZOPHRENIA

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Osteoporosis is a significant public health concern because of its morbidity and mortality associated with fractures and its associated health care costs. Patients with schizophrenia are at higher risk for developing osteoporosis as compared to the general population. Aging and gender are risk factors for developing bone loss. In our previous study, middle aged women had a significantly greater rate of bone loss compared to men of similar ages (85.7% vs 50%; $P < .05$). In this study, we evaluated the prevalence of bone density and gender differences in older patients (> 50 years) with a DSM-IV diagnosis of schizophrenia. Patients with nutritional impairments or a medical disorder known to be risk factor for osteoporosis were excluded. Bone densitometry testing was performed by dual energy x-ray absorptiometry (DEXA) (GE Lunar 4500 scanner), in the lumbar spine (L1-L4) and in the femoral neck, trochanter, and intertrochanteric regions of the proximal right femur. WHO definitions were used for osteoporosis and osteopenia. The mean age in this study ($N = 312$ patients (184 men, 130 women) was 56.7 ± 8.1 years; duration of illness, 142.6 ± 79.2 months; and chlorpromazine equivalent dose of antipsychotics, 589 ± 518mg/day (no gender differ-

ences). Cigarette smoking was significantly higher in men compared with women (66.9% vs, 11.3%; $P < .001$). The lifetime prevalence of fracture was not significantly different in men and women (24.7% vs. 21.1%). Prevalence of bone loss was 75.2% in men and 79.9% in women. The prevalence of osteoporosis was significantly different between men and women patients ($P < .010$); osteoporosis was higher in women as compared to men (39.5% vs 27.2%), while the prevalence of osteopenia was higher in men (52.7% vs. 35.7%). Women had significantly lower bone density volumes in L1-L4, neck and the trochanter region of the femur compared to men ($P < .001$). T-scores, however, only in the trochanter region of the femur, were significantly lower in women than men ($P = .035$). Smokers showed significantly lower absolute bone density (0.72 ± 1.22 vs. 0.78 ± 0.15, $P < .0003$) and t-scores (−0.42 ± 1.22 vs. 0.04 ± 1.32, $P < .003$) than non-smokers. In conclusion, bone density loss in women with schizophrenia was more severe as compared to men, however, the prevalence of bone density loss and lifetime fractures in older men was also high, thus careful attention is needed to monitor men as well as women with schizophrenia.
ID: 549015

PRELIMINARY RESULTS OF THE MEAC STUDY: METABOLIC EFFECTS OF ANTIPSYCHOTICS IN CHILDREN

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The purpose of the ongoing Metabolic Effects of Antipsychotics in Children study (MEAC) is to quantify changes in markers of adiposity and insulin sensitivity associated with antipsychotic treatment. Antipsychotic-naïve children ages 7–18 with clinically significant aggression and/or irritability (a score of $>$ 18 on the Aberrant Behavior Checklist (ABC) irritability subscale) who are already planning to start antipsychotic treatment for one or more DSM-IV psychiatric disorder(s) are randomized to 12 weeks of treatment with risperidone, olanzapine or aripiprazole following baseline evaluations of adiposity, insulin sensitivity and metabolic indices. Dual energy x-ray absorptiometry (DEXA), abdominal magnetic resonance imaging, modified frequently-sampled oral glucose tolerance tests (mOGTT), and stable isotopomer tracer methodology during hyperinsulinemic-euglycemic clamp conditions, as well as fasting labs and anthropomorphic measures, are used to assess baseline and treatment-emergent changes in adiposity and insulin sensitivity, as well as secondary measures, over the 12 weeks of treatment. Preliminary analyses, pooling treatment groups into an overall study sample, indicate that 12 weeks of initial antipsychotic treatment is associated with a statistically significant increase in adiposity as measured by DEXA percent body fat, with a mean increase of 2.91% ± 3.53 (mean ± SD) corresponding to a mean DEXA total fat increase of 2.85 kg (±9.35). The primary measure of insulin sensitivity, derived from hyperinsulinemic-euglycemic clamps, indicated a statistically significant pooled-groups decrease in whole body insulin sensitivity. Preliminary results also indicate that BMI percentile and fasting triglyceride undergo changes similar to the patterns observed in the primary measures of adiposity and insulin sensitivity. Finally, treatment produced marked improvement in the ABC irritability/aggression score. These preliminary results demonstrate important effects of antipsychotic treatment on adiposity and measures of insulin sensitivity within the first 12 weeks of treatment, relevant to long-term cardiometabolic risk prediction. Clinically available surrogates for adiposity and insulin sensitivity, BMI percentile and fasting plasma triglyceride, respectively, also indicate a similar pattern of change during treatment. Importantly, all three treatments produce clinically and statistically significant improvement in mood and behavior.
ID: 548877

ANTIPSYCHOTIC POLYPHARMACY AND RISK OF DEATH FROM NATURAL CAUSES IN PATIENTS WITH SCHIZOPHRENIA

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Concomitant prescription of more than one antipsychotic agent (antipsychotic polypharmacy) in the treatment of schizophrenia is prevalent although monotherapy is generally recommended. Mortality from natural causes is markedly increased in schizophrenia and the role of polypharmacy in this remains controversial. The objective of this study was to investigate if antipsychotic polypharmacy is associated with the excess mortality from natural causes among patients with schizophrenia. The study was designed as a population-based nested case-control study using Danish central registers. From the study population of 27633 patients with schizophrenia or other mainly non-affective psychoses, aged 18–53 years, we identified 193 cases who died of natural causes within a 2-year period, and 1937 age- and sex-matched controls. Current drug use was defined as at least one prescription filled within 90 days before the date of death or the index date. The data were analysed by conditional logistic regression. The risk of natural death did not increase substantially with the number of concurrently used antipsychotic agents compared with antipsychotic monotherapy (no antipsychotics: adjusted odds ratio 1.48 [95% confidence interval 0.89–2.46]; two antipsychotics: 0.91 [0.61–1.36]; three or more antipsychotics: 1.16 [0.68–2.00]). Current use of benzodiazepine derivatives with long elimination half-lives (more than 24 hours) was associated with increased risk of natural death in patients with schizophrenia treated with antipsychotics (1.78 [1.25–2.52]). We conclude that antipsychotic polypharmacy was not associated with substantially increased risk of natural death. However, benzodiazepines, particularly those with long elimination half-lives, should be cautiously prescribed in combination with antipsychotics. The authors were supported by the National Board of Health in Denmark, the Wørzner Foundation, and an unrestricted grant from H. Lundbeck, Denmark.
ID: 548790

PREDICTORS OF CARDIOVASCULAR MORTALITY IN HOSPITALIZED PATIENTS WITH SEVERE MENTAL ILLNESS

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People with mental illness have an increased risk of comorbid medical conditions (Sokal, et al., 2004) and premature death (Harris and Barraclough, 1998). Cardiovascular (CV) disease is the second leading cause of death in patients with schizophrenia (Osbey et al., 2000). The present study inves-
tigated predictors of CV mortality in hospitalized people with severe mental illness: psychosis (predominantly schizophrenia (SZ)), bipolar disorder (BD), or other mental illness (predominantly depression and anxiety disorders (OTH)). Clinical chart data was abstracted and available on 1828 patients (n_{SZ}=1443, n_{BD}=165, n_{OTH}=220) from inpatient State psychiatric hospitals between 1994 and 2000 in order to assess risk factors for cardiovascular (CV) mortality. Deaths were identified from the Social Security Death Index and death records were collected for all decedents. Males ($n = 1065$) and females ($n = 762$) between the ages of 35–65 were included. Groups were similar in age, smoking status, and sex, however, the SZ group had more non-whites (41%) than BD (29%) or OTH (22%). There were 60 ($n_{male} = 30$, $n_{female} = 30$) deaths in this sample. A Cox proportional hazards model, including age>55, race (white vs. non-white), sex, smoking status, and diagnosis, was used for multivariate survival analysis. Increased CV mortality was associated with age>55 (hazard ratio (HR) = 4.1, χ^2 = 15.76, $P < 0.001$), white race (HR = 2.4, $\chi^2 = 4.07$, $P < 0.05$), and smoking (HR = 2.0, $\chi^2 = 3.63$, $P = .057$). Compared with patients with SZ, increase in CV mortality was not significant in patients with bipolar disorder (HR = 1.7, $\chi^2 = 0.71$, $P = .399$), and was marginally elevated in the OTH group (HR = 2.7 χ^2=3.30, $P = .069$). Sex was not significantly associated with CV mortality, $P = .25$. These findings are consistent with numerous studies that suggest that older age and smoking are risk factors for heart disease (Hennekens, 2007). Previous studies have also indicated greater CV mortality risks for patients with anxiety and depressive disorders than patients with schizophrenia (Harris and Barraclough, 1998). Racial differences in CV mortality in patients with severe mental illness require further investigation.
ID: 548416

HANDWRITING MOVEMENT KINEMATICS FOR QUANTIFYING ANTIPSYCHOTIC-INDUCED EPS

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Ongoing monitoring of antipsychotic-induced extrapyramidal side effects (EPS) is important to maximize treatment outcome and improve medication compliance. Conventional clinical assessments of EPS appear insensitive to differences across various atypical antipsychotics and examiner bias can reduce their reliability. Instrumental methods emerged as a remedy to these problems, however, these systems have had limited clinical utility because of their complexity and cost. We developed a novel method based on quantifying handwriting movements that overcomes previous limitations of complexity and cost. In our study we test the hypothesis that handwriting movement abnormalities are associated with severity of EPS but are independent of age, severity of psychosis, depression, or other factors that can bias the clinical assessment of EPS. We also tested whether handwriting movements differed across four commonly used atypical antipsychotics. Handwriting movements from 87 psychosis patients and 45 healthy comparison subjects were quantified during a loop-drawing task. Participants were instructed to draw continuous loops 2 cm high from left to right across a digitizing tablet. Samples were recorded and analyzed using commercial software. Kinematic variables included vertical loop size and peak velocity, relative time to peak velocity, and pen contact duration per stroke for both primary and secondary submovements. Patients with clinically determined EPS exhibited smaller vertical heights ($P < .001$), lower peak velocities ($P < .05$), longer times to peak velocity ($P < .05$), and increased duration of pen contact ($P < .05$) compared to patients without EPS. Patients treated with aripiprazole or risperidone exhibited significantly more impaired handwriting movements than patients treated with quetiapine or

olanzapine, especially for peak velocity ($P < .01$), whereas, clinical EPS assessments were insensitive to these medication differences. Unlike clinical EPS assessments, kinematic handwriting variables were independent of severity of positive and negative symptoms of psychosis, depression, or demographic variables. These findings support the high specificity of our kinematic handwriting measures to EPS. Differences between various antipsychotic medications suggest that handwriting kinematics may be useful in measuring the effects of switching medication in patients with pre-existing EPS. Research supported by NIH grant R44 MH073192.
ID: 547581

NON-PHARMACOLOGICAL INTERVENTION FOR WEIGHT GAIN MANAGEMENT IN SEVERE MENTAL DISORDERS: RESULTS FROM A LARGE MULTICENTRIC STUDY

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Background: A high prevalence of metabolic abnormalities has been observed in patients with severe mental disorders and schizophrenia. Obesity interventions studies in this population are scarce. Objective: Evaluate the effectiveness of a non-pharmacological intervention in controlling body weight and metabolic parameters. Method: An open, multicentric, longitudinal study was conducted on 57 mental health services in 34 cities in Brazil. Patients included in this study received a 12-week 1-hour group intervention. Topics such healthy nutrition, lifestyle, physical activity and self-esteem were discussed with patients and their relatives. Weight, high, waist circumference and blood pressured were measured before and after the intervention. A total of 656 patients participated in the intervention. All of them were in use of some antipsychotic and/or mood stabilizers and had some concern about weight gain. Results: 512 patients completed the intervention. A significant weight loss (0.5 ± 3.4kg, $P < .000$) and a significant BMI reduction (0.2 ± 1.4 kg/m2, $P < .007$) were observed. There was a marked increase in physical activity after the intervention, at the baseline 55.2% of the patients were enrolled in some kind of exercise program, after the intervention, 72.8% were regularly practicing physical activity. Conclusion: To our knowledge, the Brazilian Wellness Program is the largest national, multicentric, naturalistic study of a non-pharmacological intervention for severe mental disorder patients showing positive outcomes on weight gain management, reducing diastolic blood pressure and increasing physical activity. Efficacy and effectiveness studies are being conducted to further inform the implementation of the wellness intervention as public mental health policy.

Table. Clinical parameters at baseline and 3 months ($n = 512$)

Variable	Baseline (mean ± SD)	3 months (mean ± SD)	Analysis	P
Weight (kg)	83.2 (18.7)	82.7 (18)	$t = 3.549$; $df = 511$	.000
BMI (kg/m2)	31.3 (5.6)	31.1 (5.6)	$t = 2.696$; $df = 510$	.007
Waist (cm) Male	109.2 (15.2)	108.6 (14.1)	$t = 1.332$; $df = 151$	.185
Waist (cm) Female	102.1 (15.5)	101.8 (13.7)	$t = 0.438$; $df = 305$	.662
Systolic BP (mmHg)	119.6 (15.4)	118.6 (14.7)	$t = 1.653$; $df = 483$	.099
Diastolic BP (mmHg)	79.8 (11.7)	78 (10.5)	$t = 3.655$; $df = 484$	.000

BMI: body mass index; BP: blood pressure; SD: standard deviation; df: degrees of freedom
ID: 546913

PIOGLITAZONE AS A TREATMENT FOR GLUCOSE AND LIPID METABOLIC ABNORMALITIES IN SCHIZOPHRENIA

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Diabetes, hyperglycemia, and hyperlipidemia more prevalent in psychiatric patients and increased by treatment with antipsychotic drugs. Research by our own and other groups have shown that some second generation antipsychotics increase insulin resistance even in patients who do not meet metabolic criteria for diabetes. Pioglitazone is a PPAR agonist which specifically acts by increasing insulin sensitivity, a mechanism of action different form other antidiabetic drugs, and has beneficial effects on decreasing triglycerides and increasing HDL. We present preliminary data from a double-blind placebo controlled study of pioglitazone as a treatment for glucose and lipid abnormalities in schizophrenia and assessment of its potential cognitive effects. Method: Patients with schizophrenia or schizoaffective psychosis who were treated with antipsychotic medications and had fasting glucose ≥ 100 mg/dl and fasting triglycerides ≥ 120 mg/dl participated in a 12 week double blind study in which they received pioglitazone or placebo. Fasting glucose, insulin, triglycerides and other metabolic parameters were measured monthly and a glucose tolerance test was performed at baseline and end of study. Cognitive functions was assessed by RBANS, CPT, and RANDT and psychopathology asessed by PANSS. Preliminary results from the first 29 patients showed that by the end of treatment patients treated with pioglitazone had lower fasting glucose and triglycerides, and higher fasting HDL than patients treated with placebo. 46% of placebo treated patients had diabetic range fasting glucose levels compared to 13% of pioglitazone patients. There was no drug differences in serum insulin but pioglitazone produced an increase in insulin sensitivity measured by the homo procedure. By the end of treatment Pioglitazone treated patients had lower 1 and 2 hr glucose glucose levels on the 75 mg GTT test than placebo patients. Pioglitazone patients showed a decrease in PANSS. There were no significant drug effects on the cognitive performance.Pioglitazone may be a useful treatment for reducing or reversing metabolic abnormalities in schizophrenic patients treated with antipsychotic medication. Because pioglitazone increases insulin sensitivity and may prevent or delayed conversion of impaired fasting glucose to diabetes it might be considered as a preventive strategy in patients treated with some antipsychotic medications.
ID: 541974

GLUCOSE AND LIPID DISTURBANCES AFTER 1 YEAR OF ANTIPSYCHOTIC TREATMENT IN A DRUG-NAÏVE POPULATION

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The objective of this study is to examine the main metabolic side effects induced by antipsychotic treatment in a cohort of first-episode drug-naïve subjects after the first year of treatment. A randomized, open-label, prospective clinical trial was conducted. Participants were 164 consecutive subjects included in a first episode program and never treated with antipsychotic medication. Patients were assigned to haloperidol, olanzapine or risperidone. The main outcome measures were changes at one year in fasting glucose parameters (glucose, insulin levels and insulin resistance index) and changes in fasting lipid parameters (total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol). At one year follow-up 144 subjects were evaluated. There was a statistically significant increase in the mean values of insulin levels (3.5 microU/ml; $P = .004$); HOMA insulin resistance index (0.7; $P = .013$); total cholesterol (22.2 mg/dl; $P < .001$); LDL-cholesterol (-15.1mg/dl; $P < .001$) and triglycerides (-36.6 mg/dl; $P < .001$). No pathological values in fasting glucose plasma levels were found at baseline and there were no changes after one year. Weight gain was positively correlated with changes in insulin increase ($r = .32$, $P = .001$); HOMA index ($r = .34$, $P < .001$) and triglyceride levels ($r = .23$, $P = .016$) and negatively correlated with HDL changes ($r = -.25$, $P = 0.007$). We did not detect statistically significant differences between treatments in any of the parameters evaluated. Fasting glycaemia and insulin concentrations at baseline do not support the hypothesis that schizophrenia is associated with an underlying abnormality in glucose metabolism. To summarize, after the first year of antipsychotic treatment we have observed an increase in insulin-resistance index and a worsening lipid profile—but no clinically relevant illness was detected. The changes in insulin and lipid parameters seem to be related to the magnitude of weight gain. There were no significant differences between haloperidol, olanzapine and risperidone concerning metabolic adverse effects after the first year of treatment. Grants: Instituto de Salud Carlos III, FIS 00/3095 and SENY Fundatio Research Grant CI 2005-0308007, Fundacion Marques de Valdecilla A/02/07. No pharmaceutical company supplied financial support.
ID: 541006

SELF-RATING OF PHARMACOLOGICAL TREATMENT (SIDE-)EFFECTS IN SCHIZOPHRENIA: A COMPARISON OF INSTRUMENTS

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Introduction: To support clinical practice as well as clinical research, self-rating scales have been developed to evaluate desired as well as undesired effects of antipsychotic treatment. Psychometric properties and other characteristics of four identified self-rating scales including their relationship with subjective quality of life will be compared. Method: Four scales of self-report of treatment effects of antipsychotics were identified through a MEDLINE and cross-references search: the Drug Attitude Inventory (DAI-10), the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS), the Subjective Wellbeing to Neuroleptics (SWN) and the Subjects' Reaction to Antipsychotics questionnaire (SRA). All scales were filled out by 320 patients with schizophrenia treated with antipsychotics together with a subjective quality of life instrument, the WHO-QoL BREF. Results: The DAI-10 contains ten items covering many different aspects of treatment with antipsychotics, such as compliance and attitudes towards neuroleptic treatment. The scope of the LUNSERS is measuring undesired effects of antipsychotics, while the SRA incorporates desired as well as undesired treatment effects. The SWN con-

sists mainly of items on aspects of wellbeing without a direct link to antipsychotics. The instruments show an acceptable internal reliability (Cronbach's alpha's varying between .64–93) with the exception of the DAI-10 (Cronbach's alpha .52), probably due to the mix of experiences. The scales did not strongly correlate (r between .11 and .51) with each other except for the SRA-subscale undesired experiences and the LUNSERS ($r = .68$, $P < .01$). Correlations with quality of life were statistically significant, with the SWN showing the strongest one ($r = .78$, $P < .01$). Conclusion: The lack of internal reliability and the conceptual mixture of items restrict the use of the DAI-10. Its strength lies in measuring compliance and attitudes towards neuroleptic treatment. The LUNSERS maybe very useful to screen extensively side-effects of neuroleptic treatment, with the caveat of overestimation of the frequency of these effects. The SWN is to be recommended as an alternative for a QoL-instrument in patients (not only with schizophrenia) using antipsychotic medication. The SRA is recommended if a clinician or researcher is specifically interested in undesired as well as desired responses attributed to the antipsychotic medication.
ID: 538965

PREDICTORS OF MORTALITY IN PATIENTS WITH SERIOUS MENTAL ILLNESS AND CO-MORBID DIABETES

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Objective: Persons with serious mental illness (SMI) have a higher rate of type 2 diabetes and a higher mortality rate than the general population. The purpose of this study was to assess baseline demographic and health-related factors in the prediction of all-cause mortality over a seven-year follow-up period in a group of diabetes patients with serious mental illness and a group of diabetes patients without serious mental illness. Methods: From 1999 to 2002, 300 patients with type 2 diabetes were recruited from community mental health centers in the greater Baltimore region and nearby primary care clinics. Of these, 100 had a diagnosis of schizophrenia, 101 a diagnosis of major mood disorder, and 99 had no identified mental illness. Patient deaths over an average seven-year period after baseline assessment were identified using the Social Security Administration's Death Master File via the website www.rootsweb.ancestry.com. Bivariate associations between predictors and mortality were assessed in the serious mental illness group and compared to those in the group without serious mental illness. This was followed-up with multivariable logistic regression. Results: A total of 21 % of persons in each group died in the follow-up period. Median age of death was 60. Age, duration of diabetes, and hospitalization for a diabetes-related condition in the 6 months prior to baseline were all predictive of mortality. In the SMI group (but not in the Non-SMI group) decedents were more likely to have been smokers than non-decedents (69% versus 49%, $P = .021$) and in the multivariable model, odds of mortality was over two times greater among smokers than non-smokers (adjusted odds ratio (AOR) = 2.3, 95% CI: [0.96, 5.3]). In the Non-SMI group those who were prescribed insulin had over a four-fold greater odds of mortality (AOR = 4.1, 95% CI: [1.3, 13.1]), however in the SMI group there was no evidence that being prescribed insulin served as a diabetes severity marker (AOR = 0.59, 95% CI: [0.21, 1.6]). Conclusions: Diabetes may contribute to the excess mortality of persons with serious mental illness. To better address

this problem, clinicians caring for persons with serious mental illness need to be especially vigilant regarding mortality risk when the diabetes illness of their patients requires hospitalization and as their patients age. Furthermore, it is important that smoking cessation be aggressively promoted among persons with SMI.
ID: 550828

SUBJECTIVE EXPERIENCE MEASUREMENT IN PATIENTS WITH SCHIZOPHRENIA/SCHIZO-AFFECTIVE DISORDER USING THE NOVEL ANTIPSYCHOTIC MEDICATION EXPERIENCE SCALE (NAMES)

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Rating scales are effective tools to assess therapeutic efficacy and patient subjective experience. Patients suffering from Schizophrenia benefit from treatment with psychotropic medications to reduce symptomatology, to reduce the frequency of hospitalizations and to provide for better community reintegration. However, medication nonadherence is problematic for the effective treatment of these patients, and patients' negative subjective responses to medications correlate with treatment noncompliance. Therefore, assessment of the level of patient subjective experience of a medication is an important correlate of treatment efficacy. Existing rating scales for psychotropics in Schizophrenia (eg, Drug Attitude Inventory (DAI) 30, AMDP-5) were developed to assess patient report of side effects prior to the advent of atypicals. However, these scales may now be less useful given the application of atypicals which have different side effect profiles. We report here a preliminary study of the validity and reliability of the Novel Antipsychotic Medication Experience Scale (NAMES), a new patient self-rating questionnaire. The NAMES, DAI 30, and AMDP-5 questionnaires were administered to patients meeting inclusion criteria: 1) patients with schizophrenia/schizoaffective disorder, between 18 and 65 years old; 2) at least 1 month of monotherapy with clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone or ziprasidone; 3) the absence of psychiatric co-morbidity. 101 outpatients completed the study. The results from the NAMES questionnaire are correlated with results from the DAI 30 and AMDP-5, with Pearson Correlation Coefficients of 0.89, and .83. The NAMES Standardized Cronbach Coefficient Alpha (SCCA) was 0.81, while the DAI 30 SCCA was 0.46, and the AMDP-5 was .32. Subjective measures assessed by the NAMES, show that the scale is both reliable and valid. Based upon a measure of internal consistency, the NAMES has a higher average inter-item correlation than the DAI 30 or the AMDP-5. Further analysis may indicate that NAMES is a better measure of patient subjective experience of treatment with atypicals than other rating scales because of administration protocol.
ID: 551878

PRE-DIABETES AND DIABETES ASSESSMENT IN VETERANS WITH SCHIZOPHRENIA

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In February 2004, the American Diabetes Association and American Psychiatric Association issued a Consensus statement on metabolic sequelae of antipsychotic agents, summarizing research over the previous ten years that documented growing awareness of this connection. The Pre-diabetes in Veterans with Schizophrenia study assessed monitoring of pre-diabetes and undiagnosed diabetes just prior to the Consensus statement, in a national sample of 39 825 Veterans Health Administration outpatients with schizophrenia, aged 50 or older, with no recorded diagnosis of diabetes and no use of hypoglycemic medications (non-diabetic at baseline). Diagnosis of schizophrenia was defined by one inpatient or two or more outpatient diagnoses over the one-year study period. The retrospective study used fiscal year 2002 data. Blood glucose tests with same-day low-density lipoprotein (LDL) tests were used as a proxy for fasting glucose, because patients are required to be fasting for the LDL test. Test time of day was not available, nor was verification of fasting status. Hemoglobin A1c tests were also extracted, as some authors advocate their use in monitoring pre-diabetes. Tests were categorized: 100–125 mg/dL (pre-diabetes fasting glucose), $> = 126$ (diabetes-indicative fasting glucose), 5.8%–6.4% (pre-diabetes A1c), $> = 6.5\%$ (diabetes-indicative A1c). Multivariable regressions modeled receipt of a fasting glucose test, receipt of an A1c test, test results consistent with pre-diabetes, and test results consistent with diabetes. Patient descriptives included average age of 60 years (SD 9.5), 60% white, 42% unmarried, with comorbid hypertension (40%), dyslipidemia (25%), and depressive disorders (22%). Approximately 27% of patients had fasting glucose tests, of whom 42% were pre-diabetic; 9% had A1c tests, of whom 28% were pre-diabetic per study definition. Test rates among patients on atypical antipsychotics were slightly higher: 29% fasting glucose, 10% A1c, but within those groups, the proportions testing pre-diabetic were identical (42% and 28%, respectively). Both glucose and A1c testing were associated with hypertension, dyslipidemia, and atypical antipsychotics. Among tested patients, pre-diabetes was associated with cardiovascular disease, older age, and being married. Dysglycemia was prevalent among schizophrenia patients, yet glucose monitoring was uncommon. Overall, few schizophrenia patients were being adequately monitored for dysglycemia.
ID: 551835

AUTONOMIC SYSTEM DYSREGULATION IN SCHIZOPHRENIA AND BIPOLAR MANIA

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Heart rate variability (HRV) reflects the interchange of the parasympathetic and sympathetic autonomic nervous system (ANS). Severe psychiatric disorders such as schizophrenia have been associated with dysfunction of the ANS, including alterations in cardiac function and HRV. Recent reports suggest that ANS dysregulation among psychiatric patients may be related to responses to physical and psychological stressors. Studies consistently demonstrate a correlation between psychosis and heightened anxiety states even when the stressful condition is relatively minor. Still, it is unclear whether this association is due to disease-related autonomic nervous system changes or a side effect of antipsychotic medication. In the present study we examined the autonomic response of hospitalized individuals with schizophrenia and bipolar-mania when exposed to a novel environment. The patients were compared to healthy comparison subjects. Subjects were fitted with a vest that contained an ambulatory monitoring device that allowed us to obtain continuous recordings of cardiac, respiratory, and motor activity. Both schizophrenia and bipolar-manic subjects exhibited increased heart rate, increased respiration, and decreased HRV

during a 15 minute exposure to a novel but benign environment. Spectral analysis of cardiac data revealed that both groups showed an increase in the Low Frequency/High Frequency ratio of the HRV signal compared to comparison subjects, indicating increased sympathetic nervous system activity. Group differences in autonomic function remained significant even after excluding variance due to locomotion, indicating that changes in cardiac activity and respiration were independent of differences in physical activity. Importantly, ANS function was not significantly affected by medications. These findings indicate that individuals with both schizophrenia and bipolar-mania exhibit an increased autonomic response to a novel environment. The data suggest that both of these disorders may be characterized by a common deficit in the ability to adapt to challenges in the environment, which may have a direct impact on cognitive, affective, and behavioral function.
ID: 551807

SUBSTANCE ABUSE IS ASSOCIATED WITH INCREASED EXTRAPYRAMIDAL SYMPTOMS IN SCHIZOPHRENIA: A META-ANALYSIS

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Background: Psychoactive substances (PAS) may interact with antipsychotics in the development of extrapyramidal symptoms (EPS) in schizophrenia, since PAS exert impacts on the basal ganglia. Clinical data have been gathered about the effects of PAS on EPS in schizophrenia, producing inconsistent results. This meta-analysis sought to determine whether PAS enhance EPS in schizophrenia patients. Methods: A search of the literature using computerized engines was undertaken. Studies were retained in the analysis if: (i) they included schizophrenia patients with and without substance abuse; and (ii) they comprised a measure of EPS using valid instruments. Results: Fifteen studies were available identified, involving 3373 patients. The composite analysis revealed a small and positive effect size ($g = 0.246$), suggesting increased EPS in substance-abusing patients. Dual-diagnosis patients were more frequently males than single diagnosis patients. Thus, we performed a sub-analysis of studies with no confounders (age, sex, negative symptoms, etc.). The pooling of these 10 studies produced a moderate and positive effect size ($g = 0.405$). Discussion: Our results show that PAS negatively impact on EPS in schizophrenia, especially when potential confounding factors are controlled. As such, these results have implications for the prevention of EPS in schizophrenia and for the design of future studies on the topic.
ID: 551548

INFLAMMATORY MARKERS IN SCHIZOPHRENIA: COMPARING ANTIPSYCHOTIC EFFECTS IN THE CATIE SCHIZOPHRENIA TRIAL

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Background: C-reactive protein (CRP), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin are systemic inflammatory markers (IM) that positively correlate with cardiovascular (CV) risk. Despite the known CV effects of atypical antipsychotics, there is limited prospective data on IM changes during treatment. Methods: IM outcomes were compared between antipsychotic treatment groups in the CATIE Schizophrenia Trial phase 1 using subjects with laboratory assessments at baseline and 3 months ($n = 789$). Results: There were significant treatment differences in CRP, E-selectin and ICAM-1 at 3 months, with an impact of baseline values on outcome. In overall comparisons, olanzapine or quetiapine arms had the highest median levels for each IM. In those with low baseline CV risk by CRP (< 1 mg/L), olanzapine was significantly different than perphenazine ($P < .001$) and risperidone ($P = .001$) after baseline adjustment. Among those with high baseline E-selectin values, olanzapine was significantly different than perphenazine ($P = .005$) and ziprasidone ($P = .002$), as was quetiapine vs. ziprasidone ($P = .004$). Olanzapine and quetiapine also had higher 3-month ICAM-1 levels than perphenazine in subjects with baseline ICAM-1 above the median, but the differences were not statistically significant after controlling for multiple comparisons ($P = .010$ for both). The 18-month repeated measures CRP analysis confirmed the significantly higher values for olanzapine in those with low baseline CRP. Conclusions: This analysis provides further evidence for differential antipsychotic metabolic liabilities as measured by changes in systemic inflammation. CRP may emerge as a useful target for CV risk outcomes in schizophrenia patients.
ID: 551428

MORPHOLOGICAL, CELLULAR AND MOLECULAR CORRELATES OF ANTIPSYCHOTIC MEDICATION EXPOSURE IN PRIMATE NEOCORTEX

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Schizophrenia is associated with a number of morphological, cellular and molecular abnormalities in the cerebral cortex. Knowledge of the extent to which prolonged treatment with antipsychotic medications contributes to these disturbances is essential both for understanding the disease process of schizophrenia and for gaining insight into the mechanisms underlying the therapeutic and adverse effects of antipsychotic medications. To address these issues, we exposed experimentally-naïve, young adult, male macaque monkeys to twice-daily oral doses of haloperidol, olanzepine or sham treatment for approximately two years. At steady state, trough plasma levels of haloperidol and olanzapine were in the range reported to be therapeutic in schizophrenia. Both the haloperidol and olanzapine-exposed groups had significantly smaller total brain weight and volume. At the cellular level, we found lower glial cell number and higher neuron density in the cortex, without a difference in total neuron number, in the antipsychotic-exposed monkeys; follow-up immunocytochemical studies revealed a significant 21% lower astrocyte number with a non-significant 13% lower oligodendrocyte number in the antipsychotic-exposed monkeys. Similar effects were seen in both the haloperidol and olanzapine groups. In contrast, none of the examined GABA-related transcripts reported to be altered in schizophrenia differed across the three groups of monkeys. Although species differences and other factors need to be considered, these findings suggest that certain morphological and cellular abnormalities identified in schizophrenia might be attributable to chronic exposure to antipsychotic medications.
ID: 551304

SOMNOLENCE AND SEDATION IN ADOLESCENT PATIENTS WITH SCHIZOPHRENIA TREATED WITH ARIPIPRAZOLE IN AN ACUTE STUDY WITH LONG TERM FOLLOW-UP

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Background: Somnolence and sedation are relatively common side effects of antipsychotics to which adolescents may be more sensitive. The purpose of this study was to evaluate characteristics of somnolence and sedation in adolescents with schizophrenia treated with aripiprazole. Methods: Data are derived from a 6-week, double-blind, placebo controlled, randomized clinical trial comparing two fixed doses of aripiprazole (10 and 30mg, $N = 302$) and a 26-week, open-label, follow-up study with flexible dosing (5-30mg, $N = 239$). Somnolence and sedation were evaluated with respect to time of onset, severity, dose-response, dose-reduction, discontinuation rates, age, gender, and ethnicity. Results: In both the short- (ST) and long-term (LT) studies, almost all reported cases of somnolence and sedation were classified as mild (ST: $n = 25$, 12%; LT: $n = 24$, 10%) or moderate (ST: $n = 8$, 4%; LT: $n = 9$, 4%), and only one patient was discontinued from the study due to somnolence. Most events (76%) started early (within 2 and 4 weeks) and had resolved within the study period. A possible dose-dependence relationship was seen, with more events reported at the 30 mg dose. In the short-term trial, Blacks reported substantially higher rates (35% in the 10 mg arm and 55% in the 30 mg arm) than the overall population (12% in the 10 mg arm and 22% in the 30 mg arm). No differences were noted in incidence stratified by age or gender. In the long-term open-label study, the overall incidence of somnolence and sedation was low (14%) and was the similar between groups switched from aripiprazole 10 mg. 30 mg or placebo. When sedation or somnolence occurred, most investigators took no action or reduced the dose rather than discontinuing study drug. Conclusions: Somnolence and sedation in adolescents with schizophrenia treated with aripiprazole, if experienced, is typically mild, transient, and manageable. In general, higher doses lead to an increased incidence in younger patients, and ethnicity may be a modifying factor and should be evaluated further.
ID: 551235

PROSPECTIVE LONGITUDINAL EVALUATION OF SERUM CREATINE KINASE LEVELS AND NEURO-MUSCULAR DYSFUNCTION IN SCHIZOPHRENIA PATIENTS: NEW RESULTS OF FOLLOW-UP STUDY

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Background: There are multiple causes of hyper-CKemia (HCK)—the elevation of serum creatine kinase (SCK) activity above upper limits. These increases may be related to underlying trait-like biological abnormalities in psychosis, phasic episodes related biological abnormalities, or the effect of drug treatment. Previously we found, that among HCKemic patients, the majority was treated with atypical antipsychotic drug (AAPD) and some of them had neuromuscular complaints. The purposes of this study were to follow-up prospectively and to estimate the incidence and severity of probable neuromuscular dysfunction in HCKemic schizophrenia and schizoaffective patients. Methods: For this study, we selected 39 HCK-emic patients suffering from schizophrenia or schizoaffective disorder. Eleven patients, treated either with clozapine, olanzapine or perphenazine had persistent/recurrent hyper-CKemia (PHCK). 25 patients had occasional HCKemia (OHCK). Blood samples for CK determinations were collected regularly up to three years of follow-up. Each year, all patients were assessed neurologically for possible muscular and peripheral nervous systems involvement. Results: During the study, SCK activity in PHCK patients was found to be persistently elevated: 400 ± 200 (mean $\pm$ SD) in range 250-950 IU/L. Five of these patients had complaints of muscular weakness, early fatigue on exercise, some muscular pains and cramps. In two of them clinical assessment revealed mild general muscular weakness, especially in the proximal parts of the limbs. This pattern was diagnosed as probable mild myopathy. In majority of OHCK patients SCK activity was reduced to the normal levels range. Some patients remained with occasional HCK without any kind of neuromuscular pathology. Conclusions: The results of this first long-term large-scale prospective comparative study indicate that among HCK-emic schizophrenia and schizoaffective patients, only PHCK pattern may consider to be a biochemical marker of the neuromuscular dysfunction. Meanwhile, OHCK is likely to be a benign phenomenon, has no clinical manifestations, and does not need to be followed-up routinely. Further investigation of neuromuscular dysfunction, its mechanisms, pathophysiological significance and possible pharmacogenetics associations in schizophrenia patients is certainly indicated. The relationship of HCK to mutations in neuregulin, dysbindin or reelin—genes related both to schizophrenia and to muscle, is also of interest.
ID: 551193

METABOLIC SIDE EFFECTS OF COMBINED ANTIPSYCHOTIC TREATMENT: RESULTS FROM A DOUBLE BLIND TRIAL OF ADJUNCTIVE RISPERIDONE IN CLOZAPINE TREATED PEOPLE WITH TREATMENT-RESISTANT SCHIZOPHRENIA

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Incomplete response to clozapine in people with treatment-resistant schizophrenia poses a significant clinical challenge. The use of a second antipsychotic has become widespread despite little evidence to support its efficacy or safety. This analysis examines the safety of combined risperidone and clozapine with respect to metabolic and prolactin-related side effects, during a 16-week, placebo-controlled, randomized trial of adjunctive risperidone (4 mg/day) in clozapine partial responders. Eligible subjects were those with DSM-IV schizophrenia or schizoaffective disorder who continued to manifest moderate illness severity (18-item BPRS total $\geq$ 45 and CGI Severity score $\geq$ 4) and persistent psychosis (four BPRS psychosis item total $\geq$ 8, with one of these items $\geq$ 4)despite adequate prior clozapine treatment. Weight and blood pressure were measured every two weeks and laboratory measures (fasting glucose, cholesterol, triglycerides, and prolactin) were obtained at baseline, week 4, and endpoint. Eighty-six subjects signed consent; 71 entered the 4-week evaluation phase; 65 were

randomized and entered the double-blind treatment phase (risperidone: 30; placebo: 35). The majority of subjects were male (risperidone group: 63.3%; placebo group: 71.4%) and Caucasian (risperidone group: 76.7%; placebo group: 62.9%). The risperidone group was significantly older (48.3 (7.2) versus 43.6 (9.6)). Fifty-two subjects (80%) completed all 16 weeks of treatment (risperidone: 25/placebo: 27). Adjunctive risperidone was not associated with weight gain or blood pressure changes compared to placebo. The risperidone group had a significantly greater increase in prolactin levels compared to placebo ($P < .001$). The presentation will include complete data on other metabolic parameters. In summary, the addition of risperidone to clozapine was associated with no significant change in weight or metabolic side effects relative to clozapine treatment alone, although prolactin levels were significantly elevated in the group receiving adjunctive risperidone. Supported by R01 MH45074 the Stanley Medical Research Institute and P30 MH068580. Janssen Pharmaceuticals provided study medication. ID: 551129

EFFECTS OF ARIPIPRAZOLE ON METABOLIC MEASURES IN PEDIATRIC AND ADOLESCENT PATIENTS: A POOLED ANALYSIS OF PLACEBO-CONTROLLED TRIALS

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The potential metabolic side effects of antipsychotics in children and adolescents are of particular concern for not only clinicians, but also patients and their caregivers in situations where an atypical agent may be beneficial. In the present analysis, the metabolic effects of aripiprazole in pediatric and adolescent patients from the aripiprazole worldwide development program were evaluated. Metabolic measures in aripiprazole- and placebo-exposed patients were compared with ANCOVA using LOCF. Aripiprazole produced no significant mean change (mg/dL) versus placebo in fasting plasma glucose (aripiprazole: +0.3, placebo: −1.2; $P = .38$), total cholesterol (aripiprazole: −5.8, placebo: −8.5; $P = .22$), or fasting triglycerides (aripiprazole: −2.5, placebo: -0.9, $P = .79$), whilst the change in body weight was significant (aripiprazole: +1.6 kg, $n = 381$, placebo: +0.3 kg, $n = 187$, $P < .001$). The results inform evidence-based clinical decisions, and reinforce the need for realistic management of weight gain and metabolic monitoring in all children/adolescents being treated with antipsychotic medications. ID: 551116

BONE MINERAL DENSITY IN PATIENTS WITH PSYCHOSIS AND NON-PSYCHOTIC SIBLINGS

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Background: Increased rates of altered bone mineral density (BMD), like osteopenia and osteoporosis, have been reported in schizoprenia, but the underlying mechanism are not yet fully elucidated. Reduced BMD, as a biological marker of diminished cumulative estrogen exposure, has been suggested to be a marker of increased psychosis risk. In the present family study we tested whether decreased BMD is also an indicator of genetic liability for the disorder. Methods: As part of an observational longitudinal study, BMD of the spine and femur was measured with dual-energy-X-ray-absorptiometry (DXA) in a subsample of 42 patients with schizophrenia, 54 non-psychotic siblings of these patients and 39 controls. Preliminary, multilevel random regression, analyses were performed to assess group differences in bone mineral density of the lumbar spine and femur (baseline measures). Results: In female patients, bone mineral density was significantly lower than in controls, in those not using contraceptives. This effect was found in both the lumbar spine ($\beta = -0.74$, $P < .024$) and femur ($\beta = -0.66$, $P < .05$). Female siblings also showed (trends of) decreased bone mineral density in the lumbar spine and femur region compared to controls. In male patients and siblings, bone mineral density was not significantly altered compared to controls. Conclusions: Both female patients and their non-psychotic female siblings may have decreased bone mineral density. This data support not only that reduced BMD, as a biological marker of diminished cumulative estrogen exposure, may be a marker of increased psychosis risk, but also that reduced BMD may be a marker of the genetic liability for schizophrenia. ID: 551025

A GUIDELINE FOR WEIGHT GAIN PREVENTION — A PILOT STUDY

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Introduction: Antipsychotic induced weight gain is a fair ordinary and well known side effect. Cardiovascular disease, glucose intolerance, and type 2 Diabetes Mellitus might be the outcome of this side effect. The weight gain is more pronounced in the first 4 months of treatment and the psychiatrist should actively help the patient to avoid it. During the psychiatric visit clinicians have some difficulties on evaluating and orienting these aspects, focusing one's attention into psychopathologic aspects. Our aim was to develop a quick supportive material and a guideline to: 1) optimize the psychiatric visit focusing on detecting, preventing and intervening to avoid medication induced weight gain; 2) to structure the clinician practice suggesting four levels of intervention according to the severity of problem: dieting, physical activities, binge eating control and pharmacologic treatment. Methods: Two different materials were developed; first a practical informative booklet for the patients, with healthy dieting and physical activities recommendations. Second, a practical guideline suggesting the physician a few questions about weight gain and appetite increase is used to establish a dialog with the patient and promote early detection of eating problems. The guideline provides 4 modules of intervention empowering the physician to promote dieting and physical activity habits changes, actively treating binge eating and increased appetite whenever necessary. Results: In our pilot study 5 physicians applied our methods to 10 schizophrenic outpatients, 9 patients finished the four months period. Mean age: 35,8, 80% were male, mean weight: 97,7 Kg, and mean BMI: 30,9 Kg/m2 at the beginning of the study; mean weight 95,2 Kg, and mean BMI 30,2 Kg/m2 at the end. One patient was prescribed with topiramate, due to obesity, one with metformin, due to glucose intolerance. Discussion: This pilot study showed that the designed material was useful in clinical practice taking less than 5 minutes. It helped the clinician to diagnose weight changes and empowered clinicians to actively implement measures to avoid this trend. Our future goal is testing this material for the weight gain prevention in larger samples at the beginning of antipsychotics use. If the major weight gain occurs during the first 4 months, we believe this is the best period for weight gain prevention with life style modifications, and the introduction of medications to treat glucose intolerance or obesity.

ID: 550873

THE ACUTE EFFECTS OF ATYPICAL ANTIPSYCHOTIC DRUGS ON GLUCOSE SENSITIVITY IN AN ANIMAL MODEL

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The atypical antipsychotics are currently the drugs of choice for psychiatric conditions including schizophrenia spectrum disorders and bipolar disorder. However, recent studies have shown that these compounds contribute as risk factors for metabolic syndrome. Untoward effects induced by these drugs, such as weight gain, hyperlipidemia, glucose intolerance and insulin sensitivity occur within patients and rodents both acutely and on a chronic time scale. The objective of this study is to examine these metabolic abnormalities through the use of a rodent model. To assess the effects of atypical drugs on glucose sensitivity, adult female Sprague-Dawley rats were treated with either a low or high dose of clozapine (2, 20 mg/kg) or risperidone (0.5, 2.5 mg/kg) and compared to vehicle treated animals. Separate cohorts of rats were subjected to an intraperitoneal glucose tolerance test (IGTT) at 1, 3 and 6 hours after antipsychotic drug treatment. For the IGTT, blood samples were drawn every 15 min for a two hour period. Blood samples were also stored for future measurement of drug and metabolite levels by HPLC-UVD. The statistical analysis indicated that there was an effect of both drug dose and time since treatment on glucose sensitivity, as measured by the IGTT. For both clozapine and risperidone, the high dose of drug caused greater glucose resistance than the low dose and vehicle treated animals, while the low dose drug caused greater insulin resistance than the vehicle treated animals. This effect was greatest one hour after drug administration and diminished over time. These data show that, at least in an animal model, both an atypical drug with a well known metabolic side-effect profile (clozapine) and a drug with more modest metabolic side-effects (risperidone) can cause acute glucose resistance, and these effects are dose-dependent. Ongoing studies will compare these findings with additional typical and atypical antipsychotics after both acute and chronic treatment.
ID: 550865

PERSISTENT ANTIPSYCHOTIC POLYPHARMACY AND EXCESSIVE DOSING IN THE COMMUNITY PSYCHIATRIC TREATMENT SETTING

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Introduction: Clinical practice guidelines have been developed to assist clinicians on the practical aspects of treating patients with schizophrenia, including treatment resistant patients. Consistent among these references is the recommendation that treatment resistant patients be trialed with clozapine monotherapy before using strategies with limited or no evidence, such as concurrent use of two antipsychotics (ie, antipsychotic polypharmacy). Antipsychotic polypharmacy practice may increase the risk of adverse events and its benefits on mental health outcome remain largely unsubstantiated. Methods: We investigated persistent antipsychotic poly-

pharmacy and excessive dosing in patients originally recruited for a study that examined the relationship of tobacco use in the context of severe and persistent mental illness. This study targeted adults who were receiving services from a community mental health team within the Vancouver Coastal Health Authority. BC PharmaNet (a province-wide network that that links all British Columbian pharmacies to a central set of data systems) was used to screen for eligible patients for this study and obtain data about prescriptions filled over at least a 90 day period. Results: Of the 514 patients recruited in the initial study, 397 patients met the inclusion criteria; 162 diagnosed with schizophrenia, 81 with schizoaffective disorder, 48 with major depression, 77 with bipolar disorder, and 29 with psychosis not otherwise specified. The highest incidence of persistent antipsychotic polypharmacy was found in individuals diagnosed with schizoaffective disorder (32.1%), followed by schizophrenia (30.9%), psychosis NOS (17.2%), bipolar disorder (15.6%) and major depression (14.6%). In the case of the atypical antipsychotics, quetiapine was the agent associated with the greatest proportion of patients treated with persistent antipsychotic polypharmacy (46.1%) followed by risperidone (37.1%), olanzapine (32.7%), and then clozapine (30.3%). Differences were noted between subjects treated by monotherapy versus polypharmacy on concurrent treatment with alternate medications. Discussion: The primary finding of this study was that 25% of our outpatient sample was treated with persistent antipsychotic polypharmacy. The relationship of polypharmacy to excessive dosing remains an important issue with respect to risk for adverse events, clinical efficacy and economic concerns.
ID: 550830

DISCORDANT CARDIOMETABOLIC RISK OF ATYPICAL ANTIPSYCHOTICS DESPITE SHARED WORSENING OF BODY COMPOSITION DURING FIRST-TIME USE IN CHILDREN AND ADOLESCENTS

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Background: Cardiometabolic effects of antipsychotics are problematic in patients with prolonged antipsychotic exposure, but have been insufficiently studied in antipsychotic-naïve and pediatric patients. Methods: Youths ($N = 272$), age 4–19 (mean: 13.9 ± 3.6) years, prescribed atypical antipsychotics for the first time, underwent assessments of weight, fasting glucose, lipids and homeostatic model of insulin resistance (HOMA-IR) at baseline, week 4, 8 and 12. Refusing/non-adherent patients, determined by interview and absent antipsychotic blood levels, served as controls. Results: After 10.3 ± 3.1 weeks, weight increased by 9.2 ± 0.6lbs $= 7.9 \pm 9.4\%$ with aripiprazole ($N = 41$), 18.0 ± 1.3lbs $= 15.5 \pm 17.9\%$ with olanzapine ($N = 45$), 12.3 ± 1.2lbs $= 9.9 \pm 12.0\%$ with quetiapine ($N = 36$), and 10.9 ± 0.6lbs $= 10.0 \pm 11.1\%$ with risperidone ($N = 135$). Controls ($N = 15$) lost weight minimally (-1.5 ± 1.6lbs $= -0.2 \pm 1.9\%$). Weight gain $>7\%/>14\%$ occurred in 58.4%/17.1% of patients on aripiprazole, 84.4%/51.1% on olanzapine, 55.6%/30.6% on quetiapine, 64.4%/25.1% on risperidone, and 0% of controls. All metabolic parameters, except HDL-cholesterol, increased significantly with olanzapine. With quetiapine and risperidone, triglycerides and triglyceride/HDL-cholesterol ratio increased significantly. With quetiapine, non-HDL cholesterol also increased significantly. Metabolic changes were non-significant with aripiprazole and in controls. New-onset dyslipidemia developed in 7.3%, 28.9%, 8.8%, and 19.4% of youths on aripiprazole, olanzapine, quetiapine and risperidone, compared to 6.7% of controls ($P = .033$). In contrast to weight gain and dyslipidemia,

acquired insulin resistance (HOMA-IR>4.39: 2.9%–17.8%) and metabolic syndrome (0%–6.5%) were relatively rare. Conclusions: Short-term, first-time atypical antipsychotic use in pediatric patients produced significant weight and triglyceride increases. Olanzapine had the most pervasive, aripiprazole had the most circumscript cardiometabolic liability. These results require careful clinical attention. Findings were more pronounced than previously reported, highlighting the need to assess antipsychotic-naïve samples.
ID: 554130

WEIGHT MAINTENANCE BY BOOSTER BEHAVIORAL SESSIONS IN SCHIZOPHRENIA SUBJECTS WHO LOST WEIGHT IN A BEHAVIORAL PROGRAM

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Introduction: Several controlled clinical trials, involving patients with schizophrenia, have established that almost half of the participants can benefit by losing weight. However, there have been no long term follow up studies, so far, on whether the loss is maintained. We report the preliminary two-year follow up results on subjects who participated in an NIMH-funded clinical trial of weight reduction in schizophrenia. The study is ongoing and hence these data are from the 23 subjects who have reached the two-year follow up time point. Methods: Subjects in this analysis are those who participated in a behavioral weight loss intervention and who succeeded in losing at least 3% of their initial weight. In order to evaluate the effectiveness of every other week individual booster sessions, subjects we re-randomized to receive individual booster sessions every other week for two years or to usual care with follow up weights gathered yearly. Results: There was some weight regain in both groups, but considerably less in the booster group, as compared to the controls. The subjects in the booster group regained 3.1 lb in the first year and an additional 1.7 lb in the second year of follow up. However, even after two years their mean weight was still 7 pounds below their weight at entry into the behavioral treatment. Controls on the other hand regained an average of 9 lb in the first year of follow up, already exceeding their average entry weight and then regained an additional 4.9 lb pounds in the second year of follow up. Thus, controls were at 5.8 pounds above their weight before entering treatment while subjects in boosters were 7 pounds below their weight at entry into the study. Conclusions: From these preliminary data, we conclude that twice monthly booster sessions appear to be effective in preventing weight regain, following intentional weight loss, for as long as two years following treatment. It remains to be investigated whether less active intervention, such as monthly boosters would be as effective, and whether more active intervention, such as weekly contact would be even more effective. These results reinforce the proposition that obesity is a chronic disorder and requires on-going maintenance after successful weight loss.

Table. Weight Change (lb): Initial and Over Two Year-Followup

Randomized To	Mean Study Entry Weight	Mean Weight at Start of Followup	Mean Weight at 1 year	Mean Weight at 2 years
Booster Treatments	228.4	217.6	220.7	222.4
Usual Care	237.7	229.1	238.1	243.0

ID: 554356

4. 4. Electrophysiology

THE RELATIONSHIP BETWEEN GAMMA BAND SYNCHRONY AND P300 BREAKS DOWN IN SCHIZOPHRENIA

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Auditory P300 amplitude reduction in schizophrenia is canonical and may be explained by poor synchronization or reduced power of the underlying neural activity. We asked if patients have reduced synchrony and power, and whether together with P300 amplitude, they make unique or overlapping contributions to the discrimination between patients and controls. We also asked whether people who have large P300s have higher power and greater synchrony of neural activity, and if the relationships between P300 and power and synchrony are different in patients and healthy controls. Methods. We recorded EEG data from 22 controls and 21 patients with schizophrenia (DSM-IV) while they performed an auditory target ($P = .10$) detection task. We used wavelet analyses to estimate total power and synchrony of delta, theta, alpha, beta, and gamma activity in a 50ms window around the peak of the P300 to the target from the single trial data. We measured P300 amplitude from the average of the single trials, in a 50ms window around its peak. Results and Conclusions. P300 amplitude and delta and theta synchrony were reduced in patients; delta power and synchrony better distinguished between groups than P300 amplitude. In spite of the strong correlation between P300 amplitude and gamma synchrony in controls ($r = .79$), and in spite of P300 amplitude reduction in the patients, gamma synchrony was not reduced in the patients. Whatever is contributing to P300 amplitude reduction in the patients (eg, gray matter volume deficits, poor clinical state, or fluctuations in attention [Ford, 1999]) is not significantly affecting gamma synchrony. The breakdown of a lawful relationship among neurobiological or neuropsychological variables in schizophrenia patients is not uncommon in the field of biological psychiatry. It suggests that the variables are affected by independent factors and the relationships between them are attenuated by additional pathophysiological processes.
ID: 540424

VISUAL ATTENTIONAL CAPTURE IN SCHIZOPHRENIA: AN EVENT-RELATED POTENTIAL STUDY

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Selection of relevant information is disrupted by schizophrenia. In the visual modality, selection capacities can be studied by resistance to interferences: patients' impairment is characterized by an abnormal persistence of attentional capture effect when control subjects manage to ignore the same irrelevant stimuli. We propose here to record event-related potentials (ERP) during a visual attentional capture paradigm. We hypothesized that electrophysiological indicator of capture will persist for patients. We recruited 10 patients with schizophrenia (DSM IV-TR criteria) and 10 healthy controls. Subjects were instructed to detect as quickly as possible the position of a black square which appears up or down on a screen. During the whole process two red circles were presented on both lateral side of the screen. Capture was induced by lateral translation of one of the circles. This translation occurred following randomized order for 48 of the 96 trials.

Behavioural effect was measured by difference of reaction time between the two conditions: non-capture (square appearance) VS capture (square appearance and circle translation). Two sets of presentations were proposed. During the first one, the translations occurred bilaterally (50/50, randomized order). During the second one all translations occurred unilaterally for the right circle. ERP were recorded with 70 electrodes montage. After pre-processing and averaging, we subtracted capture and non-capture conditions. Relevant time periods and regions were defined when this subtraction was significantly different from zero. Behavioural results are similar to previous studies: both patients and controls are "captured" by bilateral translation. For unilateral translation, patients stay captured. On contrary, controls recover non-capture reaction time. Two time windows are selected by electrical capture effect (maximal at frontal area). For bilateral capture, no difference is detected. For unilateral, the later window (250 to 350 msec.) differs between the two groups. Subtracted ERP for patients keep showing capture effect for frontal region and are significantly higher than for controls. Our results suggest that selectivity impairment for patients could be linked to incapacity to ignore irrelevant stimulus. Patients persist to engage important frontal activity to process irrelevant data. This impairment could constitute a key to explore both fundamental perceptual deficits and alteration of daily functioning.
ID: 550596

MIRROR NEURON FUNCTION IN A FIRST EPISODE OF PSYCHOSIS POPULATION

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Schizophrenia is a chronic debilitating illness characterized by the patient's inability to integrate into the social milieu, although the neural basis of this impairment is not well understood. The recent discovery of mirror-neurons has led to conjecture that the inability of patients with schizophrenia to express themselves, participate in and be attuned to social cues results from an inability to simulate the mind of others, thus misinterpreting meanings and goals of social interactions. Mirror neurons fire specifically in response to viewing actions of others and facilitate anticipation of social interaction. Their function can be measured using EEG recordings and calculating mu wave suppression index (MSI) in bilateral sensorimotor cortices as previously shown in autism spectrum disorders. Using this paradigm we conducted a pilot study with 5 normal controls and 5 subjects with a first episode (FE) of psychosis. Standard EEG disk electrodes were applied to the scalp and data recorded while the subject sat in a quiet room and watched videos on a computer screen. Videos consisted of a moving hand, two bouncing balls, a ball being passed between people, a cigarette being taken out of a case, a person pretending to smoke a cigarette, a series of moving lights that correspond to a moving person and visual white noise. Preliminary data suggests that at baseline controls have higher MSI in the right hemisphere compared to FE subjects (−0.1 vs .04 log [condition/baseline]). In addition, when viewing a moving hand, controls did not show hemispheric effects, whereas FE subjects showed a deficit in right hemispheric MSI (controls vs. FE, −0.1 vs .01 log [condition/baseline] respectively). Taken together, the data suggest that MSI, a measure of motor mirror neuron activity, is altered at baseline and in response to viewing of actions of others in subjects who have experienced a first episode of psychosis. Interestingly, a specific deficit in the right hemisphere of the sensorimotor cortex is consistent with this region's previously established role in social cognition. The loss of function in this region may be a consequence of the psychotic episode or may predate the episode representing a developmental abnormality that confers future risk of developing psychosis. To investigate this hypothesis further, we plan to test more FE subjects to increase the power of our study and test subjects with a prodromal syndrome who are at risk of developing psychosis.
ID: 550572

PERIADOLESCENT MATURATION OF DOPAMINE ACTIONS IN THE PREFRONTAL CORTEX

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Several lines of evidence suggest that the prefrontal cortex (PFC) continues its maturation well into adolescence and beyond. Anatomical studies from human and non-human primates reveal protracted changes in architecture and innervation. Dopamine fibers, in particular, as well as dopamine (DA) receptors change their density during that late developmental stage. In addition, markers of local circuit interneurons have also been reported as changing during adolescence in monkeys. As the DA modulation of local PFC circuitry may be critical for a number of high-order functions and could be a primary element in schizophrenia pathophysiology, we explored the changes in responses to DA of pyramidal neurons and interneurons in the rat PFC with *in vivo* intracellular recordings and whole-cell recordings from brain slices. D1 agonists enhance excitability of pyramidal neurons, and effect more pronounced in slices from adult rats. Co-activating D1 and NMDA receptors yielded persistent depolarizations resembling up states, but only in slices from adult rats. The DA modulation of PFC interneurons also changed during adolescence. The D2 agonist quinpirole switched from a negligible effect in slices from infant (ie, PD < 35) rats to a strong increase in excitability in slices from adult (PD > 55) rats. The data suggest that the ability of interneurons to modulate pyramidal cell activity via feed-forward inhibition becomes refined in the PFC during adolescence. A disruption in such maturation could be responsible for the emergence of symptoms in conditions such as schizophrenia.
ID: 550489

ABNORMAL PERIADOLESCENT MATURATION OF INTERNEURON FUNCTION IN RATS WITH A NEONATAL VENTRAL HIPPOCAMPAL LESION

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It is clear that a strong developmental component is important for schizophrenia pathophysiology, and there is converging evidence from human and animal studies that such developmental component may affect primarily inhibitory interneurons in several cortical regions. Such deficit is likely to cause abnormal behaviors in animals and symptoms in humans. The time course of interneuron development may provide some cues to symptom onset, as there are several critical developmental stages, including a late maturation during adolescence. Here we explored the physiological properties of neurons in the prefrontal cortex (PFC) of adult and preadolescent rats with a neonatal ventral hippocampal lesion (NVHL) or sham controls. Whole-cell recordings in slices revealed an increased excitability of PFC pyramidal neurons and an abnormal maturation of fast-spiking interneurons. D2 agonists fail to excite interneurons, yielding a hyper-excitable and noisy PFC. Thus, this model reveals an onset of abnormal excitation/inhibition balance that matches the onset of symptoms in humans; ie, during late adolescence.
ID: 550475

NEUROPHYSIOLOGICAL MARKERS OF INTER-NEURON DYSFUNCTION IN (NON-GENETIC) RODENT DEVELOPMENTAL MODELS OF SCHIZOPHRENIA

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Prefrontal cortical interneurons have been reported as abnormal in brains from schizophrenia patients in several postmortem studies. Many developmental and even pharmacological rodent models show remarkable convergence in altering cortical interneuron function. As high-frequency oscillations in EEG or field recordings are known to be related to synchronized activity in fast-spiking interneurons, and are affected in schizophrenia, it is possible that neurophysiological testing can reveal interneuron dysfunction in rodent models. Here, we tested for field potential activity in rats with a neonatal ventral hippocampal lesion (NVHL) during a behavioral session in which they had to choose a reward site based on an odor cue. During the interval between the odor and the response, the prefrontal cortex (PFC) exhibited an increase in activity in the beta band (13−30 Hz) in control rats, but not in NVHL rats. Combined with our recordings in slices showing that PFC interneurons fail to mature during adolescence in NVHL rats, the results indicate that EEG measures can identify abnormal balance of excitation/inhibition in the PFC of rodent models of schizophrenia with an approach similar to what has been used in humans.
ID: 550449

MISMATCH NEGATIVITY IS ASSOCIATED WITH GENETIC, CLINICAL, COGNITIVE, AND FUNCTIONAL ABNORMALITIES OF SCHIZO-PHRENIA PATIENTS

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Schizophrenia patients have widespread deficits ranging from abnormalities in sensory processing to impairments in cognition and daily living. Mismatch Negativity (MMN) is an EEG waveform that is a probe of the earliest automatic stages of sensory information processing and can be elicited in the absence of directed attention. To assess the genetic architecture of MMN, a candidate gene analysis was performed on 203 schizophrenia patients and 119 controls from the UCSD Schizophrenia Program using the UCSD/Consortium on the Genetics of Schizophrenia (COGS) custom 1536 SNP chip. The initial single marker analyses revealed significant associations with 25 of 94 carefully selected schizophrenia-related genes (empirical $P < .01$). These genes included BDNF, GRIN3A, DISC1, CTNNA2, NRG1, and ERBB4. Several of these genes also interact molecularly (eg, NRG1 and ERBB4). Patients had MMN deficits ($P < .01$) which were associated with impaired performance on tests of working memory ($P < .01$), verbal recall ($P < .01$), and negative symptoms ($P < .01$). MMN deficits were also associated with reduced performance on a comprehensive functional skills assessment battery ($P < .05$), and significantly ($P < 0.01$) lower ratings on several measures of functional status (eg, independence in living situation, managing finances, Scale of Functioning, Global Assessment of Functioning Scale). In contrast, MMN was not associated with performance on other cognitive measures or positive symptoms. MMN deficits reflect neural dysfunction associated with the core cognitive, clinical, functional, and even genetic abnormalities of schizophrenia patients.
ID: 550407

PREPULSE INHIBITION AND P50 SUPPRESSION IN YOUNG ADOLESCENTS AT RISK FOR PSYCHOSIS

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In schizophrenia response inhibition of repetitive auditory stimuli is assumed to be disrupted by insufficient filtering of information. These kind of sensory gating deficits have also shown to be present in patients at risk for psychosis. However, the developmental course of these psychophysiological vulnerability markers is unclear and the timing of disease related changes remains unknown. In this study, we investigated auditory P50 suppression and prepulse inhibition (PPI) in a sample of young adolescents (aged 12–18 years) at ultra high-risk for psychosis (UHR). P50 suppression and PPI of the startle reflex were measured in UHR patients ($n = 64$) and compared to a group of typically developing adolescents ($n = 67$), matched for age, sex and IQ. PPI was significantly reduced in the total UHR group, but did not distinguish between those making a transition to psychosis and other patients. There were no group differences for P50 suppression. Our results show that reduced PPI of the startle reflex is already present in young adolescents at risk for psychosis. This suggests that PPI is a relatively stable vulnerability marker, while changes in P50 suppression may only be affected later during the illness course.

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ID: 550294

CLINICAL AND COGNITIVE FEATURES OF EARLY ONSET PSYCHOSIS: PILOT DATA FROM AN EARLY PSYCHOSIS STUDY

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Background: Schizophrenia and other psychotic disorders are a major cause of disability world wide. Much of this burden is due to cognitive impairments, which predict functional outcome better than acute symptoms. The outcome is worse for younger patients, perhaps because they are more likely to have neurocognitive abnormalities at presentation. Possible deficits include impaired social cognition and working memory, and reduced gamma phase synchrony. Aims: To describe the clinical and neurocognitive features of a small pilot cohort with early onset psychosis and to identify differences in cognitive functioning in comparison with normal children of the same age. Method: The subjects for this pilot study are fourteen children and adolescents diagnosed with psychosis and fourteen normal controls matched for age, gender and years of education. The clinical group have data from questionnaires on symptoms and premorbid functioning (SCID, PSAS, RFS, PANSS, DASS, CDI, and YMRS). Subjects and controls have data from the BRID battery of tests, including cognitive and EEG measures. Results: The mean age at diagnosis was 13 (median 14), and 64% were female. Fifty seven percent had affective psychosis, 39% schizophrenia spectrum disorders and 14% Schizoaffective disorder or psychosis NOS. The results of their performance on the BRID battery of tests compared to controls is still being analysed and will be presented in this poster.
ID: 550250

P3B AMPLITUDE REDUCTION IS NOT PROGRESSIVE OVER THE COURSE OF SCHIZOPHRENIA AFTER THE ONSET OF ILLNESS

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P3b is an event-related potential that is elicited by attended, task-relevant stimuli. Auditory P3b amplitude reduction is a widely replicated finding in schizophrenia. The findings of cross-sectional studies concerning the effects of duration of illness on P3b processes are controversial. In this study longitudinal data of first-episode schizophrenia patients were evaluated to determine whether the P3b abnormality is increased over the course of schizophrenia, consistent with a progressive pathophysiological process. Subject groups comprised 11 patients with schizophrenia (10 women) and 14 age- and education-matched healthy controls (7 women). Schizophrenia patients and healthy controls were tested on two occasions with mean intertest intervals of 6.2 and 5.7 years, respectively. Schizophrenia patients were at the post-acute phase of their first-episode during the initial testing. All patients were receiving atypical antipsychotics during the first and second evaluations. All patients, but one, met remission criteria in the period between the two evaluations suggesting that our sample consisted of patients with better outcome. P3b was elicited during an oddball paradigm consisted of standard (1000 Hz, probability 0.8) and target stimuli (1500 Hz, probability 0.2). The differences in P3b amplitude and latency between the two evaluations in patients and controls were assessed with the analysis of variance repeated measures design. Groups showed the expected parietocentral distribution of P3b ($P = .001$). P3b amplitudes were reduced in patients compared to controls ($P = .03$). P3b amplitude was not different between the two evaluations. Most importantly, groups did not differ in P3b amplitude difference between the first and second evaluations. No difference was found for P3b latency. Our finding of P3b amplitude reduction in schizophrenia patients is consistent with previous studies. Our results suggested that P3b reduction is not progressive over the course of schizophrenia after the onset of illness at least in a sample with better outcome who are receiving atypical antipsychotics. To our knowledge, the present study is the first to report on the longitudinal course of P3b in schizophrenia to delineate illness progression.
ID: 550214

MISMATCH NEGATIVITY IN PRODROME, FIRST EPISODE AND ESTABLISHED SCHIZOPHRENIA: RELATIONSHIP WITH STIMULUS TYPE, GENERATOR SOURCES, GREY MATTER LOSS, AND FUNCTIONAL OUTCOME

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Mismatch negativity (MMN) is an early negative component of an event related potential and considered a robust biological marker of schizophrenia. We recorded MMN in response to duration, frequency and intensity deviance in 18 schizophrenia subjects and 18 pair-wise age- and gender-matched healthy subjects. Patients were rank-ordered according to their socio-occupational function levels. High-resolution structural magnetic resonance images were acquired to generate average cerebral cortex models using cortical pattern matching. MMN amplitude was found to be reduced in schizophrenia patients and correlated with their reduced socio-occupational function levels. Only in patients, grey matter reduction in cortical areas subserving auditory processing, motor organization and executive function was correlated with reduced MMN amplitude in response to frequency deviance. In a separate study, MMN generator source data were derived from LORETA constrained source localisation performed on current dipoles that were oriented perpendicular to the cortical surface in realistic head models (CURRY). Generator sources were largely restricted to the temporal lobes and reduced for duration deviance in young people with a recent diagnosis of schizophrenia. Our preliminary data from an ultra high-risk cohort of 72 referrals to a specialized mental health service in Newcastle further suggests significantly reduced MMN to duration deviance for those individuals who subsequently make a transition from prodrome to schizophrenia. Our findings suggest a close association of MMN to frequency deviance with cerebral pathology and clinical outcome in established schizophrenia while reduced MMN to duration deviance appears to be associated with the prodrome and first-episode phase of the disorder. Supported by the National Health and Medical Research Council of Australia and the Hunter Medical Research Institute.
ID: 550210

ELECTROPHYSIOLOGICAL CORRELATES OF EMOTIONAL EXPERIENCE IN SCHIZOPHRENIA

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Individuals with schizophrenia have repeatedly been found to report normal levels of pleasure when directly exposed to evocative stimuli. However, little is known about the neural correlates and time course of emotional experience in schizophrenia. Following a translational research approach, this study examined performance on a well-validated affective picture viewing task that elicits a characteristic pattern of Event Related Potentials (ERPs) in healthy individuals that differs between emotional versus non-emotional images. 38 stabilized outpatients and 37 healthy were shown a set of 60 standardized pictures of pleasant, unpleasant, and neural images for 6000 ms each while ERP's were recorded. Participants also provided reports of their emotional responses to the pictures. Replicating prior research, the healthy controls self-reported emotional responses that matched the intended valences of the pictures and they demonstrated significantly larger P300s and Late Positive Potentials (LPPs; 500–100 ms post-picture onset) for pleasant and unpleasant pictures compared to neutral pictures. The patients' pattern of self-reported emotions and P300s were similar to those found in controls. However, there was a significant group x valence interaction for LPPs ($F_{2,72} = 3.30$, $P < .05$), indicating that patients showed a smaller difference in LPPs between pleasant versus neutral pictures than did controls. These findings support the validity of self-reports of normal emotional responses to evocative stimuli in schizophrenia. They also suggest that individuals with schizophrenia may show disturbances in affective chronometry: while the similar mid-latency ERP's (P300s) across groups suggest intact attentional allocation to emotional stimuli in schizophrenia,

the difference in LPPs suggest a disruption in sustained attentional processing of emotional stimuli.
ID: 550101

ELECTROPHYSIOLOGICAL CORRELATES OF EMOTION ANTICIPATION IN SCHIZOPHRENIA

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Schizophrenia patients report intact in-the-moment experiences of emotional events. However, initial research based on self-report data suggests that individuals with schizophrenia show disturbances during the anticipation of forthcoming emotional events, particularly those involving pleasurable experiences. The current study examined the electrophysiological correlates of emotional anticipation using a cued, reaction-time contingent emotional picture viewing task. EEG data from 38 schizophrenia outpatients and 34 healthy controls were collected during an emotional anticipation task. On each trial, participants were first shown one of three visual cues (+, −, O) for 3000 ms, which indicated whether they would subsequently be shown a positive, negative or neutral picture. Participants then made a button press as quickly as possible after cue-offset, which determined how long the picture was shown (ie, a fast response resulted in a 5000 ms picture presentation ; a slow response resulted in a 500 ms picture presentation). A 4000 ms delay interval preceded picture presentation. Two anticipatory EEG events were analyzed: the 500 ms prior to the button press (termed Readiness Potential, RP) and the 500 ms prior to the onset of the picture (termed Stimulus Preceding Negativity, SPN). For the RP, analyses revealed a significant group main effect, $F_{1,70} = 7.40$, $P < .01$, with the RP for the controls being significantly larger than that for the patients (-9.2 μV versus −5.4 μV). There were no other significant main effects or interactions. For the SPN, analyses revealed a significant group main effect, $F_{1,70} = 10.57$, $P < .01$, with the SPN for the controls significantly larger than that for the patients (−5.4 μV versus −2.9 μV). There were no other significant main effects or interactions. The current electrophysiological findings provide further support for general disturbances in emotional anticipation in schizophrenia. Emotion anticipation is an important aspect of adaptive approach and avoidance behavior, and anticipatory dysfunctions may contribute to the hedonic and motivational deficits commonly seen in schizophrenia.
ID: 549985

ERP'S PATTERN AND PROGNOSTIC IN SCHIZOPHRENIA

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Objective: In a previous study*, we showed that clinical improvement with SGA in schizophrenia is associated both cognitive change and by P300 and P50 suppression. The aim of this study was to investigate an ERP'S pattern associated with a good prognostic in schizophrenia all validated by PANNS and GAF at 8 months. Methods: Fifty-five individuals (32 males and 23 females; mean age = 35.9) meeting DSM-IV criteria for schizophrenia, admitted for an acute relapse, were included in the study and observed within eight months period from 2005/10 to 2006/07. They were treated with the following antipsychotics (mean daily dosage) : aripiprazole (13.75 mg), rispéridone (5.06 mg), olanzapine (14.12 mg), amisulpride (1000 mg) and

Results

PANSS score reduction	Patients number	GAF score T2	Reaction time P300 reduction	Increase in Amplitude P300 μvolt	Latency P300 reduction μvolt	False alarms reduction	Omission reduction errors	P50 suppression
30 to 40%	10	64.8	−10.3	0.5	9	−1.4	−0.3	3
40 to 50%	22	69.3	2	2.5	−4.3	−0.3	−1	2
50 to 60%	18	71.9	−19.6	2.1	−6.3	−0.5	−1.2	0
More than 60%	5	74.2	−8.1	5.1	−3.3	−2.4	−2.8	0

clozapine (150 mg). Psychotropic drugs were prohibited except for benzodiazepines, zolpidem and anticholinergic medications. Clinical and electrophysiological evaluations were performed before the start of treatment (T1) and after remission (T2). Psychopathology was measured by the Positive and Negative Syndrome Scale (PANSS). GAF was evaluated in T2. Results: All patients are improved in T2. We separated them in 2 groups: under and over 50% PANSS score reduction. In the ERP'S:the reaction time P300 reduction, the increase of the amplitude of de P300 and the omissions errors reduction are improved in the same way than the PANSS score reduction and the increase of the GAF after treatment. Conclusions: Reaction time P300 reduction, increase of the amplitude of P300 and omissions errors reduction could constitute an ERP'S pattern for a good prognostic in schizophrenia. These results need to be confirmed by a larger scale and longer duration study. *The effect of second generation antipsychotic drugs on event related potentials in schizophrenia: a preliminary study: Albert BOXUS: Poster Nr 448 APA 2007 SAN DIEGO.
ID: 549876

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USING TMS-EVOKED POTENTIALS TO PROBE NEURAL RESPONSE MECHANISMS IN SCHIZOPHRENIA

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Studies of the neuropathology of schizophrenia have implicated a failure of appropriate neuronal inhibition and a disturbance of cortical connectivity as two potential models of the illness. However, direct tests of these mechanisms in patients have been limited by the practical constraints of in vivo clinical research, and empirical support has largely been indirect and inferential. Recent developments in the use of transcranial magnetic stimulation (TMS) as a neurophysiological probe of cortical activity have suggested a means to test the functional integrity and responsivity of neural circuits in a more direct manner. By combining single-pulse and paired-pulse TMS with simultaneous multi-channel evoked potential recordings, we are able to assess cortical reactivity and inhibitory and facilitative mechanisms within localized brain areas. Using lagged cross-correlations of evoked activity at different electrode sites, we can also assess neural connectivity across brain regions. This can be all be done without requiring the subject to attend to any sensory stimuli. This novel methodology has only been applied to a limited extent in the study of healthy individuals, and even less in the study of clinical populations. We will describe this methodology, including our strategy for eliminating TMS pulse artifacts using Independent Components Analysis. Our initial data, applying TMS over the left prefrontal cortex, suggest the following: 1) Schizophrenia patients exhibit abnormally sustained responses to single TMS pulses; 2) Control subjects exhibit both cortical inhibition and facilitation following appropriate paired-pulse stimulation; 3) Patients exhibit relatively normal cortical inhibition, but fail to exhibit cortical facilitation; 4) Control subjects exhibit strongly correlated activity at homologous sites over the contralateral hemisphere; 5) Patients do not show strongly correlated cross-hemisphere activity. The dual findings of sustained baseline excitation and failed prepulse facilitation, in patients, are consistent with a model of tonically increased glutamatergic tone in localized neuronal assemblies; this focal hyper-excitability is associated with disrupted functional connectivity across brain regions. These preliminary findings demonstrate that TMS-evoked potentials hold tremendous promise as an in vivo method to investigate fundamental aspects of the pathophysiology of schizophrenia.
ID: 54971

SENSORIMOTOR GATING IN FIRST-EPISODE, ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA PATIENTS: A LONGITUDINAL STUDY

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Deficits in information processing appear to be core features in the pathophysiology of schizophrenia. Prepulse inhibition of the startle response (PPI) is an operational measure of sensorimotor gating. In clinical studies, generally no effect has been found on PPI in schizophrenia patients treated with typical antipsychotics, whereas some studies found improved PPI in patients treated with atypical compounds, while others did not. These inconsistencies might be due to differences in binding characteristics of the various compounds used, in particular to their affinity for the D2 dopaminergic receptor. Alternatively, it has been suggested that PPI deficits are stable vulnerability indicators, insensitive to medical treatment. Since most previous studies were cross-sectional, longitudinal studies on drug-naïve first-episode schizophrenia patients are warranted, to avoid the possible confounding of antipsychotic medication and course of illness. In the present longitudinal study, PPI of 29 antipsychotic-naïve, first-episode schizophrenia patients was compared to that of 30 age and sex matched healthy controls at baseline, and after six months of treatment with the atypical antipsychotic quetiapine. Since a gender effect was found and relatively few females were included, it was decided to use the male data only. Consistent with literature, the patients at baseline showed significantly less PPI than the healthy controls. At follow-up however, PPI from the 11 patients who completed the 6 months treatment with quetiapine, did not differ significantly from that of the healthy controls. Since the antipsychotic-naïve, first-episode schizophrenia patients showed significantly less PPI compared to the healthy controls at baseline, this indicates that PPI deficits are present at an early stage in the development of schizophrenia. Furthermore, the results suggest that

PPI deficits in schizophrenia can be normalized by six months of treatment with quetiapine.
ID: 549589

DEFICITS IN WORKING MEMORY PERFORMANCES IN PEOPLE WITH CLINICAL HIGH-RISK FOR PSYCHOSIS: ERP EVIDENCE

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The aim of this study was to investigate whether people with clinical high-risk for psychosis show more rapid decline of P3 amplitudes with increasing working memory load of verbal and spatial n-back tasks. People with clinical high-risk for psychosis (CHR), schizophrenia patients (SPR) whose duration of illness is less than 5 years and normal controls (NC) were recruited. Subjects were asked to perform verbal and spatial 0/1/2-back tasks. Repeated measures ANOVA with PROC mixed model were performed. P3 amplitudes of 0-back were larger than those of 1- and 2-back condition ($F = 12.8$, $P < .001$). CHR as well as SPR showed smaller amplitudes of P3 than that of NC ($F = 13.8$, $P < .001$). The amplitudes of P3 in CHR declined more rapidly than those of NC when working memory load is increased ($F = 4.6$, $P = .001$). These findings provide the neurophysiological evidence that the working memory deficits may be already present in prodromal phase of psychosis. The associations of declined P3 amplitudes of working memory and psychopathology, social and role functioning will be discussed.
ID: 549427

DURATION MISMATCH NEGATIVITY IN PRODROMAL AND FIRST-EPISODE SCHIZOPHRENIA

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Background: Deficits in the automatic sensory discrimination as indexed by mismatch negativity (MMN) are well documented in chronic schizophrenia patients. The majority of previous studies, however, failed to detect MMN impairments in the early stages of the illness. In fact, six out of seven studies did not find a reduced pitch or duration MMN in patients with first-episode schizophrenia. The only study (Brockhaus-Dumke et al., 2005) that examined MMN in the schizophrenia prodrome reported a trend for at-risk patients to exhibit deficits on this paradigm. Methods: Nine at-risk individuals (AR) and 15 patients with first-episode schizophrenia (FE), recruited as part of the UCSD CARE (Cognitive Assessment and Risk Evaluation) program, and 39 age-matched normal comparison subjects (NC) underwent duration-deviant MMN testing (1000 Hz tones, standards: 50 msec, $P = .90$; deviants: 100 msec, $P = .10$) in the UCSD Schizophrenia Program Laboratory. Results: Group differences were present in the amplitude of the MMN to duration deviants at fronto-central electrodes ($F_{2,60} = 4.60$, $P = .014$). In contrast to previous reports showing no MMN deficits in FE subjects, significant and large effect size ($d = 0.85$) MMN reductions were observed in the FE (M = -2.03, SD = 1.64) relative to the NC (M = -3.85; SD = 2.12) group. Consistent with Brockhaus-Dumke et al.'s findings, the AR group's MMN amplitudes (M = -3.32; SD = 1.81) were intermediate between those of the NC group and the FE group, but those differences did not reach statistical significance ($d = 0.26$). Conclusions: In contrast to previous studies, robust and large effect size duration-deviant MMN deficits were observed in first-episode patients with schizophrenia. Individuals at risk for developing schizophrenia showed small and non-significant reductions relative to age-matched normal comparison subjects. We will assess MMN in a larger sample of at-risk individuals and further explore the association between MMN and the demographic, clinical, cognitive, and functional characteristics of the sample. Future studies are needed to delineate the nature of MMN abnormalities early in the course of schizophrenia and to clarify whether those deficits reflect premorbid neuropathology or ongoing disease processes associated with illness progression. Supported by MH60720, MH79777, NARSAD, and the VISN-22 Mental Illness, Research, Education, and Clinical Center.
ID: 549205

A NEURAL ENSEMBLE ANALYSIS OF COGNITIVE FAILURE

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It is now well established that dysfunction of the prefrontal cortex (PFC) is a key aspect of the cognitive impairments in schizophrenia. Patients exhibit significant deficits in many aspects of cognition that rely on the PFC including working memory, attention and executive function. Conceivably, these deficits could occur for a number of reasons or there may be a single underlying problem in PFC networks that affects multiple processes. As a first step in addressing this issue we have begun to investigate the network dynamics associated with the commission of errors on tasks of working memory and executive function in rats. Based on multiple single-unit recordings we found that ensembles of PFC neurons tracked each separable cognitive component of the tasks by entering distinct and coherent activity states. The organization and coherence of network activity states was largely absent on trials where rats made numerous errors and the breakdown was especially evident at the choice points of the task but not when the information was acquired or maintained over a delay. There is also accumulating evidence that the dopamine (DA) modulation of the PFC is crucial for optimal cognitive performance and this modulation may be altered in schizophrenia. The PFC DA system is believed to exhibit an inverted-U dose response curve such that too little or too much DA becomes detrimental to performance. In order to examine the effects of artificially pushing DA levels to different parts of the curve, we injected rats with either the catecholamine releaser amphetamine or the COMT inhibitor Tolcapone (Tasmar). While Tolcapone improved working memory performance, higher doses of amphetamine impaired it. Recordings of multiple single-unit activity showed that the higher doses of amphetamine decreased the ensemble organization making the overall network of recorded neurons less coherent and synchronized across all task epochs. This was a different dynamic than what was observed when untreated rats committed errors and suggested that pushing the DA system to the 'far end' of the inverted -U curve produces large-scale cortical disorganization. The next step is to determine how network dynamics within the PFC change in the context of popular animal models of schizophrenia.
ID: 548748

DURATION AND PITCH MMNS IN SCHIZOPHRENIA AND THEIR RESPONSE TO ACUTE NICOTINE TREATMENT

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While prevalence rates of smoking are reported as high as 90% in schizophrenia (SZ), the reasons for increased cigarette use in this disorder are not well understood. Nicotine is known to enhance cognition, including early sensory and later attention-dependent processes, which are impaired in SZ. Mismatch negativity (MMN) is a neurophysiologic index of pre-attentive acoustic change detection that has been found deficient in SZ and has shown sensitivity to smoking doses of nicotine. The objective of this study was to compare MMNs elicited by both tone duration and pitch deviants in smokers with and without SZ and to examine the acute effects of nicotine on MMNs in SZ. Participants included 12 stable patients with SZ and 12 non-psychiatric controls, all cigarette smokers who were smoking a minimum of 15 cigarettes per day. Mid-line (Fz, Cz, Pz) event-related potential (ERP) recordings within both a duration-MMN paradigm with 100 ms standard tones (95%) and 50 ms deviant tones (5%) and a pitch-MMN paradigm with 1000 Hz standard tones (95%) and 1100 Hz deviant tones (5%) were acquired in controls, who were assessed in one session, and patients, who were assessed in two sessions involving, double-blind randomized administration of placebo (0 mg) and nicotine gum (4 mg). Relative to controls, MMN amplitudes of patients were significantly reduced in both duration and pitch paradigms. Nicotine in patients did not alter pitch MMNs but it increased the amplitude of duration MMNs to a level comparable to that seen in controls. These findings suggest that nicotine modulation of aberrant central mechanisms underlying early detection of auditory changes in SZ may be feature specific and further studies are required to elucidate its role in relation to smoking behavior in SZ.
ID: 548055

EVENT RELATED POTENTIAL PATTERNS REFLECTING DYSFUNCTIONAL FACIAL AFFECT PROCESSING IN SCHIZOPHRENIA PATIENTS

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This study was designed to clarify the difference of facial affect processing between patients with schizophrenia and normal controls. Three ERP components were chosen as an index of three separate stages in the emotion identification processing: P100 as a basic visual processing, N170 as a facial structural encoding, and N250 as an facial affect decoding. Forty-two patients who met the DSM-IV criteria for schizophrenia and 36 normal controls were recruited. ERPs were recorded using 64 channels while participants were presented with pictures of faces showing three different emotional states such as happy, neutral, and fear. Participants were instructed to press the button when they see the emotional face. Mean amplitude of P100 response was not different between schizophrenia patients and normal controls whereas the amplitudes of both N170 and N250 in patients were significantly smaller compared to normal controls ($F_{1,76} = 9.615$, $P = .003$ for N170; $F_{1,76} = 16.854$, $P < .001$ for N250). In within group analysis, the amplitudes of N170 and N250 of patients were significantly smaller on the fear condition. Mean peak latency was not different across groups in neither P100 nor N250. However, the significantly shorter N170 latency was found in schizophrenia patients compared with normal controls($F_{1,76} = 8.195$, $P = .005$). This study suggests that the basic visual processing is not different between schizophrenia patients and normal controls. But facial structural encoding and facial affect decoding are dysfunctional in schizophrenia patients compared with normal control.
ID: 546712

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EVENT-RELATED SPECTRAL POWER DEFICITS DURING SEMANTIC PROCESSING IN SCHIZOPHRENIA

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Background: Schizophrenia patients exhibit abnormal electroencephalographic (EEG) N400 event-related potential (ERP) responses to semantically related materials. We investigated whether event-related EEG spectral power changes during semantic processing are also abnormal in schizophrenia; and if so, the extent to which they are associated with N400 abnormalities. Methods: The EEG was recorded from 16 schizophrenia patients and 16 normal control participants (NCPs), as they viewed prime words, followed after 750 ms by related (eg, METAL > STEEL) or unrelated (DONKEY > PURSE) target words, or nonwords (DRESS > ZORES). Participants' task was to indicate whether or not the target was a word, via delayed button-press. Event-related spectral perturbation (ERSP) was calculated for primes and targets, from 0–750 ms post-stimulus onset and between 1–50 Hz. Results: Across all participants, words elicited increased power from 1–15 Hz from 50–200 ms, albeit less so in patients relative to NCPs for related targets. Across all participants, words elicited decreased power from 1–20 Hz from 200–750 ms. Between 600–750 ms Hz, power decreases from 1–20 Hz were larger for unrelated versus related targets, but only in NCPs; in patients, larger power decreases for related targets correlated with disorganized symptoms. Overall, ERSP deficits did not correlate with N400 abnormalities in patients. Conclusions: Schizophrenia patients' abnormally attenuated early power increases for related targets may result from deficient use of primes to predict perceptual features of upcoming related words. In the post-N400 interval, patients exhibited deficits in modulating power decreases to targets as a function of relatedness to primes, reflecting the propensity of more disorganized patients to process related targets more like unrelated ones. ERSP and N400 ERP abnormalities in patients, however, were not associated, implicating distinct pathophysiological processes.
ID: 541887

DISTINCT NEURAL GENERATORS OF SENSORY GATING IN SCHIZOPHRENIA: BASIC MECHANISMS AND ATTENTIONAL EFFECTS

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Attentional and perceptual anomalies observed in schizophrenia have been associated with underlying sensory gating deficits. Despite progress in identifying the neural generators contributing to P50 and its suppression, a prominent measure of sensory gating, the neuroimaging methods utilized and the results obtained have been quite varied. Through the implementation of electroencephalographic (EEG) source analysis, the current study was designed to clarify the neural sources involved in the basic P50 suppression effect and its attentional modulation during a paired-stimulus design. Results obtained from healthy individuals, recent-onset schizophrenia

patients, and chronic schizophrenia patients showed involvement of a neural network, consisting of the hippocampus, thalamus, dorsolateral prefrontal cortex (DLPFC) and superior temporal gyrus (STG), in the generation of P50, its suppression and modulation by attention. P50 suppression in healthy participants was positively correlated with hippocampal and, to some extent, DLPFC activity. This pattern of relationships did not extend to schizophrenia patients, such that recent-onset patients showed a positive correlation between DLPFC activity and the P50 suppression ratio, and chronic patients exhibited no associations. When healthy participants directed voluntary attention to the first stimulus of a pair, thalamic activity was positively correlated with the P50 suppression ratio whereas no significant correlations were detected with any of the brain structures in the patient groups, despite improvements in P50 suppression. When healthy individuals directed attention to the second stimulus, suppression was disrupted and associations involving the hippocampus, DLPFC and thalamus were no longer evident. Similar to the baseline condition, recent-onset patients exhibited a positive correlation between DLPFC activity and the P50 ratio score while chronic patients showed no relationships. The current results support hippocampal and potentially DLPFC involvement in the basic P50 suppression effect in healthy individuals. In schizophrenia patients, the pattern of results is consistent with the presence of hippocampal abnormalities as reflected by P50 deficits beginning with the early stage of illness, whereas DLPFC involvement appears to deteriorate over the course of schizophrenia. Results obtained during attentional modulation of P50 further implicate disturbances in functional connectivity in schizophrenia.
ID: 550842

COGNITIVE-PERCEPTUAL AND INTERPERSONAL FEATURES OF SCHIZOTYPY ALIGN WITH DISTINCT AUDITORY ERP ABNORMALITIES

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Schizotypy is conceptualized as a dimension of liability to schizophrenia, characterized by similar but milder variants in perceptual, interpersonal, and cognitive function. These features of schizotypy are detectable in the general population and, at high levels, may define a latent class who exhibit neurophysiological traits of the schizophrenia phenotype. This study tested the hypothesis that individuals high in schizotypy express deficits similar to schizophrenia on event-related potential (ERP) measures of sensory (N100) and attentional (P300) processing. Furthermore, we sought to clarify how the Cognitive-Perceptual, Interpersonal, and Disorganization factors of schizotypy, described by Raine and colleagues (1994), differentially relate to these neurophysiological features. Sixty chronic schizophrenia (SZ) and 69 healthy community volunteers, screened for Axis I and Axis II disorders, completed the Schizotypal Personality Questionnaire (SPQ) and a two-tone auditory oddball task. ROC curves were used to identify the cut point in each SPQ factor score distribution at which 50% of healthy subjects were classified as SZ (high schizotypy) and 50% as normal (low schizotypy). High and low schizotypy subgroups were then compared to the SZ sample on N100 (standard tones) and P300 (target tones) measures by MANCOVA with age and SPQ total entered as covariates. Main group comparisons replicated usual findings of N100 and P300 amplitude reductions and prolonged P300 latency in SZ. Schizotypy subgroups classified by Cognitive-Perceptual factor scores differed on N100 amplitude only, with high schizotypy intermediate to, and significantly different from, low schizotypy and SZ. Conversely, subgroups classified by Interpersonal factor scores differed significantly in P300 amplitude, with high schizotypy intermediate to low schizotypy and SZ. No appreciable differences were observed between high and low schizotypy subgroups classified by either SPQ total or by Disorganization factor scores. These results are consistent with previous evidence for auditory ERP abnormalities in schizotypy, which appear to represent an intermediate point on the continuum from normalcy to schizophrenia. Importantly, results allude to distinct neurophysiological bases for two domains of schizotypy, with Cognitive-Perceptual features associated with basic sensory/attentional processing and Interpersonal features with more complex, context-relevant, information processing deficits.
ID: 551910

COMPARING ELECTROPHYSIOLOGICAL ENDOPHENOTYPES IN SCHIZOPHRENIA AND BIPOLAR DISORDER FAMILIES

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The use of alternative phenotypes that index specific, heritable neurophysiological deficits associated with psychosis risk provide an approach to explore the extent of etio-pathophysiologic overlap between schizophrenia (SZ) and bipolar disorder (BD). Several such distinct neurophysiological deficits have been identified including abnormalities in smooth pursuit eye movements (SPEM), pre-pulse inhibition (PPI), P50 gating, error rate in antisaccade task, oculomotor delayed response (ODR), as well impairments in several cognitive domains. In a set of studies we (1) examined to what extent these different physiological measures are independent of each other. This was carried out in a Baltimore sample that included 98 families of schizophrenia and 23 families of healthy control probands. Results suggest that SPEM, P50 gating, PPI and saccadic eye movement measures are independent domains of neurophysiological deficits. (2) In the same sample, measurements of SPEM and P50 gating were refined and heritability estimates examined. SPEM measure was refined by covertly stabilizing target image on the fovea thus isolating the predictive response. We are in the process of analyzing data to obtain heritability estimates of the refined SPEM measure. In the paired-click paradigm, we deconstructed the single-trial gating response in to different frequency bands and noted that the gating of alpha-theta band responses significantly separated SZ probands and their 1st degree relatives from the healthy control subjects. The heritability estimates associated with alpha-beta gating in SZ and control families ranged from 0.49–0.83, which were much higher than the traditional P50 gating measure. (3) These refined SPEM and sensory gating measures as well as PPI and saccadic eye movement measures were examined in another family sample collected in Dallas that included families of both SZ and BD probands. Preliminary analyses suggest that many of the neurophysiological impairments observed in SZ families are also present in BD families.
ID: 551896

ERROR-RELATED NEGATIVITY DURING OBSERVATION IN SCHIZOPHRENIA

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Deficits in neurocognition and social behavior are well-documented features of schizophrenia. There is evidence to suggest that cognitive impairment contributes to problems in social functioning, but direct correlations between these domains are modest and inconsistent. Social cognition has received some empirical support as a mediator between these constructs, yet there have been few investigations to date of the underlying neural processes associated with socially-relevant stimuli and behavior. The recent discovery of the mirror neuron system has provided a useful starting point for describing brain activity involved in the interpretations of other's actions. This study examines whether error-related negativity (ERN), an event-related potential (ERP) that follows the execution of an error on a task and that has been consistently found to be reduced in amplitude among schizophrenia patients, might reflect activity involved in the processing of error-related activity of others and whether this activity has relevance for social processing and functioning. In this study, schizophrenia patients and psychiatrically healthy controls performed the flanker task and then observed a confederate perform the same task. Participants also completed measures of neurocognition, social cognition, community social functioning, and symptomatology. It was hypothesized that 1) schizophrenia patients would show reduced ERN amplitude compared to controls while executing and observing the task, 2) ERN activity would be distinguishable from activity of the primary motor cortex as indexed by the lateralized readiness potential (LRP), 3) deficits in observational ERNs would be related to impaired social cognition and social functioning. Preliminary analyses suggest the presence of a robust ERN in control subjects and reduced differentiation of activity following errors and correct responses in patients while performing the task. During observation, although there were apparent morphological group differences and a small differentiation between correct and error trials, no significant group differences were observed. The relationship of the observation ERN with the LRP, social cognition, social functioning and symptoms of schizophrenia and the implications of this research will be discussed.
ID: 551860

EXCITATORY-INHIBITORY BALANCE AND MYELIN SIGNALING DETERMINE CRITICAL PERIOD TIMECOURSE

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Much of our adult behavior reflects the neural circuits sculpted by experience in infancy and early childhood. At no other time in life does the surrounding environment so potently shape brain function. An understanding of how this plasticity waxes and wanes with age carries an impact far beyond neuroscience, including education policy, therapeutic approaches to developmental disorders or strategies for recovery from brain injury in adulthood. Our research aimed at the interface between cell biology and neuroscience has achieved the first direct control over critical period timing in any system (Hensch 2005). Strikingly, manipulation of inhibitory transmission in the neocortex can delay the amblyopic effects of monocular visual deprivation (by gene-targeted reduction of GABA synthesis) or accelerate plasticity onset (by cortical infusion of a positive GABA receptor modulator, diazepam). Remarkably, several lines of evidence now indicate that a specific, local inhibitory circuit (parvalbumin-positive basket cells) may drive critical period onset in mouse visual cortex. Downstream of this GABA trigger lies an extracellular proteolytic cascade (tPA-plasmin) which mediates the enduring structural reorganization of cortical circuits. Ultimately, these changes become fixed to consolidate plasticity. Myelin-related factors and Nogo receptor (NgR) signaling, a major inhibitor of CNS regeneration following axonal injury, contribute to the inability to recover from amblyopia in the adult primary visual cortex. Indeed, we find the NgR 1 knockout mouse to be the first animal model which spon-

taneously recovers from amblyopia simply by reopening the deprived eye. Microarray profiling and anatomical studies of human post-mortem tissue now implicate the same mechanisms that regulate critical period onset (parvalbumin cells) and closure (myelin-NgR signaling) in the visual cortex as more broad contributors to the etiology of cognitive and psychiatric disorders in adulthood. We consider the unexpected possibility that schizophrenic symptoms may reflect excessive and enduring brain plasticity due to a failure to close early critical periods.
ID: 551833

THE EFFECT OF COLD PRESSOR STRESS ON P50 GATING: IMPLICATIONS FOR SCHIZOPHRENIA RESEARCH

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The P50 auditory sensory gating deficit has received considerable attention as a candidate endophenotype of schizophrenia and as a target of new drug development. Furthermore, recent meta-analyses suggest that this deficit has one of the highest effect sizes for differentiating people with schizophrenia from controls; however, these effects have been called into question as reported effect sizes appear to vary. Furthermore, temporary impairments in P50 expression and suppression can occur in practically anyone, and such transient disruptions are thought to result from acute autonomic activation, which can create further variability in effect sizes. Most studies report that acute stress leads to S2 suppression impairment in healthy adults. However, some evidence suggests that S1 amplitude may also be reduced by stress. The current study aimed to replicate and extend the one previous study of cold pressor test (CPT) induced disruption of P50 gating in healthy controls, using a large sample size in an attempt to identify potentially latent S1 effects and to better characterize the relationship between P50 disruption and psychophysiological measures of autonomic arousal and self-reported pain and negative affect. 40 healthy, non-smoking adults with no history of psychiatric or neurological disease completed the experiment at a small Midwestern medical school. Auditory evoked-potential, heart rate, blood pressure, and self-report data were collected across three experimental conditions: a resting baseline, immediately after a 3-minute cold-pressor, and after a 25 minute recovery period. Data collection, reduction and P50 peak-picking methods will be discussed. Results of the current study did not replicate the previously reported CPT induced changes for the sample as a whole, a result that may have been related to methodological differences between the two studies, which will be discussed. However, when baseline gating was taken into account, S2 amplitudes changed significantly across conditions. Change in P50 gating correlated significantly with increased pain perception but no other self-report or cardiovascular variables. These results support the need for further characterization of the impact of stress on P50, as this relationship continues to be complicated and unpredictable and can serve to further limit the reliability of the P50 measure in its use as an endophenotypic marker and outcome variable for therapeutic interventions.
ID: 551809

ELECTROPHYSIOLOGICAL EVIDENCE OF AB-NORMAL AUTOMATIC ACTIVATION OF SEMAN-TIC NETWORKS IN SCHIZOPHRENIA

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Abnormal activation of semantic networks characterizes schizophrenia and can be studied using the N400 event-related potential (ERP). N400 is elicited by words that are not primed by the preceding context and provides a direct measure of the neural mechanisms underlying semantic priming. Semantic priming refers to facilitated semantic processing gained through pre-exposure to semantic context, which can happen automatically if the interval between the prime and target is very short. We predicted that, relative to healthy controls, schizophrenia patients would have (1) overly inclusive semantic networks, reflected in a reduced (ie, less negative) N400 to relatively unprimed words, and (2) deficits in their use of semantic context, responding to primed words as if they were unprimed, reflected in a an abnormally increased (ie, more negative) N400 to primed words. EEG data were acquired from patients with DSM-IV schizophrenia ($n = 26$) and age-matched healthy controls ($n = 29$) during performance of a picture-word verification (match vs. non-match) choice-response task. Word targets were presented 325 ms after a picture prime, which either matched (CAMEL‡"camel"), or did not match the prime ("InCat" = In Category Non-Match: CAMEL‡"cow"; "OutCat" = Out Category Non-Match: CAMEL‡"candle"). For each subject, N400 was identified as the most negative peak between 300 and 500 ms following onset of unprimed words at electrode Pz. Although primed words do not normally elicit an N400, voltage associated with primed words was measured at the OutCat N400 peak latency. N400 was defined as the mean amplitude surrounding the N400 peak (± 30 ms), relative to a 100 ms pre-picture baseline, for primed and unprimed (InCat and OutCat) words. N400 data showed that both patients and controls were sensitive to the difference between primed and unprimed words, but patients were less sensitive than controls. Similarly, N400 data showed that both groups were sensitive to the subtler difference between classes of unprimed words (InCat vs. OutCat), but patients were less sensitive, especially those with prominent negative symptoms. Surprisingly, there were no correlations between N400 and the severity of thought disorder or delusions in patients. Thus, abnormal activation of semantic networks in schizophrenia may not be specifically related to the abnormalities in thought content and process that would seem, on theoretical grounds, to be the most dependent on semantic processes.
ID: 551753

BETA AND GAMMA CONTRIBUTIONS TO P50 SUBCOMPONENT ABNORMALITIES IN SCHIZOPHRENIA: CLINICAL CORRELATES

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Main: Studies examining impaired sensory gating of the P50 component of the auditory evoked potential (AEP) in schizophrenia (SZ) typically use a bandpass of 10–100 Hz. Recent evidence suggests that using this bandpass groups two distinct frequency bands, beta (12–20 Hz) and gamma (30–50 Hz), together and excludes important information about beta and gamma contributions, which are theoretically associated with different stages of attention. Dysfunctional attention in schizophrenia is a prominent component and serves as a potential vulnerability marker for the disorder. Impaired attention is associated with negative and/or disorganized clinical symptoms. We previously found relationships between these symptoms in patients and abnormalities in P50 subcomponents using a 10–100 Hz frequency band. This study examined the relationship between P50 subcomponents and clinical measures of SZ symptomatology using separate beta and gamma filter settings. Participants and Methods: AEP data were collected on 42 healthy adults and 39 SZ patients using a 32-channel recording array with a paired click protocol (0.5sec ISI, 10sec ITI). Amplitudes derived from a spatial PCA analysis of the data were correlated with clinical measures of schizophrenia symptomatology. Results: Temporal and spatial PCA analyses of control data revealed a fronto temporal subcomponent in the beta analysis and both a midline and later frontotemporal subcomponent in the gamma analysis. For beta, higher suppression P50 amplitudes were not associated with greater disorganized symptoms and exploratory analyses indicated an inverse relationship. For gamma, lower amplitudes were not associated with greater positive symptoms. Conclusions: This study suggests that using either a beta or a gamma filter does not capture the relationship between clinical measures and P50 abnormalities in schizophrenia as does the traditional bandpass measure. This suggests that contributions from other frequencies may be most important in indexing P50 abnormalities in schizophrenia.
ID: 551740

GAMMA BAND SYNCHRONY AS AN ENDOPHENOTYPE FOR SCHIZOPHRENIA

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The synchronous activity of cortical regions has been posited as a means by which cognitive functions are carried out by the brain. Both the power and phase of high frequency gamma band activity is augmented during the perception of objects and appears to reflect the entrainment of neural responses during cognitive demands. Individuals with schizophrenia have exhibited both diminished gamma band power and synchrony during the viewing of simple objects and contours. We have found that unaffected individuals with genetic liability for schizophrenia exhibit diminished gamma band power when identifying simple objects in visual noise. To determine whether aberrant synchrony of gamma activity during the identification of objects is also associated with genetic liability for schizophrenia we acquired electroencephalograms (EEGs) from schizophrenia patients, first-degree biological relatives of schizophrenia patients, and nonpsychiatric control subjects while they viewed objects in visual noise. Schizophrenia patients and their relatives exhibited reductions in gamma band power during the identification of target objects. To obtain uniform resolution phase synchrony across brain regions we applied a novel reduced interference complex time-frequency distribution to avoid the trade-off between time and frequency evident in wavelet analysis. Analyses revealed diminished phase synchrony to be associated with decremented gamma power in schizophrenia patients. Additional analyses will test whether first-degree biological relatives exhibit similarly diminished gamma band phase synchrony to that of schizophrenia patients, and whether phase anomalies are associated with susceptibility genes related to glutamatergic and dopamanergic systems. To date, findings suggest that deficient neural communication may underlie object identification deficits in schizophrenia and that such a deficit may mark genetic liability for the disorder.
ID: 551730

ELECTROPHYSIOLOGICAL ANALYSES OF ADOLESCENTS AT RISK FOR SCHIZOPHRENIA

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Background: Puberty is a critical period for the maturation of the fronto-limbic and fronto-striate circuits critical for executive function and affective

processing. Puberty also coincides with the emergence of the prodromal signs of schizophrenia, possibly indicating an association between these two processes. Methods: Event-related potentials (ERPs) and brain oscillatory activity in support of executive attention and affective processing were compared in 24 healthy control (HC) subjects and 21 individuals at genetic risk for schizophrenia (GHR) between the ages of 9 and 18 years. Participants were matched for age, gender, ethnicity, and parental education. Electrophysiological recordings were obtained from 32 EEG channels while participants performed an emotional oddball task, where they identified rare visual targets while ignoring emotional and neutral distracter pictures. Results: Our preliminary ERP results showed significant differences between the high-risk and control groups in early sensory components, as well as in late cognitive components. In addition, brain oscillatory activity in low-frequency ranges was significantly reduced in the high-risk group. Conclusion: Inefficient cortical information processing during puberty may be an early indicator of altered brain function in children at risk for schizophrenia, and may represent a vulnerability marker for illness onset. Longitudinal assessments will further inform about their predictive value for illness onset in populations at high risk for psychotic illness.
ID: 551662

NEURAL RESPONSE TO IMAGES FEATURING SYMBOLIC THREAT IN SCHIZOPHRENIA PATIENTS: ERPS AND EVOKED AND INDUCED EEG ACTIVITY

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Investigation of emotional experience and motivated behavior in schizophrenia includes reports of both intact functioning and illness-related abnormalities. Many of these abnormalities involve behaviors that are clinically relevant (eg, display of flat affect, anxiety related to fears of persecution), but may prove quite complex with respect to their underlying cognitive architectures. As a basis for further study of the defensive motivational system, and more specifically, how the brain processes emotionally unpleasant information within the first second of stimulus perception, we recorded electroencephalographic (EEG) data while first-episode schizophrenia patients and healthy comparison subjects viewed neutral and negative images featuring symbolic representations of threat. Representations of threat varied systematically in order to permit examination of whether particular content categories, ranging from high (eg, attack, mutilation) to low imminent threat (eg, pollution, loss), elicit group-wise differences in electrophysiological responses that are not apparent when only super-ordinate affect categories (ie, negative, neutral) are considered. Event-related potentials (ERPs) previously shown to be sensitive to affective intensity of stimuli were derived. Additionally, concomitant segments of EEG data were subjected to time-frequency transformations to measure frequency band-specific changes in signal power and phase. Collectively, these measures reflect large-scale neural activity in primary and secondary visual cortex, as well as an extended network of regions that are sensitive to the motivational salience of stimuli and interact strongly with visual cortex. Initial analyses suggest that both patients and controls show strong modulation of ERP response amplitude, and EEG power and phase (particularly in the delta/theta and alpha frequency bands) by negative content category. Group differences appear more subtle and do not appear to be associated exclusively with any one type of negative image content. Relationships between ERP and EEG measures and clinical variables, as well as possibly interacting effects of gender, will also be considered. Finally, implications of the potential influence of affect and arousal on more cognitively demanding tasks will be discussed.
ID: 551645

GENETIC ASPECTS OF MOTOR INHIBITION IN PATIENTS WITH SCHIZOPHRENIA AND THEIR NON-PSYCHOTIC RELATIVES

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The basis of deficient cognitive control in schizophrenia has been characterized in terms of impaired motor inhibition. Several investigations have revealed that individuals with schizophrenia as well as their biological relatives exhibit abnormal striatal activation associated with the inhibition of motor and eye movements (Vink et al., 2006). In addition, recent work has identified that neural activity during response inhibition is associated with the catechol-O-methyltransferase (COMT) gene and presumably the availability of prefrontal dopamine (Kramer et al., 2007). We carried out a study to determine whether aberrant neural responses of schizophrenia patients and their biological relatives during motor inhibition were associated with the Val158Met polymorphism of the COMT gene. The sample consisted of patients with schizophrenia, their first degree relatives, and healthy controls recruited for a family study based at the Minneapolis VA Medical Center. We measured behavioral responses and event related potentials (ERPs) while administering a stop-signal task. Whole blood specimens were used to gather genetic information and to determine the COMT genotype on subjects. Consistent with manipulation of response demands behavioral data show an increase in response time for GO trials as expectancy of inhibition (ie, stop signal) increases. To date, electrophysiology data has been collected on 60 patients, 29 relatives, and 49 controls. We expect to find aberrant N2 and P3a ERP components in examining inhibition-related activity in schizophrenia patients and their relatives. We also predict that the Val158Met polymorphism of the COMT gene will associate with N2 and P3 abnormalities evident in the patient and relative groups. If hypotheses are supported, evidence would be consistent with the presence of anterior cingulate and prefrontal deficits marking genetic liability for schizophrenia and a role of the COMT gene and dopamanergic mechanisms in deficient inhibitory control in the disorder.
ID: 551618

NEURAL CORRELATES OF INHIBITORY MOTOR CONTROL IN SCHIZOPHRENIA PATIENTS AND THEIR BIOLOGICAL RELATIVES

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Several lines of research indicate that individuals with schizophrenia have poor inhibitory control. Evidence suggests that deficient inhibition may contribute to errant eye movements, poor episodic memory, and deficient cognitive control in the disorder. Functional magnetic resonance imaging studies of inhibitory control have revealed abnormal striatal and prefrontal activation in schizophrenia patients and their biological relatives during inhibition of motor movements. Nonetheless, little is known about the time-course of neural anomalies associated with poor inhibitory control in schizophrenia. To investigate the relationship of neural events to deficient inhibition in schizophrenia we carried out an event-related potential (ERP) study using a motor response task previously used to examine

schizophrenia patients and their relatives (Vink et al. 2006). In the present study participants completed a stop signal task that consisted of go only blocks in which participants responded to every trial and go/stop blocks where participants were required to inhibit their response to stop trials presented pseudo-randomly between go trials. Electrophysiological data has been collected on 60 patients with schizophrenia, 29 first degree biological relatives, and 49 community controls. We hypothesize that schizophrenia patients and their relatives will exhibit impaired inhibitory control, and that these abnormalities will be associated with the amplitude of P3a and N2 ERP components. These components have been associated with decision making and early response inhibition processes in other investigations and appear to represent neural processes underlying response inhibition. A comparison will be made across schizophrenia, relative, and control groups contrasting ERP amplitudes elicited from go trials during go only blocks with those during go/stop blocks, to investigate the effects of increased inhibitory demand on motor control. To date, behavioral data are consistent with slowed response inhibition associated with schizophrenia.
ID: 551616

THE EFFECTS OF INTRAVENOUS SYNTHETIC Δ9-TETRAHYDROCANNABINOL ON P300 AND N300 EVENT-RELATED POTENTIALS DURING TARGET AND NOVELTY PROCESSING

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This study investigates the effect of intravenous synthetic Δ9-tetrahydrocannabinol (THC) on P300 and N300 event-related potentials (ERPs) to target and novel stimuli in a 3-stimulus auditory oddball paradigm. Cannabis use is implicated as a risk factor for psychotic episodes and persistent psychosis. An acute challenge of THC leads to a state modelling of psychotic symptoms; however, the precise neural mechanisms underlying the effect of THC on behaviour and cognition are unclear. One of the most robust neurobiological abnormalities observed in schizophrenia is a reduction in auditory P300 amplitude. Specifically, reductions in frontal and left temporal P300 amplitude have been associated with psychotic symptoms. The current study used ERP methods to test a THC model of psychosis. A randomised double-blind placebo controlled within subject design was used to investigate the effect of 1.25 mg intravenous THC relative to placebo on ERPs in 10 healthy adults. Auditory P300 and N300 amplitudes were measured in response to target and novel stimuli in a 3-stimulus auditory oddball task. The positive and negative syndrome scale (PANSS) was used to assess psychiatric symptoms. Data were analysed using repeated measures analysis of variance (ANOVA). Bilateral frontal and temporal P300 amplitude in response to targets was reduced under THC compared to placebo conditions. A more specific right hemisphere effect was seen for novelty P300 amplitude (P3a) and N300. There were no significant effects for P3a and P3b peak latency, perhaps indicating individual memory encoding and response strategies. Left temporal P300 effects were not found in the THC condition, indicating their possible specificity to schizophrenia. There was a trend for an increase in positive symptoms during the THC condition. A trend was found for reduced response time to targets in the THC condition compared to placebo. The current results support THC as a neuropharmacological model of schizophrenia. It is hypothesised that THC-mediated P300 amplitude reductions underlie working memory deficits during THC intoxication. These deficits are thought to impair the perception of novelty, which affects context updating and memory storage. These results may translate to psychosis, in that in-

creased endocannabinoid signalling may be responsible for reduced P300 amplitude in psychosis.
ID: 551614

AUDITORY HALLUCINATIONS AND THE CORTICAL RESPONSE TO AUDITORY STIMULATION AND SPEECH IN SCHIZOPHRENIA: AN ELECTROPHYSIOLOGICAL IMAGING (LORETA) REGION OF INTEREST STUDY

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Gamma (γ) frequencies have been associated with the sensory encoding and processing of auditory information, with auditory hallucinations (AHs) being associated with excessive γ. This finding may reflect a hyperconnectivity, which in turn could be associated with excessive processing and impaired sensory integration. Imaging studies have implicated the superior temporal cortex (STC), the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC) in AHs, and it appears that the abnormality in which the left PFC influences the left STC is a result of the failure of the ACC to modulate their interactions. Given this background, the purpose of this study was to use gamma band oscillations (GBOs) to examine inter-regional synchrony in hallucinating (HP) and non-hallucinating (NP) schizophrenia patients during passive recording conditions. We were also interested in examining how these inter-regional synchronies varied with the increasing of hallucinations. As a number of studies have suggested that hallucinations worsen in the presence of speech and especially in the presence of unintelligible speech, the study also examined GBOs in response to external speech presented during background noise conditions, and during a silence condition. There were 3 groups of 12 participants: HPs, NPs and healthy controls. EEG recordings were taken under 3 sound conditions presented randomly, and a separate recording under silent conditions. The sound conditions consisted of frequent and rare consonant-vowel syllables being presented once every ½ second during no-noise or simultaneously with white noise or traffic noise. For each of these 4 conditions, scalp electrical activity was recorded with a 40 channel system and artifact free activity was submitted to spectral analysis for computation of γ amplitudes, which were plotted across the scalp. Low-resolution electromagnetic topography (LORETA) analysis was used to estimate current source density (CSD) and its distribution in the cortex. CSD were also calculated for regions of interest (ROI) and these were used to compute coherence values between PFC, STE and ACC regions. These ROI values were computed for the background noise conditions, as well as for the discrete (external speech) sounds. Relative to NPs, we expect greater GBO and greater GBO synchrony in HPs. Furthermore, we expect this pattern to be more evident in the speech/noise conditions.
ID: 551577

AROUSAL EXPERIENCE IN SCHIZOPHRENIA: SUBJECTIVE AND PHYSIOLOGICAL ASSOCIATIONS

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Background: Since Bleuler it has been widely acknowledged that disturbed affective arousal is a primary characteristic of schizophrenia. However,

despite a large number of studies on affective (emotional) experience, relatively little research has focused on the experience of arousal in schizophrenia and findings are inconsistent. Moreover, it remains unclear whether underlying physiological responsivity in schizophrenia individuals (SZ) is in concordance with subjective experiences of arousal, and how this compares to non-schizophrenic individuals. Method: Skin conductance (SC) was assessed in 20 medicated SZ and 30 control subjects (CS) during exposure to picture ($n = 40$), sound (40), and printed word (40) stimuli that varied in level of arousal and valence connotation. Results: Subjective ratings indicated a similar response pattern in SZ and CS, but SZ demonstrated an attenuated subjective arousal experience; very calm stimuli were experienced as less calm, and very arousing stimuli as less arousing. For physiological findings, SZ exhibited overall reduced SC responses to all stimuli. Despite this, SZ and CS showed a similar SC response pattern to stimuli rated very calm and moderately arousing; lower SC responsivity to very calm stimuli. A marked difference between groups was evident for stimuli rated as very arousing. As expected, CS exhibited increased SC responsivity to all stimuli rated as very arousing. SZ showed a decrease in SC responsivity to very arousing stimuli based on normative ratings; lowest SC responsivity to stimuli rated as very arousing that also had a normative rating of very arousing. Background: Our findings suggest a physiological deficit in arousal experience in schizophrenia, which may be particularly related to highly arousing stimuli. Other schizophrenia studies have demonstrated deficits or attenuated responses in neurophysiological processing of stimuli of high emotional valence (fear), and the findings presented here suggest that similar anomalies may exist for highly arousing stimuli (stressors, threats). This dissociation between physiological and subjective arousal experiences may contribute to the restricted affective arousal often associated with schizophrenia.
ID: 551576

EFFECTS OF ATTENTION ON ERP COMPONENTS FOLLOWING P50 SUPPRESSION IN SCHIZOPHRENIA PATIENTS

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Aberrations in attention and sensory perception have long been associated with schizophrenia. It has been proposed that these attentional deficits may be due to an inability to filter out extraneous sensory information, resulting in an inability to process and integrate sensory stimuli from the environment. A deficit in this filtering process, as indexed by the P50 component of the event-related potential (ERP), has been demonstrated in patients with schizophrenia across different phases of the illness. Recent research suggests that disruption in P50 suppression in patients with schizophrenia may be associated with abnormalities in subsequent neurocognitive processes (Boutros, Korzyukov, Jansen, Feingold, and Bell, 2004). The first phase of the present study was designed to elucidate whether disruption of P50 suppression influences later ERP components in patients with schizophrenia. Ratio measures of successive components (eg, N100, P200) were examined to determine if suppression is also diminished at these later components. To establish whether suppression of these components may be related to one another, the second phase of this study involved single-trial analysis in healthy participants and patients with schizophrenia. The third phase of this study evaluated the effects of directing voluntary attention during a P50 paired-stimulus paradigm. The P50 ratio in schizophrenia has been shown to be transiently enhanced through the manipulation of attention to the first stimulus in a pair and diminished by directing voluntary attention to the second stimulus (Yee et al., in submission). Preliminary results indicate that in comparison to healthy participants, schizophrenia patients showed increased ratio values at later ERP components,

paralleling results finding disruption of P50 suppression. Additionally, it appears that directing attention to the first stimulus may not necessarily enhance suppression at these later components in either sample, but that voluntary attention directed to the second click resulted in reduced suppression of later ERP components, with the strongest effects observed in healthy comparison subjects. These findings suggest that although gating abnormalities extend beyond the P50 component, it may not be possible to sustain attentional or top-down modulation in schizophrenia beyond a very early stage of auditory processing, consistent with abnormalities in fronto-temporal connectivity (Mathalon, Heinks, and Ford, 2004).
ID: 551515

INCREASING VISUAL STIMULUS COMPLEXITY AND EVENT-RELATED POTENTIALS IN SCHIZOPHRENIC PATIENTS

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Disturbances of global information processing as well as disturbances of specialized networks are fundamental in schizophrenia. The aim of this study was the comparative examination in healthy subjects and schizophrenic patients of different ERP-generating networks by gradually increasing the complexity of a visual stimulus. We examined 19 patients (6f, 13m) and 15 (7f, 8m) healthy subjects, matched for age and education. ERP were elicited by black and white patterns (21x16 squares) of increasing complexity: i) regular checkerboard (= simple stimulus), ii) irregular random pattern (= complex pattern stimulus), and iii) random pattern with embedded letter (= complex semantic stimulus). The number of black/white squares was 1:1 for all stimuli. All stimuli had the same task relevance (button press). ERP were analysed for 2000ms (500ms pre-trigger) from Fz,Cz,Pz, and from C3/C4 and P3/P4. Bandpass was 0.02 to 30 Hz, sampling frequency 256 Hz. ERP were evaluated by comparisons of the curves (Blair and Karniski) and of the area under the curves (AUC). In both groups, all visual stimuli generated positive ERP between 300–500 ms, larger in healthy subjects ($8\mu V$—$10\mu V$) than in patients ($5\mu V$—$6\mu V$), potentials remaining positive with about $2\mu V$ till the end of analysis time(1500 ms). In healthy subjects only, the ERP of both complex stimuli differed significantly from the simple stimulus by a distinct negative component of about $-4\mu V$ between 400–600 ms (N500). The ERP of the complex semantic stimulus differed significantly from the complex pattern stimulus by a late positive component between 900–1500 ms. Both effects were not found in schizophrenic patients. Stimuli of same modality and task relevance but different complexity generate different ERP, pronounced in healthy subjects only. The introduction of irregularity (simple to complex pattern stimulus) seems to generate an informational content, which seems to activate an information-related ERP generator, leading to the N500 component. The further introduction of a semantic content seems to activate a further neuronal processor, resulting in a prolonged positive potential after 600 ms. Both of these effects are missed in schiophrenic patients. This reveals a distributed disturbance of information processing in schizophrenia, affecting multiple neuronal networks.
ID: 551510

COMT AND HIPPOCAMPAL FUNCTION: THE COMT INHIBITOR TOLCAPONE MODULATES FIELD EXCITATORY POSTSYNAPTIC POTENTIALS IN CA1 SCHAFFER COLLATERAL AND PERFORANT PATHWAYS

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Catechol-O-methyltransferase (COMT) metabolises catecholamines and has been shown to modulate prefrontal dopamine levels. Inhibition of COMT improves PFC-dependent task performance and a functional polymorphism in the COMT gene (Val158Met) has been linked with performance on a range of cognitive tasks. COMT has therefore attracted attention as a possible therapeutic target for treating cognitive dysfunction in schizophrenia. More recently, evidence has emerged for a role for COMT outside of the PFC: the Val158Met polymorphism has been associated with hippocampal activation during emotional processing, consistent with the high expression of COMT mRNA in this region. Therefore, we investigated the effect of the COMT inhibitor tolcapone on CA1 Schaffer collateral and perforant pathway field excitatory postsynaptic potentials (fEPSPs) in hippocampal slices. Hippocampal slices (350 μm thickness) were prepared from male Hooded Lister rats aged between P35–P42, transferred to an interface chamber and superfused continuously with artificial cerebrospinal fluid (aCSF). After resting for two hours, stimulating electrodes were placed in the stratum radiatum and the stratum-lacunosum moleculare of CA1, to evoke fEPSPs via the Schaffer collateral and perforant pathways, respectively. Field potentials were monitored via a recording electrode placed in the stratum radiatum of CA1. Tolcapone was perfused in aCSF once fEPSP slopes had stabilised. Between 30 and 60 minutes post-perfusion, 20 μm tolcapone dramatically suppressed fEPSP slope in both the Schaffer collateral and the perforant pathways (by approximately 60% after 60 minutes). Investigation of the effects of other doses of tolcapone, and their reversibility by dopamine receptor antagonists, are ongoing. We demonstrate a striking effect of the COMT inhibitor tolcapone on both Schaffer collateral and perforant pathway field potentials. These preliminary data support emerging evidence of a role for COMT in modulating hippocampal function, in addition to its importance in PFC. Our research is currently investigating the extent to which tolcapone's effects on Schaffer collateral and perforant pathway fEPSPs is dopamine-dependent and the dose-dependency of this effect. Such studies are critical, given the marked non-linearity of dopamine's effects on cortical function, and the potential roles of COMT in both the pathophysiology and pharmacotherapy of schizophrenia.

ID: 551470

THE EFFECT OF INTRAVENOUS SYNTHETIC THC ON EEG OSCILLATIONS DURING A SELF-PACED MOTOR TASK

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Electroencephalogram (EEG) oscillations have been shown to be altered in schizophrenia and it has been hypothesised that deficits in synchrony may be involved in the disease process. It has previously been reported that in a self-paced motor task inter-trial coherence at gamma frequencies is reduced in subjects with schizophrenia. An acute challenge of Δ9-tetrahydrocannabinol (THC) can trigger psychotic symptoms, and cannabis use is a risk factor for development of schizophrenia. The purpose of this study was to investigate the effect of acute THC on the synchrony and amplitude modulation of EEG oscillations during a self-paced motor task. A randomised, double-blind, within subject, design was used with 10 healthy adults. THC intravenous (1.25 mg), or placebo, was administered prior to participants completing a self-paced button pressing task. EEG was recorded using a 64 channel electrode cap based on the 10–20 system. Wavelet analysis was used to determine amplitude, spatial synchrony and inter-trial coherence of the Mu and gamma rhythms at frontal, central and parietal electrode sites. EEG oscillations were found to be significantly altered in the drug state compared to placebo. Aberrant neural oscillations may be related to the positive psychotic symptoms and changes in consciousness produced by THC.

ID: 551326

ACTIVATION OF CB1-R DISRUPTS SENSORY GATING AND NEURONAL SYNCHRONIZATION IN RATS—RELEVANCE TO SCHIZOPHRENIA

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Impaired auditory gating and abnormal neuronal synchrony are considered as indicators of dysfunctional information processing in schizophrenic patients, and possible underlying mechanisms of their impaired sensory and cognitive functions. Since cannabinoid receptors and endocannabinoids have been linked to psychiatric disorders, including schizophrenia, the aims of the present experiments were to evaluate the effects of cannabinoid-1 (CB1) receptor activation on sensory gating and neuronal oscillations in rats. In our experiment, auditory sensory gating has been recorded from the hippocampus (CA3) and entorhinal cortex in anaesthetized rats. Neuronal network activity was recorded from the hippocampus (CA1, CA3), medial septum, entorhinal cortex and medial prefrontal cortex. Firing rate and oscillatory activity of septal single units were monitored simultaneously with hippocampal and cortical field potential oscillations in anaesthetized rats. In the auditory gating experiment, event-related spectral perturbations and inter-trial coherence analysis were applied to hippocampal and cortical recordings. In freely-moving rats, hippocampal and cortical oscillations were monitored in home cage and in rats exposed to novel environment. Effects of systemic administration of the selective CB1 receptor agonist CP-55940 were evaluated on these parameters. Thus, CP-55940 significantly disrupted auditory gating both in the hippocampus and entorhinal cortex via interfering with event-related network oscillations in anaesthetized rats. Spontaneous theta field potential oscillations were disrupted in the hippocampus and entorhinal cortex, with simultaneous interruption of theta-band oscillations of septal neurons. Administration of the CB1 receptor antagonist AM-251 reversed both the agonist-induced gating deficit and the diminished oscillations. In freely-moving rats, CP-55940 significantly reduced theta and gamma power in the hippocampus, whereas in the entorhinal cortex only gamma power was attenuated. However, novelty-induced theta, beta and gamma activities were significantly diminished by CP-55940 both in the hippocampus and entorhinal cortex. Our data indicate that activation of CB1 receptors interferes with neuronal network oscillations and impairs sensory gating function in the limbic circuitry, further supporting the connection between cannabis abuse and increased susceptibility of developing schizophrenia spectrum disorders.

ID: 551293

THE STABILITY OF PREPULSE INHIBITION OF THE STARTLE REFLEX IN SCHIZOPHRENIA: A 5 YEAR FOLLOW-UP STUDY OF ANTIPSYCHOTIC NAÏVE, FIRST-EPISODE SCHIZOPHRENIA PATIENT PRELIMINARY RESULTS

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Deficits in information processing appear to be core features in the pathogenesis of schizophrenia. Prepulse inhibition of the startle response (PPI) is an operational measure of sensorimotor gating. PPI deficits are generally regarded as endophenotypes for schizophrenia. However, the stability of PPI both over time, and during the course of antipsychotic treatment, is still largely unclear. In an earlier study, we reported that neither a three months treatment with zuclopenthixol (typical antipsychotic) nor with risperidone (atypical antipsychotic) improved the PPI deficits of antipsychotic naïve, first-episode patients with schizophrenia. The current study is

a 5 year follow-up investigation of that original study. At baseline, 25 drug-naive first-episode schizophrenic patients and 23 healthy controls matched for gender and age, participated in the project. Three PPI measures were examined at baseline, after 3 month of randomized antipsychotic treatment (risperidone or zuclopenthixol) and after 5 years follow-up. Currently, 18 patients and 16 healthy controls were reexamined at the 5 year follow-up. Patients showed PPI deficits compared to healthy controls at baseline. At the 5 years follow-up no significant group differences were found although only one of the PPI measures improved significantly in the patients. The current preliminary results support the notion that PPI deficits are fundamental trait markers of schizophrenia that are already present at an early stage in the development of the disease. However, the deficits seem to diminish over time, most probably due to the disease process it self, or to the effects of antipsychotic treatment.
ID: 551250

TIME-FREQUENCY ANALYSIS OF PREATTENTIONAL COGNITION IN SCHIZOPHRENIA PATIENTS IN TAIWAN

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Disturbances of auditory information processing have repeatedly been shown in schizophrenia. Event-related potentials are currently utilized to study information processing under the influence of neuropsychiatric disorders and are candidate endophenotypes of schizophrenia. This study tried to focus on event-related potential components such as P50 and mismatch negativity (MMN) between control and schizophrenia groups in Taiwan. In addition, this study also compared the time-frequency analysis and averaged event-related potentials of these event-related potentials. In 50 schizophrenia patients and 50 controls EEG was recorded using an auditory paired click paradigm for P50 and duration MMN (500msec SOA) for MMN. Participants are seated in a comfortable recliner in a sound-attenuating, electrically shielded booth and instructed to relax with his/her eyes open and to focus on a fixation point (P50 session) or the video monitor (MMN session). The stimuli are generated by and data is recorded by Neuroscan STIM and ACQUIRE system. Electrodes are used at up to 36 recording sites. Auditory stimuli are presented to subjects binaurally via foam insert earphones. Written informed consent were all obtained from the above subjects. In addition to the effect of clozapine versus other antipsychotics was confirmed, the relationship of psychopathology dimensions were also explored. In time-frequency analysis of single trial MMN, schizophrenia have lower inter-trial phase coherence than controls. The induced gamma activity did not show large difference between controls and patients. The results support the view that deficits at sensory preattentive information processing are essential in schizophrenia patients. These deficits may also play a role in the basic integrated neural network activity.
ID: 551095

SOURCE LOCALIZATION OF SENSORY GATING: CONCURRENT ASSESSMENT OF EEG AND FMRI, PRELIMINARY RESULTS

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Reduced sensory gating appears to be among the core features in schizophrenia. The sources of sensory gating however are largely unknown. The aim of the current study is to identify these sources. To our knowledge this is the first study in which concurrent EEG and fMRI assessment of P50 suppression was performed. Twenty healthy male volunteers were tested with identical paradigms in two separate sessions: an EEG setting, and an EEG concurrent with fMRI setting. Instead of the classical P50 suppression paradigm an especially constructed paradigm was used for the fMRI environment, in which the auditory stimuli were replaced by weak electrical stimuli. Two interstimulus intervals (ISIs) were used: 500 and 1000 ms. The preliminary results from the 16 subjects who were analyzed in the EEG setting and 9 from the fMRI setting so far showed significant P50 suppression only in the 500 ms interval, not in the 1000 ms ISI. The contrast between the 1000 ms and 500 ms ISI revealed activation in the temporal region based on the results from the 9 subjects who were analyzed so far in the fMRI setting. The results indicate that the EEG data between the two settings are compatible. Furthermore the electrical P50 suppression paradigm gives results that are consistent with classical auditory paradigms. The fMRI results suggest that the temporal cortex is involved in P50 suppression.
ID: 551072

SOPRES (STUDY ON THE PSYCHOPATHOLOGICAL PROGRESS OF THE PRE-PSYCHOTIC STATE) IN TAIWAN: EVENT-RELATED POTENTIAL FINDINGS

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A prospective study Study On the psychopathological progress of the PRE-psychotic State, SOPRES was initiated in Taiwan and sponsored by Taiwan National Health Research Institute since 2006. Four psychopathological stages (First episode psychosis; Very high risk stage; Intermediate risk stage; Very early stage) and normal control were recruited for comparison of P50/N100/MMN results. Ninety-six prodrome patients and fifty controls were recruited. Participants are seated in a comfortable recliner in a sound-attenuating, electrically shielded booth and instructed to relax with his/her eyes open and to focus on a fixation point (P50 and N100 session) or the video monitor (MMN session). The stimuli are generated by and data is recorded by Neuroscan STIM and ACQUIRE system. Electrodes are used at up to 36 recording sites. Auditory stimuli are presented to subjects binaurally via foam insert earphones.P50 and N100 suppression were assessed with an auditory double-click paradigm, while MMN were given with standard (90%, 50 msec duration) and deviant (10%, 100 msec duration) tones presented in pseudorandom order and 500msec SOA. Certained P50/N100 suppression indices and MMN differed between groups. Among the analyzed P50 parameters, the P50 suppression ratio reached significant differences between healthy controls and very high risk stage patients, and between healthy controls and the first episode psychosis subgroup. The results support the view that deficits of sensory preattentive information processing may be essential in prodromal patients, especially those with higher clinical risk.
ID: 551038

EVIDENCE FOR NEURODEGENERATION? FURTHER REDUCTION IN P300 AMPLITUDE OBSERVED OVER 3 YEAR FOLLOW-UP IN FIRST EPISODE SCHIZOPHRENIA

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A reduction in the amplitude of the P300 waveform in the auditory oddball paradigm in schizophrenia is a well replicated finding. However very few studies have examined the stability of this finding over time and none in a group of patients with their first episode of schizophrenia. This study followed up 25 subject with their first episode of schizophrenia (male = 17, female = 8) over a 2–3 year period as part of a larger program of research. The subjects with schizophrenia were noted to have decreased P300 amplitude at their initial recording when compared to normal controls. This reduction in P300 amplitude increased over the 2–3 year follow-up despite a reduction in symptomatology. This finding was not explained by changes in overall medication burden. This study suggests that the reduction in P300 amplitude continues to develop over the early stages of schizophrenia. This is at odds with other work that has observed stability in the P300 component over similar periods of time in subjects with chronic schizophrenia. One possible explanation for this finding is that the P300 amplitude changes reflect an ongoing pathological process that has stabilised with chronic illness.
ID: 551016

TREATMENT RESISTANT P300 ABNORMALITIES IN A LARGE GROUP OF ANTIPSYCHOTIC NAÏVE, FIRST-EPISODE PATIENTS WITH SCHIZOPHRENIA

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Evidence is accumulating that cognitive deficits form core features in schizophrenia. It has been suggested that treatment with atypical antipsychotics can ameliorate these deficits. However, studies have often been confounded by patients either being medicated or chronically ill, making it hard to differentiate between medication effects and progress of the disease. In addition they frequently suffer from low subject populations, giving rise to power issues. In the present study the influence of a six months treatment period with quetiapine (atypical antipsychotic) was investigated on psychophysiological parameters of selective attention in a large group of first episode, antipsychotic naïve schizophrenia patients and age and gender matched healthy controls. Thirty-four antipsychotic naïve patients with first-episode schizophrenia and 40 age and sex matched healthy controls were tested in a selective attention paradigm at baseline and at 6 months follow-up. The patients were treated with quetiapine during the period between baseline and follow-up, the controls received no treatment. Both at baseline and at follow-up, the patients showed highly significant reduced P300 amplitudes compared to the healthy controls. No treatment effects were found. The results indicate that deficits in P300 amplitude, and thus attention deficits, are present at an early stage in the development of schizophrenia. Furthermore, the results indicate that a 6 months treatment period with quetiapine does not ameliorate these attention deficits. The results are consistent with the concept that P300 amplitude deficits represent stable endophenotypes for schizophrenia.
ID: 550938

EFFECTS OF WORD FREQUENCY ON SEMANTIC MEMORY IN SCHIZOPHRENIA

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Semantic memory deficit may represent a biological marker for schizophrenia. Findings based on the N400 component of the event-related brain potential, which reflects on-line access and integration processes, indicate patients are compromised in discriminating the semantic features of words, and that executive function may play a key role. Typical antipsychotic medication (haloperidol) appears to improve, but not normalize, patients' N400 priming effect, which is consistent with moderating vulnerability-trait status. This hypothesis requires examination based on newer generation medications. In the present study, N400 was elicited with a semantic-priming paradigm designed to engage executive processes (slow presentation rate, resource-demanding task). N400 was recorded in 14 schizophrenia outpatients (M = 34.3 yrs) and 14 healthy controls (M = 31.4 yrs) while they performed a delayed letter probe task that was incidental to the linguistic characteristics of word pairs, which varied in semantic association (related, unrelated) and word frequency (very low to very high). Prime-target stimulus-onset asynchrony = 1 s. At testing, patients were receiving clinician's-choice atypical antipsychotics; patients and controls were group-matched for age, gender, and demographics. The N400 priming effect differed between groups ($P < .01$), with only controls showing the typical pattern of greater N400 negativity for unassociated than associated words. N400 to word frequency also differed between groups ($P < .05$); controls' N400 became more negative with decreasing word frequency ($P < .05$) while patients failed to discriminate word frequency ($P = $ n.s.). Cumulative findings showing N400 priming disturbance in patients receiving both traditional (typical) and newer generation (atypical) antipsychotics are consistent with the hypothesis that semantic memory deficit represents a moderating trait for schizophrenia. Results also support the assumed importance of executive processes for semantic memory function in schizophrenia, and implicate a failure to engage brain processes associated with the access and integration of stored information.
ID: 550924

EFFECTS OF CHRONIC EXPOSURE TO CANNABINOIDS ON SENSORY GATING AND NEURAL SYNCHRONIZATION IN HUMANS.

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Recent research has shown that schizophrenia (SZ) may be associated with abnormalities of the endogenous cannabinoid system. This line of evidence is in accord with numerous longitudinal studies, which have demonstrated increased rates of psychosis in long-term cannabis users. However, it remains unclear how chronic exposure to cannabinoids is related to the emergence of SZ-like perceptual/cognitive features. Given that cannabinoid receptors (CB1) are thought to modulate neural oscillations necessary for sensory and cognitive processes, it has been postulated that a possible neurophysiological link between SZ symptomatology and cannabis' neurobehavioral effects involves alterations in neural synchrony. The current set of studies therefore assessed the effect of chronic cannabis use on neural synchronization (using EEG) during paired-click auditory

P50 gating and broadband (5–50 Hz) auditory steady-state responses (ASSRs), both tasks which have been consistently shown to be aberrant in SZ. As expected, it was found that cannabis users exhibited increased SZ spectrum traits (schizotypy) compared to drug-naive controls, and that overall levels of cannabis chronicity (total years of use) was positively correlated with schizotypy scores. In terms of auditory P50 gating, cannabis users demonstrated abnormal gating in a pattern similar to that previously reported in SZ. Moreover, time-frequency analyses revealed that the cannabis-related gating deficit observed at click S2 was accompanied by altered theta and gamma oscillations. Similarly, the effect of chronic cannabinoids on the ASSR revealed a selective decrease in spectral power at 5 Hz (theta-range) and 40 Hz (gamma-range). Taken together, these frequency-specific deficits in the generation and maintenance of theta and gamma-range neural synchrony are in concurrence with recent work in animals, demonstrating a general role of the cannabinoid system in mediating GABAergic network oscillations. Further, these data indicate that chronic cannabis use, mostly likely via CB1 downregulation/desensitization, induces psychotomimetic features through dysregulation of the GABA system.
ID: 550913

HERITABILITY OF ACOUSTIC STARTLE, PREPULSE INHIBITION AND ONSET LATENCY IN SCHIZOPHRENIA AND CONTROL FAMILIES

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Background: Patients with schizophrenia have difficulty screening out irrelevant stimuli, and often have the experience of sensory flooding. These "gating deficits" may contribute to the thought disorder, cognitive fragmentation, and hallucinations that are so debilitating to these individuals. The acoustic startle response is a reflex contraction of the skeletal muscles in response to a sudden acoustic stimulus. The modulation of this reflex by a preliminary nonstartling stimulus is termed prepulse inhibition of acoustic startle (PPI), a paradigm used as an operational measure of sensorimotor gating. Many patients with schizophrenia have impaired PPI, and several lines of evidence suggest that PPI may represent a heritable endophenotype in this disease. The purpose of this study was to examine heritability of acoustic startle measures in a sample of schizophrenia and control families. Methods: We examined baseline startle, habituation, PPI, and onset latency of the startle response in 40 schizophrenia patients (SCZ), 58 of their first-degree relatives (SCZ-FAM), and 100 healthy controls (CONT) from 45 families. The startle session consisted of pulse alone trials to evaluate baseline startle, and prepulse+pulse trials with interstimulus intervals of 30, 60 or 120 ms between the prepulse and pulse. Heritability analyses were conducted using a variance-component approach that adjusted for age, gender, race and smoking status. We also examined differences in startle measures between subject groups. Results: We found a significant heritability of 45% for PPI at the 60-ms interval, and 67% for baseline startle. Onset latency heritability estimates ranged between 39% and 90% across trial types. There was no significant heritability of startle habituation. We did not find differences between CONT and either SCZ or their families for PPI, baseline startle, or habituation. Onset latency was longer in SCZ and SCZ-FAM than CONT. Conclusions: PPI at the 60-ms interval, baseline startle, and onset latency were significantly heritable in this sample of schizophrenia and control families. No PPI impairments were detected in SCZ or SCZ-FAM compared to CONT. Latency was longer (ie, slower) in SCZ and SCZ-FAM than in CONT. Our data indicate that assessing family members of schizophrenia patients in a between group design may not be sufficient to detect the heritability of putative endophenotypes. Supported by VA Merit Review Grant (E Duncan).
ID: 550870

ALTERED D2 MODULATION OF PREFRONTAL CORTICAL INTERNEURONS IN DEVELOPMENTAL ANIMAL MODELS OF SCHIZOPHRENIA

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We have recently shown that rats with a neonatal ventral hippocampal lesion (NVHL) exhibit an abnormal periadolescent maturation of prefrontal cortical interneurons. Specifically, activation of D2 dopamine receptors becomes strongly excitatory on parvalbumin GABA interneurons during adolescence in naive rats, and this maturation does not occur in rats that wit a NVHL. Adult NVHL rats also display sensorimotor gating deficits and other behavioral anomalies similar to those observed with prenatal maternal infection. We tested whether an immune challenge localized to the hippocampus would cause similar deficits with intra-hippocampal injections of the bacterial endotoxin LPS during postnatal day 7–8. Adult rats with LPS, but not sham treatment exhibited deficits in prepulse inhibition of the acoustic startle response and increased levels on cytokines in several brain regions. Whole-cell recordings from fast-spiking interneurons revealed that slices obtained from sham treated animals exhibited the normal D2-mediated increase in excitability, whereas similar recordings in slices from LPS-treated rats failed to yield that response. Thus, the data show that activation of immune responses in the ventral hippocampus can yield anomalies similar to what a lesion or prenatal immune challenge may cause, suggesting that the hippocampal region may be a critical target of maternal infection.
ID: 551940

THE EFFECT OF ATTENTIONAL TASK ON PREATTENTIVE ERP MEASURES OF SENSORY PROCESSING IN SCHIZOPHRENIA PATIENTS

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Mismatch Negativity (MMN) and P3a are considered preattentive and automatic event-related potential components because they can be elicited in the absence of directed attention. Deficits on these measures reflect abnormalities in the earliest stages of sensory information processing. The degree of automaticity of MMN and P3a measures in nonpsychiatric subjects and schizophrenia patients, however, has been a topic of debate. The aim of the present study was to assess the role of attentional task manipulations on MMN and P3a in nonpsychiatric comparison subjects and schizophrenia patients. Standard ($P = .84$, 1000 hz, 50 ms), duration deviant (DD, $P = .08$, 1000 Hz, 100 ms), and white noise deviant (WND; $P = .08$, white noise, 50 ms) stimuli were presented with a fixed SOA of 500 ms across 4 identical

paradigms that varied in attentional task. During ERP recording, subjects 1) passively watched a silent video (Video), 2) performed the identical-pairs CPT (CPT), or were instructed to press a button when they heard either the 3) DD (Auditory Target Detection-DD; ATD-DD) or 4) WND (Auditory Target Detection-WND; ATD-WND). 20 schizophrenia patients and 20 control subjects participated. The patients had significant reductions in both MMN ($F_{1,33}$ = 5.47, $P < .05$) and P3a ($F_{1,33}$=12.62, $P < .001$) across conditions. No significant group X condition interactions were present for MMN or P3a amplitudes or latencies. Attentional (condition) effects were observed for both MMN ($F_{1,33}$ = 90.39, $P < .001$) and P3a ($F_{2,32}$=2.58, $P = .09$) where amplitudes in Video and ATD conditions were larger than in CPT conditions. A significant effect of condition on MMN ($F_{2,32}$ = 20.36, $P < .001$) and P3a ($F_{2,32}$ = 13.29, $P < .001$) latency was present with longer latencies observed in the ATD condition. The results of the present study indicate that there are subtle effects of attention on ERP components that can be elicited in the absence of directed attention (ie, "pre-attentive"). Across all tasks and conditions, schizophrenia patients had robust MMN and P3a deficits in response to task irrelevant stimuli.
ID: 555045

IMPACT OF NEUROCHEMICAL MANIPULATION ON SENSORY GATING IN HEALTHY SUBJECTS WITH LOW GATING LEVELS

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Deficient early information processing has been considered a central feature of schizophrenia spectrum disorders. A fundamental feature of information processing is the ability gate extraneous stimuli and to attend to salient features of the environment. Two operational measures of gating are prepulse inhibition (PPI) and suppression of the P50 event-related potential (P50 suppression). PPI refers to the attenuation of the startle reaction elicited by an intense pulse stimulus when its presentation is preceded by a weak prepulse. Similarly, in P50 suppression the first stimulus not only produces an auditory evoked potential (AEP) but also activates gating, resulting in a suppression of the P50 AEP to the second stimulus. Patients with schizophrenia exhibit deficits in PPI and P50 suppression. Since PPI and P50 can be induced in healthy volunteers, patients and rodents, and many findings related to the neural regulation of gating in animal studies have been supported by studies in humans, these paradigms represent excellent tools for translational research. These gating measures provide a unique opportunity to characterize the neurochemical basis of information processing and might be useful for the discovery of novel compounds with antipsychotic properties. We have developed a model to investigate the possible effects of antipsychotics on PPI and P50 suppression in healthy volunteers rather than in patients. Studying healthy volunteers has the potential to overcome confounding effects of previous medication exposure in patients, the wide range in severity of psychopathology and the generally non-random allocation of patients to treatment regimens. We previously found that the antipsychotic clozapine increased PPI in subjects exhibiting low baseline sensorimotor gating. In contrast, the antipsychotic haloperidol did not increase PPI in subjects exhibiting low baseline gating levels. Furthermore, haloperidol increased P50 suppression in those subjects with low P50 suppression levels, and reduced P50 gating in individuals with high P50 gating levels. The poster summarizes the results of further psychoactive compounds, including aripiprazole, risperidone and amisulpride which have been tested on our model of gating in healthy humans exhibiting low baseline gating. The data elucidate the applicability of our translational model to serve as a useful tool for the assessment of the efficacy of novel pharmacotreatment strategies for patients with schizophrenia.
ID: 554152

MATURATION OF TASK-RELATED NEURAL SYNCHRONY AND ITS RELEVANCE FOR THE DEVELOPMENT AND PATHOPHYSIOLOGY OF SCHIZOPHRENIA

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Schizophrenia is associated with an onset of symptoms during late adolescence and early adulthood, suggesting that aberrant brain maturation during this period may be involved in the expression of psychosis. In the current study, we examined task-related neural synchrony during human development as well as its impairment in patients with schizophrenia with electro- and magnetoencephalography (EEG, MEG) to examine the developmental role of synchronized, oscillatory activity in the pathophysiology of schizophrenia. Development of neural synchrony was investigated during perceptual integration in healthy children, adolescents and adult participants ($N = 68$) between 6–21 years. Perceptual integration was assessed with Mooney faces which consist of degraded pictures of human faces where all shades of grey are removed. EEG-recordings were analysed for spectral power as well as for phase-synchronisation of induced oscillations. Behavioral data showed that improved detection rates and reaction times with age were accompanied by pronounced increases in spectral power and phase-synchrony in the theta-, beta- and gamma-band. This development occurred in two distinct phases the transition being characterized by a marked reorganization of network topology and reduction of neural synchrony during adolescence. Following late adolescence, we observed significant increases of spectral power and phase-synchronization in the theta-, beta- and gamma-band during early adulthood. EEG/MEG experiments using the same experimental paradigm show that patients with first-episode and chronic schizophrenia are specifically impaired in indexes of neural synchrony that undergo important changes during adolescence. Thus, patients with schizophrenia are characterised by reduced high-frequency gamma-band activity and decreased long-range synchronisation in the theta- and beta-band during perceptual organisation. These data suggest close relations between the expression and the increase of temporal precision of synchronous, oscillatory activity, the reorganization and maturation of functional networks. Specifically, we propose that the pronounced changes in neural synchrony during adolescence reflect a critical developmental period that is associated with a major rearrangement of functional networks that may be related to the development of schizophrenia during the transition from adolescence to adulthood.
ID: 552124

MULTIBLOCK AUDITORY APPROACH IN SCHIZOPHRENIA PATIENTS

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The schizophrenia research area is one of the most challenging ones among the other pathologies, as the disorder requires advanced and combined efforts to verify onset and progress. This validates any method to tackle this problem with parameters including cost effectiveness, clinical relative

ease of application, test-retest etc. Accordingly, a multi-level auditory battery is being developed in our laboratory with different features. The presentation will provide the results from the same individuals mainly in three major test divisions: (A) the modified optimal MMN, (B) the modified DL and (C) simple auditory event related potentials. The modified MMN was applied while watching a black and white silent movie. The stimuli consisted of duration, intensity, frequency and location deviants applied in a pseudo-random design. The modified DL paradigm consisted of consonant vowels (/ba/, /da/, /ga/, /ka/, /pa/ and /ta/) presented through a headphone diotically or dichotically. The simple AERP consisted of stimuli of sinusoidal waveforms presented binaurally, where the target occurred in 20 percent of cases (1500 Hz standard, 1600 Hz target). The EEG recording was done using a 64-channel Neuroscan amplifier and the Embedded Microcontroller based Interactive Stimulus Unit (EMISU). The subject group was formed of 13 patients (age 23–54 years, mean 37.0) with schizophrenia (DSM-IV criteria) and 13 healthy control subjects (age 21–50 years, mean 34.2). The preliminary results were as follows: (A) duration and frequency deviations to be diminished in schizophrenia patients in respect to controls ($P < .05$). The MMN procedure, effectively distinguished the four above mentioned auditory specifications in both patients and controls. The grand average wave forms before subtraction point to a distinctly different wave pattern with clear responses in the controls. (B) The DL pointed to Right Ear Advantage both for patients and for controls. The error rates were higher for patients than controls ($P < .05$). C) The simple P300 component was diminished in patients ($P < .05$). The overall results could carry out various auditory components in a joined battery design. The cost-effectiveness, comparative ease of application, objective assessment features can become useful parameters for monitoring the brain information processing in schizophrenia as well as other cases. (Supporting projects DEU.2006.KB.SAG.038–017).

ID: 552106

5. 5. Eye Movement Physiology

SCHIZOPHRENIA AND BIPOLAR PATIENTS MANIFEST A COMMON INTERMEDIATE PHENOTYPE OF DEFICIENT SENSORIMOTOR TRANSFORMATION

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Background: Pursuit eye tracking deficits that are regarded as intermediate phenotype for schizophrenia may result from distinct disturbances of neurocognitive processes including visual motion processing, sensorimotor transformation, or the utilization of predictive mechanisms. Which of these disturbances are the primary causes of the eye tracking phenotype, and whether they are present in other psychotic disorders is yet unclear. Methods: First-episode patients with either bipolar disorder ($N = 33$), major depression with psychosis ($N = 23$) or schizophrenia ($N = 73$) were matched to 111 healthy subjects. Participants performed three smooth pursuit paradigms at different target speeds (4°, 8°, 16°, 24°, 32°) to evaluate sensorimotor transformation and predictive pursuit abilities. All patients were unmedicated at the time of testing with 108 patients being antipsychotic-naïve and 21 patients having a median life-time exposure to antipsychotics of two weeks. Results: Pursuit initiation gain was impaired in patients with bipolar disorder and schizophrenia ($P = .014$) but bipolar patients initiated pursuit later than all other groups ($P = .007$). Visual motion processing during pursuit initiation as indicated by the saccade error in a step-ramp task was not impaired in any group. While maintenance pursuit gain with unpredictable ramp targets was reduced in all three patient groups compared to healthy participants ($P < .001$), bipolar patients exhibited more severe impairments than did patients with schizophrenia ($P < .001$) or psychotic major depression ($P < .001$). No difference between groups was found for smooth pursuit of predictive pursuit. Conclusions: During initiation and maintenance of pursuit of unpredictable targets, which are dependent on direct transformation of sensory input signals into motor commands, disturbances were more severe in patients with bipolar disorder than in patients with schizophrenia although both groups were impaired. In patients with psychotic major depression, sensorimotor transformation impairments were detected, but only during maintenance pursuit. These findings imply that psychotic disorders, especially bipolar disorder and schizophrenia, both manifest a common intermediate phenotype of impaired sensorimotor transformation abilities pointing to disturbances in fronto-striatal circuits. In contrast, core visual motion processing related to extrastriate area V5 appears to be unaffected in all three patient groups with psychosis.
ID: 549036

TAKING ANIMAL BEHAVIORAL PHARMACOLOGY PARADIGMS INTO CLINICAL TRIALS TO EVALUATE COGNITIVE OUTCOMES

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Selecting cognitive tasks for schizophrenia trials has many challenges. Investigators typically choose between well-standardized neuropsychological tests that tap into a generalized cognitive deficit vs. tasks that evaluate particular cognitive functions known to be regulated by specific brain circuits and transmitter systems chosen on the basis of drug mechanism of action. This presentation will make the case for the benefits of the latter approach using tests of sensorimotor skills, working memory, procedural learning and voluntary inhibitory control. It will contrast findings from neuropsychological and translational oculomotor testing and fMRI studies in untreated first episode patients examined before and 6-weeks after antipsychotic treatment. Data will be presented from our Pittsburgh and Chicago studies (now 60 total patients) where similar recruitment strategies, treatment and cognitive measures were used. The data shows robust pretreatment neuropsychological deficits in schizophrenia and marginal change after treatment, consistent with many studies. In the same patients, while the magnitudes of pretreatment oculomotor and neuropsychological deficits were similar, oculomotor measures had significantly greater sensitivity to the neurocognitive impact of antipsychotic treatment. Further, unlike the profile of modest consistent change of neuropsychological performance after treatment, oculomotor findings indicated greater post-treatment changes, some beneficial and some adverse. The neurophysiological findings are consistent with behavioral pharmacology research with nonhuman primates performing the same tasks after D2 antagonists are given. Preliminary data with fMRI studies using oculomotor tasks show treatment effects that are larger even than laboratory neurophysiological testing. These data will be used to illustrate the greater sensitivity and selectivity of translational neurophysiological measures compared to neuropsychological tests for assessing the neurocognitive effect of antipsychotic treatment. Such neuroscience measures may be useful cognitive outcomes in clinical trials—perhaps especially in Phase 2 proof of concept studies. Translational outcome measures that build on animal model platforms in which the neurophysiology and neurochemistry of brain systems supporting task performance are well characterized may be especially useful in this regard.
ID: 550508

IS MOTION PERCEPTION DEFICIT IN SCHIZOPHRENIA A CONSEQUENCE OF EYETRACKING ABNORMALITY?

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Background: Studies have shown that schizophrenia patients have motion perception deficit, which is correlated with poor eyetracking performance. These findings suggest that motion perception may cause eyetracking abnormality in schizophrenia. However, eye movement closely interacts with motion perception. In this study, we examined how the known eyetracking difficulties in schizophrenia patients may interact with their motion perception. Method: Two speed discrimination experiments were conducted in a within-subject design. In Experiment 1, the stimulus duration was 150ms to minimize the chance of eyetracking occurrence. In Experiment 2, the duration was increased to 300ms, increasing the possibility of eye movement intrusion. Regular eyetracking performance was evaluated in a third experiment. Results: At 150ms, speed discrimination thresholds did not differ between schizophrenia patients ($n = 38$) and controls ($n = 33$). At 300ms, patients had significantly higher thresholds than controls ($P = .03$). Furthermore, frequencies of eyetracking during the 300ms stimulus were significantly correlated with speed discrimination in controls ($P = .01$) but not in patients, suggesting that eyetracking initiation may benefit controls but not patients. The frequency of eyetracking during speed discrimination was not significantly related to regular eyetracking performance. Conclusions: Speed discrimination, per se, is not impaired in schizophrenia patients. The observed abnormality appears to be a consequence of impairment in generating or integrating the feedback information from eye movements. This study introduces a novel approach to motion perception studies, and highlights the importance of concurrently measuring eye movements to understand interactions between these two systems;

the results argue for a conceptual revision regarding motion perception abnormality in schizophrenia.
ID: 550203

BEHAVIORAL CHANGES FOLLOWING DAILY PRACTICE OF SACCADE TASKS IN SCHIZOPHRENIA

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It has been well documented that people with schizophrenia show impairment in tasks requiring executive control such as inhibition. A simple test of inhibition is the antisaccade task, which requires a glance towards the mirror image of a peripheral cue. The goal of the current study is to determine how practice on the antisaccade task changes performance on that task and on related tasks known to assess executive control. Participants with schizophrenia and healthy comparison subjects were assigned a single saccade task to practice daily—either antisaccades or prosaccades (glances towards a cue)—over a two-week period. Generalized executive control was evaluated at pre- and post-test using two tasks. First, an ocular motor delayed response (ODR) task was selected as a direct measure of changes due to practice on a related, but distinctly different, saccade task. Second, the Wisconsin Card Sorting Test (WCST) was selected as a means of evaluating whether changes in executive control could be generalized beyond saccade tasks. Preliminary results suggest that the healthy comparison group that practiced antisaccades showed improved antisaccade performance across the duration of the study, as well as improved performance on other executive function measures. The schizophrenia group that practiced antisaccades also showed an improvement in performance across executive control measures. The schizophrenia group that practiced prosaccades, however, showed poorer performance specifically on the ODR task by making more anticipatory saccades. In sum, practice with saccade tasks resulted in modest improvement in saccade task performance in both schizophrenia and comparison groups. An exception is that the schizophrenia prosaccade-practice group showed more disrupted performance. This study provides evidence that saccadic performance can be malleable within certain parameters. The results are also are interesting for their practical implications. If improvement on other tasks of executive control continues to be seen in the schizophrenia antisaccade practice group, it suggests that purposefully practicing executive control may be explored as a means of improving activities of daily living. This research was supported in part by a grant from the National Institute of Mental Health (MH076998) and by the University of Georgia Honors Program's Center for Undergraduate Research Opportunities and the CURO 2008 Biomedical and Health Sciences Research Fellowship.
ID: 551748

SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER, BUT NOT PSYCHOTIC DEPRESSION, SHARE INTERMEDIATE PHENOTYPE FOR RESPONSE SUPPRESSION DEFICITS DURING EARLY COURSE OF ILLNESS

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Background: Response suppression deficits due to reduced voluntary control of behavior have been investigated using antisaccade tasks and are considered a promising intermediate phenotype for schizophrenia. Disturbances in frontostriatal systems are believed to be the cause of this deficit. Recently, multiple similarities across schizophrenia and psychotic mood disorders have been demonstrated, including responsiveness to antipsychotic medications, MRI morphometry, genetic linkage findings, and cognitive performance deficits. Yet, few oculomotor studies have investigated the diagnostic specificity of this effect across psychotic disorders. Methods: Unmedicated first-episode psychosis patients with schizophrenia ($N = 31$), psychotic bipolar disorder ($N = 21$), or psychotic major depression ($N = 15$) and 45 age- and IQ-matched healthy participants performed gap/overlap antisaccade and visually-guided saccade control tasks. Results: Both schizophrenia and psychotic bipolar patients showed similar and higher antisaccade error rates than healthy individuals and psychotic depression patients whose performance did not differ. No impairment of the latencies of correct antisaccades was evident for any patient group. Also, no group differences were observed for the accuracy or speed of visually-guided saccades, indicating intact sensory-motor systems across patient groups. For all groups, gap trials resulted in greater antisaccade error rates and shorter antisaccade latencies as well as less accurate and faster reflexive saccades compared to overlap trials. Conclusions: Results suggest that a reduced ability to suppress context inappropriate behavior, reflected in increased antisaccade error rates, may represent a shared intermediate phenotype for schizophrenia and psychotic bipolar disorder. Contrary to one of our previous studies, psychotic depression patients did not demonstrate antisaccade performance impairments. These findings suggest that both schizophrenia and psychotic bipolar disorder patient groups may experience a disruption of the prefrontal-striatal circuitry, via similar or different pathophysiologies, causing comparable cognitive abnormalities across the disorders. Supported by R01 MH62134, R01 MH080066, NARSAD.
ID: 551541

THE RELATIONSHIP BETWEEN OCULOMOTOR MEASURES OF PREDICTIVE PURSUIT AND NEUROPSYCHOLOGICAL MEASURES OF WORKING MEMORY IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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Oculomotor deficits have been well-documented in patients with schizophrenia (SZ) and a subset of their unaffected relatives, likely reflecting alterations within the prefrontal cortex (FEF) and genetic liability for the disease. Investigation of specific components of the smooth pursuit eye movement system has shown deficits in the predictive pursuit mechanism as seen by a reduced gain (ratio of the eye velocity to target velocity) in response to a briefly invisible target. Newer techniques, such as a novel covert stabilization technique developed by Hong et al. (2007), allow more precise measurement of the brain mechanism underlying this predictive mechanism by stabilizing the target image on the fovea and eliminating overt awareness on target removal. Although fewer studies of eyetracking dysfunction have been conducted in patients with bipolar disease (BD), and particularly their families, some data have suggested deficits in affective disorders that parallel those seen in SZ. Independently, deficits in working memory have been established in both groups of patients and family members. The working memory system

has been hypothesized to be the cornerstone of executive function processes, mediated in the prefrontal cortex, and found to be impaired in these disorders. The primary goal of this research is to characterize the relationship between deficits in these two areas across both diagnostic groups and relatives, as working memory is thought to contribute to the predictive pursuit mechanism, and both may be promising endophenotypic markers of psychosis. Thus far 147 patients have been enrolled with diagnoses spanning the diagnostic categories as follows: 46 SZ, 30 schizophrenia relatives, 34 BD, 25 bipolar relatives, and 12 comparison subjects. A broad battery of neuropsychological tests and oculomotor tasks were performed as part of larger genetic phenotyping study. Results from neuropsychological measures of working memory (Wechsler Letter-Number Sequencing and Spatial Span) will be correlated with predictive pursuit measures of eyetracking, specifically predictive acceleration and predictive gain. Data from both a traditional measure of predictive pursuit abnormalities and from a newer novel covert stabilization technique developed by Hong et al. will be presented.
ID: 551212

PREDICTION IN SMOOTH PURSUIT OF SCHIZOPHRENIC PATIENTS

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Background: The mechanisms of smooth pursuit eye movement (SPEM) deficits in patients with schizophrenia are still under debate. Pursuit blanking experiments have been used to test prediction components of pursuit performance (eg, Becker and Fuchs, Barnes et al.). A recent pursuit blanking fMRI study (Nagel et al. 2007) indicates that temporal (STG), frontal (FEF) and cingulate brain areas (ACC) are more activated during predictive pursuit in schizophrenia patients compared to healthy controls, that seem to rely more on cerebellar mechanisms (Crus VIIIA). In a laboratory experiment we wanted to test the oculomotor functions at different target velocities and blanking durations in order to obtain more evidence for the role of prediction during smooth pursuit eye movements of patients with schizophrenia. Methods: Twenty patients and 20 age- and gender-matched controls performed a pursuit blanking task at two target velocities (10, 15°/s) and two blanking intervals (666, 1000 ms). Eye movements were recorded by high resolution infrared videobased oculography. Results: Patient's smooth pursuit velocity was significantly lower compared to healthy controls. After the target was blanked off, the deceleration of eye movement velocity started after the same time interval in both groups. However, the deceleration velocity was significantly slower in the patient group than in controls. The acceleration after reappearance of the target started earlier in controls than in patients but the acceleration itself was the same in both groups. Conclusion: When a movement has to be continued after the stimulus has disappeared, patients with schizophrenia seem to rely to a higher extent on mechanisms of prediction and velocity storage than healthy subjects. Our results could explain why patients with schizophrenia are considerably impaired during pursuit of randomized step-ramp but much less during highly predictable sinusoidal stimuli.
ID: 552599

6. 6. Epidemiology

MENSTRUAL DISORDERS IN SCHIZOPHRENIA, POSSIBLE CAUSES AND CONSEQUENCES

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Menstrual Disorders (MDs) like oligomenorrhea or amenorrhea are often found in women with schizophrenia. Although MDs are often considered to be antipsychotic medication related, a systematic literature review did not support this view (Ouwehand and Knegtering in preparation). The understanding of mechanisms involved in MDs may increase our understanding of the pathogenesis of MDs and schizophrenia. Method: After being treated for 6 weeks with an antipsychotic information on MDs (using the ASFQ (Knegtering et al. 2003)), medication and blood levels of antipsychotics and hormones were evaluated in all women with schizophrenia aged 17 till 40 years attending the University Medical Center of Groningen. Results: 71 women fulfilled inclusion criteria (including no known organic causes for MD), mean age 27 (SD7) years. 22 women used Oral Contraceptives (OC). 43 used prolactin elevating antipsychotics (classical antipsychotics, risperidone), 28 prolactin sparing (clozapine, quetiapine, olanzapine, sertindole, aripiprazole). Women using prolactin elevating antipsychotics reported more often MDs (13 out of 27 = (48%)) than women using prolactin sparing antipsychotics (4 out of 22 = (18%)), (χ^2, P = .015). OC and age did not predict MD. Prolactin levels predicted MDs (ANOVA F = 5.278, P = .025). Independent of prolactin levels these women with schizophrenia reported more MDs in comparison to epidemiological comparable groups (prevalence in normal population of same age is about 1% (van der Linden et al. 2004)). Conclusion: Prolactin elevation during treatment with antipsychotics for six weeks was associated with more frequent MD. Prolactin may not be to only factor involved. Before the introduction of antipsychotics high numbers of MD have been reported in women with schizophrenia. More studies are warranted to understand the pathophysiology of schizophrenia and MD in women.

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TIME-TO-PREGNANCY AND RISK OF SCHIZOPHRENIA IN OFFSPRING

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Abstract: Several studies have reported advanced paternal age as a risk factor for schizophrenia. Given the likely role of paternal reproductive health in this relationship, other factors associated with male fertility should be examined. One variable that has been utilized in prior studies of fertility, time-to-pregnancy may serve as a useful indicator. Using data from the prospective Jerusalem Perinatal Study (JPS), a pregnancy cohort, data from prenatal interviews was linked to systematically collected data on mental health outcomes in offspring. Examining those subjects with intentionally conceived pregnancies, a modest increase in risk of schizophrenia in offspring was measured in those with time-to-pregnancy >6 months (OR = 1.63, 95% CI: 1.02, 2.60). When the relationship was examined on the basis of parents' ages at conception, it was discovered that the risk was further increased for subjects with fathers >35 years old and increased time-to-pregnancy (OR = 2.49, 95% CI: 1.05, 5.89). Maternal age did not appear to have the same influence on risk associated with time-to-pregnancy in this sample. For subjects from more religiously observant families, the risk associated with increased time-to-pregnancy was statistically significant (OR = 2.09, 95% CI: 1.07, 4.1), possibly due to reduced misclassification. These findings suggest that biological mediators related to paternal reproductive health, associated with increased paternal age and increased time-to-pregnancy may be responsible for increasing the risk of schizophrenia. Additional research using both epidemiologic approaches and laboratory methods are currently underway.
ID: 550801

CLINICAL AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA AMONG A PREDOMINANTLY TREATMENT-NAÏVE COHORT IN RURAL ETHIOPIA

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Background: The established view that schizophrenia has a favorable outcome in developing compared to developed countries has been recently challenged. However, systematic studies from developing country settings are scarce. We present the clinical and functional outcome of schizophrenia among a predominantly treatment-naive cohort in a rural community setting in Ethiopia. Methods: Cohort was identified in a 2-stage sampling design using key informants and measurement-based assessment. After screening 68 378 adults, ages 15–49 years, 321 cases with schizophrenia (82.7% men and 89.6% treatment-naive) were identified and systematically followed-up for 3.4 years. Results: Almost a third (30.8%) of cases were continuously ill and most of the remaining cohort experienced an episodic course. Only 5.7% of the cases enjoyed a near-continuous complete remission although 27.4% were in complete remission in the month of the final follow-up assessment. Living in a household with 3 or more adults, later age of onset, and taking antipsychotic medication for at least 50% of the follow-up period independently predicted complete remission. Functioning and other measures of health related quality of life were significantly diminished in cases as compared to the general population of the area at baseline and follow up. The level of functioning observed in cases from Butajira was also lower than that reported for cases from developed countries. Conclusion: Both the functional and clinical outcome of schizophrenia in this setting appears to be worse than reported elsewhere in developing countries. Additionally, functional outcome in this setting appears to be even worse than that reported in developed countries. Thus our findings support the observation that the outcome of schizophrenia in developing countries may be heterogeneous rather than uniformly favorable.
ID: 550785

SCHIZOPHRENIA AMONG THE BORANA PASTORALIST COMMUNITY IN SOUTHERN ETHIOPIA: A RE-VISIT OF CASE ASCERTAINMENT METHODOLOGY

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There are few reports on the prevalence of psychotic disorders among isolated population groups. The major challenge is establishing a methodologically sound system of case identification. In our population based survey of the Borana pastoralist community in Ethiopia, we found an overall prevalence of psychiatric disorders, assessed using the Composite International Diagnostic Interview (CIDI), of 21.6%. However, no case of schizophrenia was identified. We set out to investigate whether this was because of the absence of schizophrenia or a function of the how serious mental disorder is conceptualised in the Borana pastoralist community. We conducted 6 Focus Groups (FG) with key members of the Borana pastoralist community, in order to investigate how serious mental disorder is conceptualized. Subsequently, the FG participants were used as Key Informants (KI) to identify cases with a possible psychotic disorder, based on their conceptualization. Cases identified by KIs were interviewed by a trained psychiatrist using a semi-structured interview instrument, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) to confirm presence of disorder. Out of 56 individuals invited to the FGs, 49 (87.5%) participated. Participants were 25–60 years of age and 26 (46.4%) were women. The concept of serious mental disorder among the FG participants was informed by traditional beliefs and attributions. However, there was a marked overlap between the behavioural, emotional and biological signs identified by FG participants and those described in modern classification systems. Following the FG, participants identified 6 individuals with schizophrenia and 13 with a psychotic mood disorder that were subsequently confirmed through SCAN interviews. Concepts of serious mental disorder in the Borana pastoralist community reflected traditional beliefs and practices. Nevertheless, individuals with a psychotic disorder were easily identified by key informants. The inability of the CIDI to identify any cases of schizophrenia in our initial prevalence survey cannot be fully attributed to the distinct local conceptualizations of these disorders. Studies of psychotic disorders in such communities may benefit from combining structured interviews with the key informant method.
ID: 550758

REHOSPITALIZATION RATES OF PATIENTS DISCHARGED WITH HALOPERIDOL OR OLANZAPINE OR RISPERIDONE OR SULPIRIDE OR ZIPRASIDONE OR CLOZAPINE AND ITS RELATION TO PREVIOUS TREATMENT

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It is well established that antipsychotics represent the mainstay of treatment for schizophrenia. An important outcome variable for drug effectiveness is relapse/rehospitalization prevention. Based on the previous review we hypothesize that second generation antipsychotics are superior to conventional antipsychotics for preventing relapse and rehospitalizations. Hence, the aim of this study was to observe rehospitalization rates of patients discharged on a regimen of haloperidol or olanzapine or risperidone or sulpiride or ziprasidone or clozapine. Data were collected from charts and hospital database. Survival curves were estimated by the product-limit (Kaplan-Meier) formula. A total of 118 patients entered the selection and were followed-up from discharge date (between January 2000 and December 2004) until December 2007. The percentage of patients remaining discharged were 70% for haloperidol, 86% for olanzapine, 59% for risperidone, 90% for sulpiride, 75% for ziprazidone and 75% for clozapine. There were no significant differences in readmission rates among groups (Log Rank = 10,84, $df = 5$, $P = .055$). The results demonstrate lower rehospitalization rates for sulpiride and olanzapine and lower rate for risperidone, with clozapine, haloperidol and ziprasidone in an intermediate position. Risperidone along with haloperidol and olanzapine were the most frequent choices for naïve patients and clozapine, according to our expectations, was started in most patients with history of use of three or more antipsychotics previous to hospitalization. It is interesting to observe that there is a significant trend that could indicate differences among antipsychotics in rehospitalization rate that is not statistical different in this study due to a small sample size.
ID: 550754

SPECIFICITY OF ASSOCIATION BETWEEN CHILDHOOD ABUSE AND PSYCHOSIS IN A CLINICAL FIRST-EPISODE SAMPLE

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Childhood adversity has been associated with increased risk of developing psychotic symptoms in adulthood but these studies are methodologically limited. Therefore, this study sought to explore the prevalence of childhood abuse amongst those with and without a psychotic disorder using detailed assessments of a large epidemiological case-control sample. Information relating to different types of childhood maltreatment (parental neglect and antipathy, physical and sexual abuse) was obtained using the Childhood Experiences of Care and Abuse Questionnaire (CECA.Q). Data were collected on 182 first-presentation psychosis cases and 246 epidemiologically-matched controls drawn from two UK centres as part of the ÆSOP study. Initial exploration of the data demonstrated that there was good test-retest reliability over 7 years (physical abuse: $k = 0.634$, $P < 0.001$; sexual abuse: $k = 0.590$, $P < .01$) and convergent validity (specificity: 100% physical abuse and 98% sexual abuse) for reports of childhood abuse from participants diagnosed with psychosis. Analysis revealed that psychosis cases were three times more likely to report severe physical abuse from mother that commenced prior to 12 years of age, even after adjustment for other forms of adversity, gender, ethnicity, age at interview, study centre and parental social class (OR = 3.15, 95% CI = 1.13–8.78, $P = .028$). Further, there was a trend for reports of severe childhood sexual abuse to be associated with around a two-fold increased risk for psychosis but this failed to reach significance after adjustment for all confounders (OR = 2.09, 95% CI = 0.95–4.96, $P = .065$). Paternal physical, parental neglect and antipathy did not significantly predict psychosis case status. These findings provide more comprehensive evidence of the association between childhood adversity and development of psychosis in adulthood and lend support to the hypothesis that it is particularly intrusive early life events which are important in the aetiology of psychotic disorders. Further analyses are underway to explore the potentially mediating role of familial susceptibility and candidate genes.
ID: 550749

DESCRIPTIVE EPIDEMIOLOGY AND COMORBIDITY OF SCHIZOPHRENIA VS. BIPOLAR DISORDER IN THE NATIONAL HOSPITAL DISCHARGE SURVEY (NHDS)

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Introduction: Medical morbidity and mortality rates in schizophrenia and bipolar disorder patients are elevated compared to the general US population. More than 50% of patients with schizophrenia and bipolar disorder have been diagnosed with one or more comorbid conditions. In addition to providing descriptive epidemiology, the purpose of this study is to identify serious medical comorbidity occurring more frequently among those hospitalized with schizophrenia than those with bipolar disorder. Methods: Using the 1979–2003 National Hospital Discharge Survey (NHDS), we evaluated temporal trends in the proportional morbidity (PM) of schizophrenia and bipolar disorder, demographic characteristics and the most frequent comorbid conditions among hospitalizations with schizophrenia, compared to hospitalizations with bipolar disorder. The demographic characteristics and comorbidity are presented for the NHDS sample of 5 731 450 records. Results: Percent of hospitalized with schizophrenia versus bipolar disorder was higher among males (PM ratio 1.5) than females, blacks (2.7) and other (1.6) compared with whites, age group 45–64 (9.8) followed by 15–44 (9.3) and 65+ (8.0) compared with those younger than 15, Northeast and West (1.2) followed by Midwest (1.1) compared with South. There was a significant increase over time in the proportion of discharges with schizophrenia and bipolar disorder and a significant decrease in the mean length of hospital stay. Compared with bipolar disorder discharges, those with schizophrenia have a significantly higher proportion of comorbidity with the following system groups of medical conditions: neoplasms (overall PM ratio 1.1), diseases of blood-forming organs (1.2), respiratory (1.1), genitourinary (1.1) systems, as well as diseases of the skin and subcutaneous tissue (1.2). In addition, we identified a number of serious specific medical conditions occurring at least 1.5 times more frequently among discharges with schizophrenia. Discussion: We found that compared with bipolar disorder, those hospitalized with schizophrenia were more likely to have some serious comorbidity both at the system level and for certain specific conditions. These finding may justify higher scrutiny for those conditions during clinical examination of schizophrenia patients. Closer attention to prevention, early diagnosis and treatment of comorbid conditions may decrease medical morbidity and mortality and improve the prognosis of schizophrenia patients.
ID: 550643

ADULT-ONSET SCHIZOPHRENIA IN THE US MILITARY: PATTERNS BY SEX, RACE AND AGE

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Background: There is substantial uncertainty about some aspects of the epidemiology of schizophrenia, and data are sometimes conflicting. There is limited prevalence data on US civilian population, and less incidence data, especially for subgroups. US prevalence is approximately 1%, with conflicting data for sex, age, and racial groups. Incidence estimates include 0.1–0.4/1000/yr (Jablensky, 1992 WHO international

estimate), and $0.08-.43/1000/yr$ (10th–90th%) (McGrath, 2004, international estimate). The prevalence of severe mental illnesses among military personnel is lower than among the general population due to self-deferral, medical screening at entry, and rapid attrition from military. Methods: We used hospitalization data from the Defense Medical Epidemiology Database for 1998–2007. Only first event hospitalizations were included. Analyses were conducted at 3-digit ICD-9 code level. This report is a descriptive and graphical presentation of the data to provide insight into patterns of disease. Results: During the study period (1998–2007) there were 1,995 first-time military hospitalizations for schizophrenia, occurring across 13 787 901 person years (PY), for an overall incidence density (ID) 0.15/1000/PY. Over the study period the rate of first time hospitalization for schizophrenia changed little, with a marginally significant decrease among men (0.16 to 0.14, $P = .07$). There were no changes over time by race or age. The female:male IDR was 1.1 ($P > .10$). The ID ratio (IDR) among blacks (compared to whites) was 2.4 ($P < .01$). Relative to those 40+, the IDR was 14.4 ($P < 0.01$) for <20, decreasing to 2.4 ($P < .01$) for those 35–39. Among whites rates decreased consistently with age; among blacks rates increased from <20 to 20–24, then declined. At all age groups rates were higher among blacks than whites. Among men rates declined consistently with age; among women rates were flat for ages 20–24, 25–29, and 30–34, and then declined. For younger personnel rates were higher among men; among older they were higher among women, with rates crossing at the 25–29 age group. Discussion: There are substantial differences in patterns of schizophrenia by sex, race, and age. While overall patterns provide some insight, only by reviewing data on subgroups can these more specific patterns be discerned. These analyses clearly indicate that there are certain groups at relatively high risk, and may provide guidance in early detection of schizophrenia.
ID: 550641

SYSTEMATIC REVIEW AND META-ANALYSIS OF POPULATION-BASED STUDIES OF PREMORBID INTELLIGENCE AND SCHIZOPHRENIA

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Introduction: Previous studies have reported lower premorbid intelligence in children and adolescents who will later develop schizophrenia. (1) Method: We systematic reviewed the literature until August 2008, and to the increase external validity of the research question only selected population-based prospective, retrospective and nested case-control studies for meta-analysis. Included studies reported a standardised measure of intelligence completed in childhood or well before any symptoms of illness. Separate meta-analysis was completed for full-scale, verbal and performance IQ scores. Regression analysis was carried out to examine a dose-response relationship between low IQ and risk of schizophrenia. Meta-regression was used to examine associations between study effect sizes, mean age of onset, and age at IQ assessment. Results: We identified 12 studies comprising 2654 cases and 728143 controls. Full-scale, verbal and performance IQ all showed significant premorbid decrements (effect size 0.43–0.45) in future cases of schizophrenia. There was no significant difference between premorbid verbal and performance IQ in schizophrenia cases. A clear dose

response effect was observed between low IQ and risk of schizophrenia, while risk increased by 3.7% with decrease in each IQ point (Coef. −0.037, SE 0.0013, $P < .0001$). There was a significant association between magnitude of IQ decrement and age at onset of illness ($P = .0007$) and a marginal trend for greater decrement when IQ was assessed at later ages ($P = .06$). Discussion: Compared with their peers, children who will later develop schizophrenia show a consistent decrement of around 6–7 IQ points in both verbal and non-verbal IQ. There is also a dose response relationship between low IQ and risk of schizophrenia. Associations with age of onset and age of testing, suggests a progressively widening gap between normal and schizophrenic brain development from birth until symptom onset.

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 ID: 550635

SOCIAL CHARACTERISTICS OF NEIGHBORHOODS AND THE INCIDENCE OF PSYCHOTIC DISORDERS

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One of the most consistent findings in the epidemiology of schizophrenia is that those who live in cities are at greater risk. It is much less clear which risk factors drive this increased risk, because few attempts have been made to move beyond the crude measure of urbanicity. Social factors across different levels of organization may be involved, in particular those involving availability of and access to social capital. We conducted a first contact incidence study of psychotic disorders between 1997 and 2005 in the city of The Hague, the Netherlands ($n = 618$) and investigated associations between individual and neighborhood characteristics and the incidence of psychotic disorders, using multilevel Poisson regression analysis. First, after adjustment for individual level age, sex, marital status and ethnic minority status, measures of neighborhood socioeconomic level, residential mobility, population density, voter turnout at local elections and crime level were all significantly associated with the incidence of psychotic disorders in a dose-response fashion. We calculated a cumulative score of neighborhood social disadvantage, based on these five indicators and divided it into tertiles (low, medium and high social disadvantage). The individual level adjusted incidence rate ratio (IRR) of psychotic disorders was 1.89 (95% Confidence Interval = 1.38–2.60) for individuals living in the socially most disadvantaged neighborhoods and was 1.35 (95% CI = 0.95–1.92) for those living in moderately disadvantaged neighborhoods compared to those living in the most advantaged areas (Wald χ^2 [$df = 2$], 18.19, $P < 0.0005$). Second, we investigated the effect of the ethnic composition of neighborhoods on the incidence of psychotic disorders, not only among ethnic minorities, but also among native Dutch. In neighborhoods with a very high proportion of non-Western ethnic minorities, the incidence rate for native Dutch was 35.4 per 100 000 (95% CI = 18.2–62.1), indirectly standardized to age, sex and neighborhood socioeconomic level. In neighborhoods with a relatively low proportion of ethnic minorities, the incidence rate for native Dutch was 21.1 (18.4–24.2). Among ethnic minorities, the pattern was opposite. These results are suggestive for an ethnic density effect both in ethnic minorities and in native Dutch. Thus, neighborhood social characteristics strongly influence the incidence of psychotic disorders within an urban environment in interplay with individual factors.
 ID: 550624

THE RATE OF TB IN INDIVIDUALS WITH SCHIZOPHRENIA: CLUES TO INFLAMMATORY MECHANISMS?

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Previously our group hypothesized that some psychotic disorders are the result of disruption of the microvascular circulation of the brain brought on by inflammatory processes. If inflammation is a contributing factor to the development of psychosis, individuals with chronic inflammatory illnesses, should display a higher incidence of psychosis as compared to the general population. One such cause of chronic inflammation and activation of cytokine systems is tuberculosis (TB). TB susceptibility is genetically mediated in part, based on twin and family studies in the literature. TB infections generate circulating inflammatory agents that can have distant effects. Objective: To determine if individuals with schizophrenia have a higher rate of tuberculosis as compared to individuals without schizophrenia but who share similar contagion-risk factors. Method: An analysis of the rates of tuberculosis in a historic (born 1860–1935) population of psychiatric patients who had been institutionalized long term in Minnesota State Hospitals. Complete psychiatric and medical records including autopsies were available. Psychiatric diagnoses were updated independently by two clinicians according to RDC criteria. Results: The rate of TB in people with schizophrenia was approximately 20% compared to 0.5 % in affective illnesses and 0.5% in organic psychoses. Conclusions: The implication from this study is that the individuals with schizophrenia have a higher incidence of tuberculosis. There are at least two possibilities to consider. Chronic circulating inflammatory processes may impact the brain leading to schizophrenia. Alternatively, schizophrenia and TB susceptibility may both be consequences of inherited perturbations of the immune system and innate inflammatory processes triggered by unspecified environmental or epigenetic factors.
ID: 550604

PRENATAL EXPOSURE TO TOBACCO IN PATIENTS WITH FIRST EPISODE PSYCHOSIS

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Smoking during pregnancy impairs placental development and is associated with fetal undernourishment, slow fetal growth, and low birthweight. In addition, nicotinic aceylcholine receptors are expressed early in fetal development and animals exposed to nicotine in-utero have abnormal neuronal proliferation and differentiation, and show developmental disruptions in cholinergic and catecholaminergic systems. The neuronal consequences of prenatal nicotine exposure in humans are not well defined but those born to mothers who smoked during pregnancy are at increased risk for a range of physical, behavioral, cognitive, and psychiatric problems and are more likely to initiate smoking in adolescence. Many of these same problems are observed in patients with psychosis, but have not been investigated in relationship to maternal smoking. The goals of the present study were 1. to determine if the mothers of first episode psychotic (FEP) patients were more likely to have smoked during pregnancy than other women, and 2. to determine if the known correlates of this early risk factor are observed in FEP patients. An initial FEP sample ($n = 80$), a geographically distinct FEP replication sample ($n = 96$), and a healthy control group ($n = 58$) were recruited, and the results from a 1993 Canadian smoking survey were acquired. Birth history was obtained from maternal report. FEP, control and survey groups were compared for the proportion who were prenatally exposed to nicotine. Exposed and unexposed individuals were compared for

health-related and cognitive correlates of exposure to nicotine. The percentage of mothers who smoked during pregnancy was similar in the two FEP samples (30%, 33%) and significantly greater than that of the control and survey samples (15%, 19%). Prenatal tobacco exposure was associated with low birthweight, poor academic achievement during childhood and cigarette smoking in all three samples, and with obesity in FEP patients. The present findings suggest that patients with psychosis are more likely to have been prenatally exposed to nicotine than is observed in the general population. As with the general population, prenatal exposure to nicotine is associated with an increased risk of health-related and cognitive problems in psychotic patients. The relatively high proportion of psychotic patients exposed to nicotine in utero suggests that the negative correlates of this early risk are likely to be commonly observed in patients with psychosis.
ID: 550573

GLUCOSE TOLERANCE IN NEWLY DIAGNOSED, ANTIPSYCHOTIC-NAIVE PATIENTS WITH NON-AFFECTIVE PSYCHOSIS

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Some studies suggest patients with schizophrenia have an increased risk of diabetes prior to antipsychotic use. Small sample sizes and the potential for confounding by hypercortisolemia have decreased confidence in those results. We administered a two-hour oral glucose tolerance test to 50 newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis and 50 matched control subjects. The patients had significant increases in two-hour glucose (respective means [SD] for the patient and control groups were 111 mg/dL [35.2] and 82 mg/dL [19.3]; $t = 5.15$, $P < .001$). The prevalence of impaired glucose tolerance or diabetes was 16% of patients vs. 0% of control subjects ($P < .003$). These differences could not be attributed to differences in cortisol concentrations, smoking, gender, neighborhood of residence, demographic variables, body mass index, aerobic conditioning, ethnicity, socioeconomic status, or age. Fasting glucose and hemoglobin A1c concentrations did not differ between the two groups. Patients with nonaffective psychosis appear to have an increased prevalence of abnormal glucose tolerance prior to antipsychotic treatment. These underlying problems may contribute to the metabolic side effects of antipsychotic medications.
ID: 550568

ALCOHOL INDUCED PSYHOTIC DISORDER AND DELIRIUM IN THE GENERAL POPULATION

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Objective: We estimated the lifetime prevalence (LTP) of alcohol-induced psychotic disorder and delirium in the general population, and compared subjects with alcohol dependence with and without psychosis. Method: In a nationally representative survey of 8028 persons aged 30 or over, the life-time diagnosis of alcohol dependence was assessed in the CIDI interview (1). In the re-assessment of psychotic disorders (2), the whole sample was screened using CIDI, health examination and national registers. Best-estimate DSM-IV-TR diagnoses were formed by combining SCID-I interview and case note data. Prior hospital treatments were collected from the National Hospital Discharge Register. Number of deaths during eight year follow-up was obtained from the National Register of Deaths. Results: The LTP was 0.41% (95% CI = 0.29–0.57) for alcohol-induced psychotic disorder ($n = 31$) and 0.18% (95% CI = 0.11–0.32%) for alcohol-induced delirium ($n = 14$). 6 subjects had had both diagnoses, and when each individual was only counted once, the LTP for the total alcohol-induced psychotic syndromes (AIPS) was 0.51% (95% CI = 0.38–0.70). The highest LTP (1.77% 95% CI = 1.06–2.94) was found among men aged 45–54. Among subjects with the diagnosis of alcohol dependence ($n = 482$) the LTP for AIPS was 4.79%, and for all psychotic disorders 9.17%. Being 45–54 years, belonging to low socioeconomic groups, reporting mental health or alcohol problems in fathers, having had high number of hospital treatments or hospital treatments for alcohol-related disorders were associated with AIPS among alcohol dependents. 35.9% and 7.0% of subjects with AIPS and with alcohol dependence died in the follow-up, respectively. The hazard ratios for mortality among subjects with AIPS were 13.0 compared with the total population and 9.4 compared with other alcohol dependents. Conclusions: Alcohol-induced psychotic disorder and delirium are common in the general population, especially among working-aged men. They are associated with high number of hospital treatments and with high mortality.

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ID: 550544

BDNF VAL66MET GENOTYPE, MALE GENDER AND ADOLESCENT CANNABIS USE DETERMINE AGE OF ONSET OF PSYCHOSIS: A STUDY IN A LARGE SAMPLE OF PSYCHOTIC PATIENTS

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Several factors have been suggested to decrease age at onset of psychosis, including male gender, cannabis and other drug use and BDNF Val66Met genotype. The BDNF Val66Met polymorphism, of which Met-substitution is associated with reduced intracellular trafficking and activity-dependent BDNF secretion, was genotyped in a sample of 587 patients with psychosis. Survival analyses with time from birth to age at first admission as indicator for survival time were fitted as a function of several predictor variables, as were multivariate Cox regression models. BDNF Val66Met genotype was significantly associated with survival time (log-rank test: $\chi^2 = 4.3$, $P = .039$), with Met-carriers being admitted for the first time a mean of 1.2 years earlier. Gender, adolescent cannabis use (<16 yrs), lifetime stimulant, cocaine or psychedelics use were also significantly associated with survival time (log rank test $P < .05$). In the multivariate Cox regression models BDNF Val66-Met Met genotype (Hazard Ratio (HR) 1.23, $P = .026$), adolescent cannabis use (HR 1.59, $P = .005$) and male gender (HR 1.58, $P < .001$) remained significant predictors of earlier age at onset. Results did not considerably change when analyses were restricted to patients with an age at onset below 35 years. No interaction effects were observed. These results confirm findings of earlier studies suggesting an effect of BDNF Val66Met genotype,

cannabis use before age 16 (but not later cannabis use) and male gender on age of onset of psychosis in a mainly Caucasian population.
ID: 550516

PATERNAL AGE IS ASSOCIATED WITH INCREASED MORTALITY RISK IN PSYCHOTIC DISORDERS

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Increasing paternal age is a replicated risk factor for schizophrenia in the offspring, while schizophrenia is associated with increased mortality. A previous study of men with psychosis found that paternal age was correlated with suicide. We examined paternal age and mortality in $N = 834$ patients with psychosis born in Helsinki, Finland, between January 1, 1951 and December 31, 1960. Subjects were followed until June 2006 (ages 46–55). Offspring of fathers who were under 20 years old were omitted from the analyses because of small numbers. In multivariate Cox proportional hazard models, after adjustment for maternal age, gender, and age of onset of psychotic symptoms, paternal age (as a continuous variable) was a significant predictor of suicide mortality (Hazard Rate Ratio (HRR) = 1.05, 95% CI = 1.01–1.10, $P = .020$). By contrast, increasing maternal age was associated with decreased risk of suicide mortality (HRR = 0.923, 95% CI = 0.87–0.98, $P = .012$). In males, paternal age was associated with increased suicide risk (HRR = 1.05, 95% CI = 1.00–1.11, $P = .050$), and maternal age was associated with decreased suicide risk (HRR = 0.90, 95% CI = 0.83–0.97, $P < .01$). In females, the effect of paternal age on suicide risk was not statistically significant, although the point estimate was the same as in males (HRR = 1.054, 95% CI = 0.97–1.15, $P = .22$). Paternal is associated with a linear increase in suicides in males with psychosis. The pathway(s) associated with this increased mortality remain to be determined. The relative contribution of biological and psychosocial factors are unclear.
ID: 550435

EVIDENCE THAT ONSET OF CLINICAL PSYCHOSIS IS THE OUTCOME OF PROGRESSIVELY MORE PERSISTENT SUBCLINICAL PSYCHOTIC EXPERIENCES: IMPLICATIONS FOR EARLY INTERVENTION

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Objective: It may be possible to intervene early in the prodromal phase of psychosis. However, very little is known about the course of psychometric risk indicators of psychosis in epidemiological samples of young people. To examine the hypothesis that developmental expression of psychometric risk in the form of subclinical psychotic experiences is usually transitory, but in some instances may become abnormally persistent and progress to a clinical psychotic state. Design: Prospective cohort study. Expression of psychosis was assessed, using self-report and interview, four times over a period of 8.4 years. General population of adolescents, 845 individuals aged 14–17 years at baseline, in Munich, Germany (Early Developmental Stages of Psychopathology Study). A distinction was made between psychotic experiences with impairment (clinical psychosis; defined as psychotic experiences with Help-seeking and/or Dysfunction) and without impairment (subclinical psychosis). Transition from subclinical psychosis at T0-T2 to clinical psychosis at T3 was examined as a function of the level of prior persistence of subclinical psychosis (present never, once, twice or thrice at T0, T1 and T2). Results: The more subclinical psychosis persisted over the period T0-T2, the greater the risk of transition to clinical psychosis at T3 in a dose-response fashion (subclinical psychosis expression once over T0-T2: OR = 1.5 (CI: 0.6–3.7), post-test probability (PP) = 5%; twice: OR = 5.0 (CI: 1.6–15.9), PP = 16%; at all three measurements: OR = 9.9 (CI: 2.5–39.8), PP = 27%. Of all clinical psychosis at T3, a third (38.3%) was preceded by subclinical psychotic experiences at least once, and a fifth (19.6%) at least twice. Conclusions: A significant proportion of psychotic disorder may be conceptualised as the rare poor outcome of a common developmental phenotype characterised by persistence of psychometrically detectable subclinical psychotic experiences. Early intervention efforts may target the factors that make the common and transitory developmental expression of subclinical psychosis persist.
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OBSTETRIC FACTORS, PRENATAL INFECTIONS AND SCHIZOPHRENIA IN ADOLESCENCE AND EARLY ADULTHOOD

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Several studies have reported an association between obstetric complications and schizophrenia. Especially children born small for gestational age (SGA) have been reported to have an increased risk of schizophrenia. No studies have however quantified whether the effect of SGA was related to individual or familial factors. In addition, we also studied whether individuals exposed to prenatal infections have an increased risk of schizophrenia. Data from three population based registers, the Danish Medical Birth Register, the Danish Psychiatric Central Register and the Danish National Hospital Register were used. We used an historical population based cohort design and selected all individuals born between 1979 and 1996 ($n = 921\ 397$). We identified all individuals who were listed in the Psychiatric Register as having been first admitted to hospital from 1989 through 2006 with schizophrenia ($n = 1823$). We accounted for the potential confounding effect of parents age at child's birth, urbanicity, parents history of at least one psychiatric diagnosis. Individuals being small for gestational age are more likely to develop schizophrenia, than individuals not being small for gestational age (RR = 1.3). Results further indicate that having an older sibling who were also small for gestational age increased the risk for schizophrenia (RR = 2.0). Maternal infection during pregnancy increased the risk by 1.4. Schizophrenia risk was associated with maternal infections requiring hospitalization, especially infections during second trimester. The association between being small for gestational age and schizophrenia may be due to risk factors aggregating in families and shared by schizophrenia and SGA, rather than an effect of SGA per se. This work was supported by the Stanley Medical Research Institution.
ID: 550356

ARE SELF-REPORTED AUDITORY HALLUCINA- TIONS AMONG ADOLESCENTS VERIFIED ON CLINICAL INTERVIEW?

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The prevalence of auditory hallucinations among adolescents ranges from 5–30% in population-based surveys. The rate of such self-reported hallucinations varies with developmental age and degree of certainty required. In order to assess the significance of these self-reported symptoms we need to know how many of these adolescents will turn out to have psychotic-type symptoms on clinical interview. We administered a self-report questionnaire comprising seven questions assessing psychotic-type symptoms (rated as 'yes', 'maybe' or 'no') to 334 11–13 year old school children attending primary schools in Dublin. Thirty-eight percent of the sample answered 'yes' or 'maybe' to at least one of these symptoms. With regard to auditory hallucinations specifically: 15.6% of the sample answered 'yes' and 20.1% answered 'maybe' to this question. We interviewed adolescents who answered 'yes' to 2 or more questions (n = 22) and a comparison group of adolescents who endorsed one or none of these symptoms (n = 22), using the semi-structured K-SADS diagnostic interview schedule administered by a trained psychologist or psychiatrist. Subjects were interviewed within 1–2 months of completing the self-report questionnaire. Symptoms were rated as 'definite' and 'possible' at a consensus meeting involving 3 clinicians. On interview, 17 adolescents were found to experience 'definite' psychotic symptoms and 5 experienced 'possible' psychotic symptoms. We found that answering 'yes' to the auditory hallucination question (Have you ever heard voices or sounds that no-one else can hear?) on the screener questionnaire was highly predictive of 'definite' clinician-rated auditory hallucinations on interview (PPV 92.3%; NPV 95.7%; Sensitivity 92.3%; Specificity 95.7%) and was also highly predictive of any clinician-rated 'definite' psychotic symptom on interview: (PPV 100%; NPV 84.6%; Sensitivity 76.4%; Specificity 100%). Answering 'maybe' to the auditory hallucinations question was not predictive of clinician-rated psychotic symptoms on interview. Our results indicate that adolescents are willing to reveal psychotic-like symptoms using questionnaire methods and that the answers can be confirmed by clinical interview. In this age-group self-report of hearing voices is the most useful predictor of psychotic symptoms on subsequent interview. This research was supported by the Health Research Board (Ireland). ID: 550353

STRUCTURAL BRAIN ABNORMALITIES IN PATIENTS WITH SCHIZOPHRENIA AFTER 2ND TRIMESTER FETAL EXPOSURE TO IL-8

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Maternal infection during pregnancy has been repeatedly associated with increased risk for schizophrenia. Nevertheless, most viruses do not cross the placenta; therefore the damaging effects on the fetus appear to be related to maternal antiviral responses to infection, such as proteins linked to inflammation (ie, proinflammatory cytokines). In the present cohort, fetal expo- sure to increases in maternal levels of the proinflammatory cytokine interleukin-8 (IL-8) was related to increased risk of schizophrenia spectrum disorders (SSD). The purpose of the present study was to determine whether fetal exposure to IL-8 led to structural brain abnormalities among SSD patients. Methods: Subjects were 17 cases diagnosed with SSD and 8 controls from a birth cohort study, the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study. Psychiatric morbidity was deter- mined through semi-structured interviews (DIGS) and medical records re- view. Levels of IL-8 were ascertained from sandwich enzyme-linked immunosorbent assays from archived prenatal sera collected during the 2nd trimester of pregnancy. Coronal T1-weighted magnetic resonance images were acquired using a 1.5-Tesla Siemens system and 3D MP-RAGE sequences. Volumes were determined through manually tracing regions of interest (ROIs). ROIs were divided by intracranial volumes to form ratios and then log-transformed. Results: Results indicated that fetal exposure to increases in IL-8 were associated with significant increases in ventricular cerebrospinal fluid (CSF) and significant decreases in right cau- date, left entorhinal cortex, and right posterior cingulate volumes. In con- trast, there were no significant effects of IL-8 on any ROIs for controls. Conclusion: Results indicate that cases are preferentially sensitive to fetal exposure to IL-8 compared to controls. Among cases, fetal exposure to IL-8 appears to affect dopamine-rich structures implicated in motor functioning and memory, cognitive domains commonly disrupted among schizophrenia patients. Fetal exposure to increases in IL-8 also was related to the most replicated brain anomaly in schizophrenia, increases in ventricular CSF. Overall, these findings suggest that there is likely a genetic or environmental factor associated with schizophrenia that renders the aforementioned fetal brain structures especially sensitive to maternal inflammatory immune responses. ID: 550332

THE DEVELOPMENTAL TRAJECTORY TO SCHIZOPHRENIA—EVIDENCE FOR GENETIC AND ENVIRONMENTAL INFLUENCES

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Childhood developmental abnormalities have frequently been described in schizophrenia. We wished to determine whether childhood developmental abnormality in schizophrenia is genetically mediated. We also wished to elucidate the relationship between obstetric complications and develop- mental deficits. The study population comprised all those born in Helsinki between 1962 and 1969 who had developmental records archived in the Hel- sinki City Archives. Through linking the Finnish Population Register and the Finnish Hospital Discharge Register we identified 189 individuals who had received a diagnosis of schizophrenia and 115 unaffected siblings who were born between 1962 and 1969 and had developmental information available. We also identified a control group, matched to cases and siblings on gender and year of birth (n = 304). Prospective, standardised develop- mental data for each subject was retrieved from the archives of 'Well Baby' clinics. The majority of children in Finland attend these clinics for monthly check-ups in their first year of life. The age in months at which the following series of motor developmental milestones were achieved significantly dif- fered between cases, sibling high-risk and control groups: turns-over, raises into a sitting position, raises to stand, walks supported and pincer grip. Cases were significantly slower to reach these milestones compared to sib- lings, who in turn were significantly slower to achieve them compared to matched controls. Apgar scores were significantly lower among the cases than the siblings or comparison groups. There was also an additive effect between low apgar score and motor developmental delay such

that exposure to both risk factors increased risk for schizophrenia to a significantly greater extent than exposure to only one of these risk factors. These findings support delayed motor development in the first year of life as an endophenotype for schizophrenia, indicate that motor deficits may be a genetic marker of vulnerability to schizophrenia and suggests that obstetric complications may additively interact with this endophenotype. Funding: The Wellcome Trust, NARSAD and The Health Research Board of Ireland.
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PSYCHIATRIC OUTCOMES AMONGST OFFSPRING WITH PARENTAL HISTORY OF MENTAL DISORDER

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Whilst parent-offspring associations for specific mental disorders are well established, knowledge of the broader range of psychiatric outcomes amongst offspring with parental history of serious mental illness (SMI) is not. The aim of the current study was to examine the full range of potential mental health outcomes occurring in a large national cohort, amongst offspring of parents with SMI compared to the general population. The cohort was obtained from linked Danish national registers and consisted of all offspring born in Denmark between1980 and 1992. Offspring were followed from their 14th birthday for the development of a range of psychiatric disorders (including schizophrenia, bipolar disorder, schizoaffective disorder, affective disorder, anxiety and somatoform disorders, personality disorder, substance abuse, and mental retardation) based on outpatient and inpatient hospital data. Offspring exposure groups were defined on the basis of parental history of mental illness and compared to those offspring without any parental history. Poisson regression modeling was used to obtain rate ratios for each exposure/outcome pair with account taken of offspring gender, age and calendar year. Parental SMI (in one or both parents) was found to be positively associated with all of the offspring psychiatric outcomes examined. Offspring with parents (one or both) without SMI but with a history of other psychiatric illness were also found to be at increased risk of developing any of the range of psychiatric outcomes. The strongest associations were found between history of parental illness in both parents and offspring illnesses. Offspring of two parents with SMI were almost 19 times more likely to develop schizophrenia for example. The elevated risks were not confined to concordant parent-offspring associations (eg, offspring of two SMI parents were also 9 times more likely to develop substance misuse disorders). The gender of the affected parent had only limited impact on offspring risk of illness. The impact of parental history of serious mental illness is not confined to elevated offspring risk of concordant disorders. Offspring are at increased risk of a wide range of mental disorders. This implies an important role for environmental factors and genetic factors giving rise to broad, as well as specific vulnerabilities, in the aetiology of familial risk.
ID: 550285

SCREENING FOR SUBCLINICAL PSYCHOSIS IN THE GENERAL ADOLESCENT POPULATION

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The aim of this study was to design a psychometric instrument with good sensitivity and specificity for the identification of subclinical psychotic symptoms in the general adolescent population. A screening questionnaire with seven questions designed to assess psychotic symptoms was administered to 334 children aged 11–13 years. (1) "Some people believe that their thoughts can be read by another person. Have other people ever read your mind?"; (2) "Have you ever had messages sent just to you through TV or radio?"; (3) "Have you ever thought that people are following or spying on you?"; (4) "Have you ever heard voices or sounds that no one else can hear?"; (5) "Have you ever felt you were under the control of some special power?"; (6) "Have you ever seen things that other people could not see?"; (7) "Have you ever felt like you had extra-special powers?". Answers were scored as follows: No = 0 points; Maybe = 0.5 points; Yes = 1 point. Using stratified random sampling we called adolescents with scores greater than or equal to 2 on the screener for clinical interview. We also called a comparison sample of adolescents who scored 0 or 1 on the screener for interview. In total, 44 adolescents were interviewed using the K-SADS interview schedule by a trained clinical interviewer (psychiatrist or psychologist). The results of these interviews were used to conduct sensitivity and specificity analyses for the questionnaire in the identification of psychotic symptoms. Twenty two participants reported no psychotic symptoms at interview, 17 reported 'definite' psychotic symptoms, and 5 reported 'possible' psychotic symptoms. Symptoms were rated as 'definite' or 'possible' by a consensus meeting after the interview. Three questions from the screening questionnaire (questions 3, 4 and 6) proved to have good predictive power for the detection of 'definite' psychotic symptoms on clinical interview. Table 1 shows that endorsement of these 3 core questions provided good predictive validity for subclinical psychotic symptoms. Our results suggest that a simple 3-item pen and paper questionnaire could be used to accurately screen for subclinical psychotic symptoms in early adolescence.

Table. Predictive validity of three core questions for psychotic symptoms

	PPV	NPV	Sensitivity	Specificity
Endorsement of at least one question	64%	95%	94%	67%
Endorsement of at least two questions	88%	89%	93%	82%
Endorsement of all three questions	100%	82%	65%	100%

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UNEMPLOYMENT AND RISK OF PSYCHOSIS IN BLACK AND MINORITY ETHNIC (BME) GROUPS

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Introduction: Unemployment is closely related to both relative deprivation and social drift of those predisposed to psychosis. Within a stress-vulnerability model of psychosis, unemployment would be plausible as a risk factor as well as early consequence of disease onset. However it has hardly been studied as an epidemiological risk factor for psychosis. Some black and minority ethnic groups with high rates of psychosis also have high rates of unemployment. The purpose of this study was to test the hypotheses that (i) the incidence of psychosis is higher in unemployed people and (ii) unemployed people from BME groups have a higher incidence of psychosis than unemployed White people Method: All patients who presented for the first time with an ICD-10 diagnosis of any psychotic illness, in a defined area of southeast London from 1998–2004 were identified. Electoral ward level data from 2001 census was used to calculate crude and standardised incidence rates of psychosis amongst unemployed people, by ethnicity (indirectly standardised to (a) the total employed population and (b) the employed white population, stratifying for age and gender). Standardised incidence ratios were calculated for each ethnic group. Results: Of

the 178 patients with psychosis, 100 cases occurred amongst employed people and 78 amongst the unemployed. The incidence of psychosis was very high amongst unemployed people and extremely high amongst Black Caribbean and Black African people. 3.4% (95% CI = 2.2–5.0%) of unemployed Black Caribbean people become psychotic per year and 2.5% (95% CI = 1.6–3.9%) of Black African people. Standardised to the employed population of the area, White unemployed had an almost 5-fold increased risk of psychosis (SIR 4.96; 95% CI = 2.71–8.32) compared to a 25-fold increase for Black Caribbean (SIR 24.9; 95% CI = 16.2–36.4) and more than 18-fold increase for Black Africans (SIR 18.7; 95% CI = 11.9–28.1). More markedly, when standardised to the employed White population of the area, White unemployed had an almost 12-fold increased risk of psychosis (SIR 11.8; 95% CI = 6.4–19.7), compared to a 60-fold increase in Black Caribbeans (SIR 60.1; 95% CI = 39.3–88.1) and more than 40-fold increase in Black Africans (SIR 40.7; 95% CI = 25.8–61.1). Conclusions: The incidence of psychosis is higher overall in people who are unemployed. Unemployed people from BME groups have a much higher incidence of psychosis than White people.
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HEARING VOICES IN CHILDHOOD: A PREVALENCE AND CASE-CONTROL STUDY OF AUDITORY HALLUCINATIONS IN MIDDLE CHILDHOOD

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Introduction: Voice hearing does occur in middle childhood, but little is known about its prevalence, etiology and consequences. Our aim is to investigate prevalence and characteristics of auditory vocal hallucinations (AVH) in 7-and-8-year-olds, as well as associations with pre- and perinatal influences, early development and current behaviour problems. Methods: AVH were assessed with the Auditory Vocal Hallucination Rating Scale in 3870 children; prospectively recorded data on pre- and perinatal complications, early development and current problem behaviour were analyzed in children with AVH and matched controls. Results: The one-year prevalence of AVH was 9%. 15% of AVH children reported severe suffering and AVH elicited more anxiety in girls. The prevalence for AVH was higher in rural areas but AVH were more severe, more often externally attributed and of greater functional impact in the urban environment. There was some evidence for an association with prenatal maternal infection and slower motor development in early life. Only weak associations were apparent between AVH and current problem behaviour. Conclusions: AVH in 7/8 year olds are prevalent but of functional consequence in only a minority. Nevertheless, there may be continuity with more severe psychotic outcomes given severe suffering in a subgroup, associations with early developmental deviance and evidence for a poorer prognosis in an urban environment.

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PSYCHOLOGICAL SCALES AS VULNERABILITY INDICATORS FOR SCHIZOPHRENIA

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We study the predictive power and associations of several schizotypal and temperament scales with respect to familial risk and developing of schizophrenic psychoses in a population-based birth cohort. Temperament and Character Inventory, Physical Anhedonia Scale, Social Anhedonia Scale, Perceptual Aberration Scale, Hypomanic Personality Scale, Bipolar II Scale, and Schizoidia Scale were included in the 31-year follow-up survey of the prospective Northern Finland 1966 Birth Cohort (N = 4,926). We compared subjects without any previous hospitalisations (N = 4,786) to those with previous hospital diagnoses for schizophrenia (N = 39) (concurrent validity) and to those who in the eight year long follow-up were hospitalised due to schizophrenic psychosis (N = 12) (predictive validity). We also compared the subjects with schizophrenic psychoses and subjects with other psychiatric disorders (discriminant validity, N = 101 for concurrent and N = 72 for predictive analyses). Familial risk was estimated through parental diagnoses of psychosis in hospital discharge register data (1972 to 2005). The Perceptual Aberration Scale was the best scale for concurrent (Effect Size, d = 1.89) and discriminant validity (d = 0.64). Subjects having a high score in Hypomanic Personality Scale (OR 10.72; 95% CI = 2.87–40.06) were in the highest risk for developing schizophrenic psychoses. High harm avoidance (d = 1.14 for concurrent cases) was a dominant temperament characteristic in schizophrenia when compared to controls. Controls with familial risk differed mostly from those without familial risk by having low physical anhedonia (d = −0.20) and high hypomania (d = 0.18). Subjects with schizophrenic psychoses differed in most of the scales from healthy controls and in a few from subjects with other psychiatric disorders. Many of the scales were useful predictors of developing schizophrenic psychoses; however scales were not very diagnosis specific. These scales are probably not useful as screening instruments but some (eg, Perceptual Aberration Scale) can be used as intermediate phenotypes when studying schizophrenia and related psychoses.
ID: 550223

ADVANCED PATERNAL AGE IS ASSOCIATED WITH IMPAIRED NEUROCOGNITIVE OUTCOMES DURING INFANCY AND CHILDHOOD IN A GENERAL POPULATION BIRTH COHORT.

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Background: Advanced paternal age (APA) is associated with an increased risk of neurodevelopmental disorders such as autism and schizophrenia, as well as with dyslexia and impaired intelligence. The aim of the study was to examine the relationship between paternal age and neurocognitive measures of children using a large birth cohort. Method: A sample of white singleton children ($n = 25,131$) was drawn from the US Collaborative Perinatal Project. The outcome measures were assessed at 8 months, 4 and 7 years (Bayley scales, Stanford Binet IQ, Graham-Ernhart test, Wechsler Intelligence Scale for Children, Wide Range Achievement Test). The main analyses examined the relationship between neurocognitive measures and paternal or maternal age when adjusted for potential confounding factors. Results: Advanced paternal age showed significant associations with poorer scores on all measures of the neurocognitive measures apart from Stanford Binet Intelligence Scale. The findings were consistent in direction and effect size at all three ages. In contrast, advanced maternal age was generally associated with better scores on these same measures. Discussion: The offspring of older fathers show subtle impairments on tests of neurocognitive ability during infancy and childhood. In light of secular trends related to delayed fatherhood, the mechanisms underlying these findings warrant closer scrutiny.
ID: 550204

NEURODEVELOPMENTAL RISK FACTORS FOR SCHIZOPHRENIA: POPULATION-BASED COHORT STUDIES

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Inspired in part by the pioneering work of Barbara Fish and Sarnoff Mednick, a number of studies have observed that obstetric complications are associated with increased risk for schizophrenia later in life. Such factors are also related to increased severity of certain neuropathological features of schizophrenia, including hippocampal and cortical gray matter reduction. However, it remains to be determined whether such complications result from the schizophrenia genotype (as in G-E covariation) or interact with genetic susceptibility to the disorder in disease expression. We conducted searches of the Finnish National Hospital Discharge and Perinatal Registers to ascertain pregnancy and birth information on 6471 offspring of parents with schizophrenia in the country of Finland, compared with 25 884 gender matched controls born on the same day and in the same obstetric units as the case offspring. A number of pregnancy and birth complications were found to be elevated in the offspring with schizophrenic mothers. However, there were no such increases among offspring of schizophrenic fathers. These results are consistent with the view that the occurrence of such complications is independent of genetic predisposition to schizophrenia, but may be influenced by maternal health risk behaviors, such as smoking. In another study, we examined whether neurotrophic factors, which are stimulated as part of a neuroprotective response to fetal distress, are differentially expressed in cord blood samples at the time of birth following particular obstetric stressors among individuals who developed schizophrenia as adults, as compared with demographically matched controls. This study utilized a nested case-control design including 111 cases with psychotic disorders (70 with schizophrenia) and 333 controls matched for gender, race, and date of birth, drawn from the Philadelphia cohort of the National Collaborative Perinatal Project. Among controls, birth asphyxia was associated with a significant (10%) increase in BDNF in cord samples, while among cases, asphyxia was associated with a significant (20%) decrease in BDNF. These findings provide serologically based prospective evidence of disrupted neurotrophic signaling in response to birth asphyxia in the molecular pathogenesis of schizophrenia and encourage search for genes that confer heightened susceptibility via disruptions in BNDF.
ID: 550055

LEPTIN AND ADIPONECTIN CONCENTRATIONS IN ANTIPSYCHOTIC-NAÏVE PATIENTS WITH NONAFFECTIVE PSYCHOSIS

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Some evidence suggests newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis have an increased risk of diabetes. Diabetes is associated with abnormal circulating concentrations of the adipokines leptin and adiponectin. We measured leptin and adinponectin in 32 fasting, newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis and control subjects ($N = 53$). The patients had a significant increase in leptin concentrations ($P > .001$ for the variable of patients vs. control subjects) after accounting for the variance due to age, gender, socioeconomic status, body mass index, smoking, cortisol, and aerobic conditioning (as measured by resting heart rate); the two groups were very similar with regard to race and neighborhood of residence so these two variables were not included in the multivariate analysis. Using the same variables, we found no significant patient/control difference in adiponectin. The difference in leptin, which could not be accounted for by a difference in body mass index, coupled with the evidence for an increased risk of diabetes, raises the possibility that patients with schizophrenia have increased visceral fat.
ID: 550050

THE FUTURE OF HIGH RISK RESEARCH

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During the five decades since Dr Barbara Fish initiated her groundbreaking research into the neurobiological antecedents of schizophrenia in children,

an impressive volume of literature spanning epidemiology, developmental neurology, cognitive psychology, neurophysiology and behavioural genetics has brought forth novel insights into the nature of "high risk". Recent research has not only vindicated the original evidence for an inherited neurointegrative vulnerability and the syndrome of pandysmaturation, but has by extension contributed to a more general understanding of schizophrenia as a basically neurodevelopmental disorder. Yet important gaps in knowledge remain. Neurobehavioural and mental disorders other than schizophrenia have until recently been less incisively investigated, and the study of gene-environment interactions and epigenetic regulation (both predicted by Dr Barbara Fish) is only now beginning to gather pace. The future of this area of research is bright and full of hope: the working alliance between developmental and clinical neuroscience, epidemiology and genetics is likely to unravel many of the present complexities and ultimately lead to practical means of risk containment and reduction.
ID: 549620

GENETIC AND ENVIRONMENTAL INFLUENCES ON THE OVERLAP BETWEEN PREMORBID IQ, PREMORBID SOCIAL ADJUSTMENT AND SCHIZOPHRENIA: A POPULATION-BASED TWIN AND SIBLING STUDY

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Background: Low premorbid IQ and abnormal premorbid social adjustment are consistent risk factors for schizophrenia in both prospective and cross-sectional studies. There are many potential explanations for the correlation between premorbid functioning and schizophrenia. As far as we know, no previous study has used the twin method to test competing explanations for the relation. In this study we used data from a population of twins and siblings in the Israeli Conscripts Cohort to examine the extent to which the covariation between premorbid functioning and schizophrenia is due to genetic overlap or environmental effects. Methods: Using the Israeli Conscripts Cohort, we ascertained 7321 pairs of same-sex monozygotic and dizygotic twins, and 251 500 pairs of same-sex siblings with information on intellectual and behavioral functioning at age 17. Linkage to a national psychiatric hospitalization registry identified 58 twin pairs discordant for schizophrenia, and 5 concordant twin pairs. There were 2234 discordant siblings-pairs, and 71 concordant siblings-pairs. Results: A significant phenotypic correlation ($r = -.15$) was observed between premorbid IQ and schizophrenia. Genetic factors were the main source of this correlation. Premorbid processing speed ability had the greatest genetic correlation with schizophrenia, followed by non-verbal reasoning ability. Both genetic and environmental factors contributed to the premorbid social adjustment <–> schizophrenia relationship ($r = -.14$ and $r = -.06$, respectively). Conclusions: Findings suggest that specific candidate genes and neurobiological processes should be tested in relation to both premorbid functioning and schizophrenia phenotypes. Further study of the potential mechanisms through which environmental factors confers risk for both premorbid functioning and schizophrenia is needed.
ID: 549618

SELF-REPORTED PSYCHOTIC SYMPTOMS IN THE COMMUNITY, AND RISK OF LATER HOSPITALIZATION FOR NON-AFFECTIVE PSYCHOTIC DISORDERS

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Research suggests that low-grade psychotic experiences in the general population are a common phenomenon, and previous studies indicate that persons experiencing low grade psychotic experiences are at increased risk for suffering from clinically diagnosed psychotic disorders. The aim of the current study is to assess the predictive validity of self-reported psychotic symptoms on risk for later psychosis, and to identify the effect of poor education achievements (less then 12 years of formal education) or cannabis abuse on risk for later hospitalization, in those persons experiencing psychotic symptoms. This study utilizes data from an epidemiological study of young adults aged 25–34 conducted in the 1980's in Israel. A random sample of 4914 subjects were screened for psychiatric symptoms using a standardized clinical interview. The interview included questions regarding psychotic symptoms (delusions, hallucinations, thought broadcasting, etc). Data on later psychiatric hospitalization was ascertained in 2008 using a psychiatric hospitalization registry, enabling up to 25 years follow-up. Similar to data from previous studies, 25% of the subjects interviewed reported having experienced one or more psychotic symptoms during their lifetime. Self-reported psychotic symptoms increased risk of later hospitalization for psychosis (OR = 3.04, 95% CI: 1.19–7.76). In terms of population attributable risk, 34% of hospital admissions for psychotic disorders could be attributed to the presence of psychotic symptoms at baseline. In individuals with psychotic symptoms, poor educational achievements or cannabis abuse did not further increase risk for later hospitalization. In individuals aged 25–34, a quarter of the population suffers from psychotic symptoms, and these symptoms are associated with increased risk of later hospitalization for a psychotic disorder. These data suggest that screening for psychotic symptoms might enable early identification and intervention, hence decreasing hospitalizations for psychotic illness. Lower educational attainment or a history of drug abuse did not increase risk for later hospitailzation among those with psychotic symptoms.
ID: 549612

BIRTH WEIGHT AND RISK OF SCHIZOPHRENIA OR OTHER MENTAL DISORDER: IS IT CONFINED TO SMALL BABIES?

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Studies have shown a link between low birthweight and adult mental illness, but have focused on the WHO threshold of 2.5kg, and on schizophrenia as

the sole outcome. Our objectives were to examine whether: (i) increased risk for adult schizophrenia is specifically associated with birthweight <2.5kg rather than being spread across the birthweight range; (ii) excess risk is confined to schizophrenia, or also linked with other adult mental illness. We used a population-based cohort design using data from two adjacent Scandinavian countries: all singleton live births in Sweden during 1973–1985 and in Denmark 1979–1986 (N = 1.64 million in total). These births were linked to comprehensive national registers of inpatient psychiatric treatment, with follow-up to December 31, 2002 in Sweden and June 30, 2005 in Denmark. Our main outcome measures were the odds of birthweight less than 4000–4499g in consecutive 500g strata down to 500–1499g among people admitted with any psychiatric diagnosis, schizophrenia or affective disorder versus the general population. For all diagnostic groups combined, there was a clear trend in increasing odds ratios with decreasing birthweight across the birthweight range: 3500–3999g OR = 1.1; 3000–3499g OR = 1.2; 2500–2999g OR = 1.5; 2000–2499g OR = 1.8; 1500–1999g OR = 2.0; 500–1499g OR = 2.2. This pattern was mirrored in the two specific diagnostic groups. We found no indication of specificity of effect with either schizophrenia or affective disorder. Country of birth, year of birth and sex had a modest combined confounding effect in the inter-country cohort. In Sweden, socioeconomic status also had little confounding effect, although maternal antenatal smoking was a stronger confounder. Even when the cohort was restricted to term births, the patterns of birthweight risk across the normal range persisted. Our findings suggest that the association between birthweight and risk of mental disorder occurs across the normal birthweight range and that there is no evidence of a threshold effect. We do not find that risk is specific to a particular diagnosis. Findings suggest that the range of (environmental and other) causes of poor fetal growth interact with more specific causes of individual diagnoses (genes, postnatal experiences) to enable expression of a particular mental disorder. Future prevention strategies might usefully target the majority at medium risk rather than a high risk minority.
ID: 549598

PREVALENCE OF CELIAC DISEASE AND GLUTEN SENSITIVITY IN THE CATIE STUDY POPULATION

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Celiac Disease (CD) and schizophrenia (SZ) share approximately overlapping prevalence but epidemiologic data show higher prevalence of CD among SZ patients. The reason for this higher co-occurrence is yet unknown but the clinical knowledge about the presence of immunologic markers for CD or gluten intolerance in SZ patients may have implications for treatment. We evaluated antibody prevalence to gliadin (AGA), transglutaminase (tTG) and endomysium (EMA). AGA, tTG and EMA was assayed in 1410 SZ patients who were part of the Clinical Antipsychotic Trials of Intervention Effectivness (CATIE) study and 6796 controls. Psychopathology in SZ patients was assessed using the Positive and Negative Symptoms Scale or PANSS. Chi-square test was applied to assess for difference in the frequency of IgA AGA and tTG antibodies. Regression analyses were conducted to predict PANSS scores from AGA and tTG antibodies adjusting for age, gender, and race. Among SZ patients 22% had moderate to high levels of IgA AGA compared to 7.9% of the controls (χ^2 = 1234.6, df = 2, P < .001.) Moderate to high levels of tTG antibodies were present in 4.7% of SZ patients vs. 2.4% of the controls (χ^2= 68.9, df =2, P < .001.) Regression analyses failed to predict PANSS scores from AGA and tTG antibodies. Persons with schizophrenia have higher titers of antibodies related to celiac disease and gluten sensitivity. Our findings might have implications for the treatment of SZ patients given that a gluten-free diet may contribute to the improvement of symptoms.
ID: 549343

COMPLEX GENETIC VARIATION IN BDNF AND COMT GENES INTERACTS WITH ADOLESCENT CANNABIS USE IN THE DEVELOPMENT OF PSYCHOSIS.

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Interaction between adolescent cannabis use (<16 yrs) and BDNF functional haplotypic variation can be plausibly hypothesized, given the importance of both the endocannabinoid system and neurotrophins in processes of neurodevelopment, neuroplasticity and cognition. Furthermore, gene-environment interaction between adolescent cannabis use and COMT Val158Met was previously suggested. 2 SNPs within the BDNF gene were genotyped: the functional Val66Met polymorphism, of which Met-substitution is associated with reduced intracellular trafficking and activity-dependent BDNF secretion, and rs988748, which was reported to form a haplotype with Val66Met. Five polymorphisms in the COMT gene were also genotyped, four of which were recently described to form three common functional haplotypes that better index COMT enzymatic activity than Val158Met alone (rs6269, rs4633, rs4818, Val158Met). rs737865, a polymorphism associated with schizophrenia in a recent meta-analysis (Allen et al. Nature Genetics, 2008), was also genotyped. Case-only haplotype analysis in 587 psychotic patients revealed a significantly higher odds for adolescent cannabis use for the BDNF Met/rs988748_G haplotype compared to the other BDNF haplotypes (OR 2.04, P = .033) as well as a trend for a higher odds for the 4-SNP COMT high activity 'LPS' haplotype compared to the other COMT haplotypes (OR 1.60, P = .055). Remarkably, the association between COMT LPS haplotype and adolescent cannabis use was dependent of rs737865 genotype (LPS/rs737865_T: OR 2.11, P = .016; LPS/rs737865_C: OR 1.25, P = .469), and there was a trend towards antagonistic BDNF x COMT interaction (β =−0.83, P = .065). The associations between adolescent cannabis use and BDNF and COMT haplotypes remained significant and similar in magnitude after controlling for other psychotogenic drugs, and the gene-by-gene antagonistic interaction now also reached statistical significance (β =−1.04, P = .048). No significant association was found between BDNF or COMT haplotypes and cannabis use started after the age of 16, or with use of any of the other substances. In conclusion, complex haplotypic variation within BDNF and COMT interacts with adolescent cannabis use in the development of psychosis, and these haplotypes may act through independent pathways. Therefore, these findings may serve as a 'magnifying glass' in order to elucidate the pathophysiological mechanisms driving the psychotogenic effects of cannabis.
ID: 549322

INCREASED PREVALENCE OF ANTIBODIES TO TOXOPLASMA IN RECENT ONSET PSYCHOSIS

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Background: Increased rates of infection with Toxoplasma gondii have been found in individuals with recent onset psychosis but this issue has

not been studied in samples in the United States. Methods: We measured IgG class antibodies to Toxoplasma gondii in $N = 127$ individuals with recent onset psychosis, $N = 457$ individuals with multi-episode schizophrenia, and $N = 164$ individuals with multi-episode bipolar disorder. We compared serological evidence of Toxoplasma infection in these groups with that of $N = 283$ control individuals without a history of psychiatric disorder. All participants were from central Maryland in the US. Within the recent onset group, we also determined the correlates of Toxoplasma seropositivity. Results: There was a higher prevalence of serological evidence of Toxoplasma infection in individuals with recent onset psychosis (21.3%) than in controls (13.8%) (OR 2.06, 95% CI = 1.1–3.7, $P < .020$ adjusted for age, gender, race, and education). Within the recent onset group, the prevalence of Toxoplasma seropositivity was highest among individuals with a diagnosis of schizophrenia (29.6%) compared with bipolar disorder (18%) or other diagnosis (15.2%). Within the recent onset group, Toxoplasma seropositivity was correlated with receipt of olanzapine (OR 3.2, 95% CI = 1.2–9.0, $P < .025$ adjusted for age, gender, race, education, and diagnosis). Serological evidence of Toxoplasma infection within the recent onset group did not differ by age, gender, or race (all $P > .1$). The seroprevalence of Toxoplasma in the individuals with multi-episode schizophrenia and multi-episode bipolar disorder did not differ significantly from that of the controls. Conclusions: Our results add to the growing body of literature indicating that individuals with recent onset psychosis have an increased rate of exposure to Toxoplasma gondii compared to controls living in the same geographic region. Our findings support a possible role for Toxoplasma gondii in the etiopathogenesis of schizophrenia and provide a rationale for trials of anti-Toxoplasma medications in individuals with schizophrenia.
ID: 549197

ENVIRONMENTAL AND FAMILIAL DETERMINANTS OF ADVERSE NEUROPSYCHIATRIC OUTCOMES IN HIGH RISK CHILDREN OF MOTHERS WITH SCHIZOPHRENIA AND OTHER PSYCHOSES

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This study is designed to untangle environmental and familial contributions to risk of adverse neuropsychiatric outcomes (intellectual disability; psychiatric morbidity) in genetically high risk children of women with psychoses. We linked the Statewide midwives register (308 022 births) and psychiatric case register (79 599 women) to identify 3174 high risk children born 1980–92 to mothers with schizophrenia, bipolar disorder or unipolar depression, and a comparison group of 3129 children born to unaffected mothers. Psychiatric status and cognitive level were determined for mothers, fathers and children, and data collected on obstetric complications. Time-to-event data were analysed using Cox regression. Of 6303 children, 750 had had a psychiatric illness: 18.1% of schizophrenia offspring, 20.1% of bipolar offspring, 16.0% of unipolar offspring and 5.6% of comparison children. Maternal psychosis and obstetric complications were independently associated with risk of psychiatric illness in offspring. In this young cohort, 57 children had a diagnosis of psychosis: 3.1% of schizophrenia offspring, 1.2% of bipolar offspring, 0.9% of unipolar offspring and 0.4% of comparison children. Maternal schizophrenia (OR 8.0, CI 3.6–18.2) and bipolar disorder (OR 2.6, CI 1.1–6.0) were associated with risk of psychoses. The effect for obstetric complications variables was not significant although the odds were el-

evated. There were 129 children with intellectual disability (AAMR criteria). Odds of intellectual disability was increased 3-fold in case compared to comparison children. Parental cognitive level, maternal psychosis, paternal psychiatric illness, and labour/delivery complications were independent risk factors for intellectual disability. Case children were more likely than comparison children to have psychiatric illness co-occurring with intellectual disability ($P < .000$). In conclusion, children of mothers with psychoses were at significantly greater risk of neuropsychiatric outcomes compared to children of unaffected mothers. Environmental insults and familial liability exerted independent effects on risk of intellectual disability and of psychiatric illness across all case groups. Risk of psychoses was differentially distributed but numbers were small and further analysis is warranted using a dataset under construction of half a million children.
ID: 548805

CHILDHOOD TRAUMA AND INCREASED STRESS-SENSITIVITY IN PSYCHOSIS: AN EXPERIENCE SAMPLING STUDY

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Background: Increasing epidemiological evidence suggests that traumatic experiences in childhood are associated with the development of clinical and sub-clinical psychosis in adulthood. However, the mechanism through which trauma leads to an increased risk for psychosis remains unclear. Previous studies have demonstrated that increased sensitivity to daily life stress is part of the underlying vulnerability for psychosis. The current study hypothesises that early trauma increases the risk for psychosis through sensitizing people for the small stresses of daily life. Method: The sample consisted of three groups: patients with a diagnosis of psychotic disorder with a recent onset (<10 years) ($n = 47$), their first degree relatives ($n = 43$) and healthy control subjects ($n = 48$). The Experience Sampling Method (ESM; a structured diary technique) was used to assess stress-reactivity in daily life defined as (1) emotional reactivity (increase in negative affect) and (2) psychotic reactivity (increase in psychosis intensity) in reaction to stress. Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ). Results: Group was significantly associated with trauma level ($F = 8.14$, $P < .0001$), with patients reporting significantly more trauma compared to the relatives and controls. A history of severe trauma significantly increased the emotional ($B = 0.11$ (SE = 0.03), $P < .001$) and the psychotic ($B = 0.17$ (SE = 0.03), $P < .001$) reaction to stress in the patients. Conclusions: The results support previous findings that patients with psychosis report increased levels of childhood trauma compared to controls. In addition, the findings suggest a mechanism of sensitization underlying the trauma—psychosis association, since a history of childhood trauma results in increased psychotic en emotional reactions to stress.
ID: 548793

BARBARA FISH'S LANDMARK STUDIES AND THEIR INFLUENCE ON PARENT-BASED HIGH-RISK STUDIES DURING THE PAST 50 YEARS

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With the assistance of Barbara Fish herself, the speaker summarizes the landmark studies of Barbara Fish beginning in the 1950's, and discusses their place in the zeitgeist of American psychiatry at that time, their

influence on the ensuing multitude of parent-based high-risk studies beginning in the 1970's, following the NIMH and Danish studies in the mid-1960, and their indelible foot prints observed in ongoing high-risk studies of that type. Fish's concept of "pandysmaturation" (PDM) is for example applied to the speaker's prospective high-risk study data, within the framework of the now pervasive "neurodevelopmental" model for serious psychopathology.
ID: 548789

PATIENTS WITH FIRST EPISODE PSYCHOSIS TAKE MORE AND STRONGER CANNABIS THAN CONTROLS.

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Background: Epidemiological studies have reported that the increased risk of developing psychosis in cannabis users is dose related. In addition, experimental research has shown that the active constituent of cannabis responsible for its psychotogenic effect is Delta-9-Tetrahydrocannabinol (THC) (Murray et al. 2007). Recent evidence has suggested an increased in potency (% TCH) in the cannabis seized in the UK (Potter et al. 2007). Hypothesis: We predicted that first episode psychosis patients are more likely to use higher potency cannabis and more frequently than controls. Methods: We collected information concerning socio-demographic, clinical characteristics and cannabis use (age at first use, frequency, length of use, type of cannabis used) from a sample of 191 first-episode psychosis patients and 120 matched healthy volunteers. All were recruited as part of the Genetic and Psychosis (GAP) study which studied all patients who presented to the South London and Maudsley Trust. Results: There was no significant difference in the life-time prevalence of cannabis use or age at first use between cases and controls. However, cases were more likely to be regular users ($P = .05$), to be current users ($P = .04$) and to have smoked cannabis for longer ($P = .01$). Among cannabis users, 86.8% of 1st Episode Psychosis Patients preferentially used Skunk/Sinsemilla compared to 27.7% of Controls. Only 13.2 % of 1st Episode psychosis Patients chose to use Resin/Hash compared to 76.3% of controls (OR* = 7.4, 95% CI = 3.4–17.2, Adjusted for age, gender, ethnicity, level of Education and employment status).The concentration of TCH in these in South East London, ranges between 8.5 and 14% (Potter et al. 2007). Controls (47%) were more likely to use Hash (Resin) whose average TCH concentration is 3.4% (Potter et al. 2007). Conclusions: Patients with first episode psychosis have smoked higher potency cannabis, for longer and with greater frequency, than healthy controls.
ID: 546713

THE SCHIZOPHRENIA PARADOX REVISITED: LIFETIME REPRODUCTIVE OUTPUT OVER TWO GENERATIONS IN A SWEDISH COHORT BORN 1915–1929

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Background: Schizophrenia is a highly heritable disorder of early onset, which severely curtails reproductive output, yet it persists at a relatively constant population prevalence over time (the schizophrenia paradox). It has been suggested that the fitness disadvantage associated with schizophrenia might be compensated by increased fitness in unaffected relatives, otherwise the prevalence of schizophrenia would fall to zero in a few generations. Little is known about reproductive success in affective psychoses. To study these questions with a minimum of bias requires longitudinal population data over several generations. Methods: We conducted a historical cohort study using a Swedish birth cohort of 12 168 individuals born 1915–29, and followed up until 2002. By linking to data from population registers, we identified patients with schizophrenia ($n = 58$) or affective psychosis ($n = 153$) and their unaffected siblings, and compared their biological fitness over two generations with that of the population, adjusting for a range of socio-demographic variables from throughout the lifespan. This is the first study to use prospectively collected data across the entire reproductive lifespan of a defined population, and to include data on grandchildren as well as children. Results: There was strong evidence that patients with schizophrenia had fewer children (fertility ratio = 0.42 [95% confidence interval (CI) = 0.31–0.56]) than the healthy population. Much of this reduction was related to low marriage rates in schizophrenic patients. The unaffected siblings of schizophrenic patients showed no evidence of any compensatory increase in fitness. There was a trend towards enhanced fertility among the offspring of schizophrenia patients, although this was not enough to compensate for the reduced fertility in patients, so schizophrenic patients still had fewer grandchildren overall than the healthy population (Fertility Ratio = 0.52 [95% CI = 0.33–0.80]). Patients with affective psychosis did not differ from the general population on any fertility measure, and neither did their siblings and offspring. Conclusions: Schizophrenia, but not affective psychosis, is associated with reduced biological fitness. This persists into the second generation, but with tentative evidence of compensatory increase in fitness in the offspring of schizophrenic patients.
ID: 543922

EARLY EXPOSURE TO CANNABIS AND RISK FOR PSYCHOSIS IN YOUNG ADOLESCENTS IN TRINIDAD

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Introduction: Cannabis is worldwide the most frequently used illicit drug, in particular among young people. Cannabis use increases the risk for psychosis, but these psychotogenic effects of cannabis may be restricted to exposure during early adolescence. Method In a general population based study, 472 participants (aged 12–23 years) were randomly selected from different schools in Trinidad (Republic of Trinidad and Tobago). Subjects completed questionnaires on past and current cannabis use and psychotic symptoms (using the Community Assessment of Psychic Experiences, a self-report questionnaire for psychotic experiences). Results Cannabis use increased the risk to experience psychotic symptoms and this effect was conditional upon early exposure. Exposure before but not after the median age of 14 years predicted psychotic symptoms (respectively β: 0.71, 95% CI = 0.22; 1.19, $P = .004$ and β: −0.11, 95% CI = −0.57; 0.36, $P = .66$). The developmental effect of cannabis use was independent of use of other drugs or current use of cannabis. Conclusion Early onset of cannabis use is associated with a greater risk of developing psychotic symptoms than later onset of use. It seems that cannabis early exposure effects are developmental in nature and that they do not simply reflect effects of long-term exposure associated with earlier onset of use. Thus, early adolescence may be a critical period with regard to the psychotogenic effect of cannabis. In addition, this is the first study, to our knowledge, to show psychotogenic effects of early cannabis exposure in a non-western society,

where cannabis use has a long, non-stigmatized history for medical and recreational use.
ID: 540988

GENDER DIFFERENCES OF PERSONS WITH SCHIZOPHRENIA IN RURAL CHINA

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The gender characteristics of persons with schizophrenia in rural community are still unknown. The goal of this study is to explore the gender differences of persons with schizophrenia in a longitudinal study in rural China. Methods: A 10-year follow-up investigation among a 1994 cohort ($n = 510$) of patients with schizophrenia was conducted in Xinjin County, Chengdu, China. All the patients and their informants (100%) were followed up in 2004 using Patients Follow-up Scale (PFS). Results: The results indicated that male patients had significantly higher level of education and rates of unmarried and divorced than females. Female patients had significantly more family members. Male patients had significantly worse social function. The rate of homelessness was significantly higher in male than in female (Log-rank test, $\chi^2 = 4.00$, $P < .05$). The mortality rate was significantly higher in male {2913 per 100 000 person-years (95% CI = 2174–3652)} than female patients {1661 per 100 000 person-years (95% CI = 1150–2172)} (Hazard ratio 2.0, 95% CI = 1.3–3.2, $P < .005$). Although there were no significant differences of suicidal attempts between male and female patients, the suicide rate was significantly higher in male {753 per 100 000 person-years (95% CI = 373–1133)} than female patients {249 per 100 000 person-years (95% CI = 50–448)} (Hazard ratio 3.1, 95% CI = 1.2–8.0, $P < .05$). Conclusions: The outcome of male patients is worse than females in rural China. Higher mortality and suicide in male than female patients may contribute to the higher prevalence of schizophrenia in women than in men in China. Specific intervention strategies for improving the outcome of the illness should be developed for male and female patients with schizophrenia. Acknowledgments: This work was supported in part by GRIP 1 R01 TW007260–01 (M.S. Ran, PI) from the Fogarty International Center of NIH.

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A FURTHER EXPLORATION OF THE GENDER DIFFERENCES IN THE AGE OF ONSET OF SCHIZOPHRENIA

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Background: Whether the well-replicated association between male gender and early onset of schizophrenia constitutes a biological characteristic of the disorder (deLisi, 1992) or reflect a differential risk factor profile across men and women modulating the timing of onset remains unclear. Methods: All new cases who met RDC diagnostic criteria for schizophrenia, in Camberwell and in Dumfries and Galloway over 20 years (1979–1998; $n = 615$) were retrospectively identified. A standardised checklist and the OPCRIT computer algorithm were used to generate diagnoses and extract premorbid risk factors. The association of gender with age of onset was examined using univariate and multivariate statistics. As age of onset was non-normally distributed Mann Whitney U test was used in univariate and an amixture analyses was used to generate age of onset groups for ordinal logistic regression. Results: All risk factors were strongly associated with age of onset in univariate analyses except winter birth and family history of other psychiatric disorders. Admixture analyses identified 3 age of onset classes: an early onset (age at first presentation <42 year), a late onset (age 42–64 years) and a very late onset schizophrenia group (after age of 64). Ordinal logistic regressing gender on age of onset found a highly significant association across the age groups with the highest probability of effect estimate varying with gender in the early onset group (0.69 reducing to 17.38 in the LATE and a probability of only 13.42 in the VERY LATE onset group). The probabilities of variation in effect of gender across the age groups was very much reduced after adjusting for being single, unemployed , premorbid social and occupational adjustment, premorbid cannabis use, urban environment, ethnic minority status, family history of schizophrenia, with the probability of change in effect of just 0.12 in the early onset group, 0.07 in the late onset group and 0.05 in the very late onset group (the proportional odds assumption was valid in both sets of analyses). Conclusion: This study supports the assertion that the association between age of onset and gender can be largely explained by differential exposure of other known risk factors, and is consistent with previous studies which have demonstrated a strong confounding effect of social demographic variables (Jablensky and Cole, 1997).
ID: 551904

MORE PREMORBID CANNABIS USE WITH THE VAL ALLELE OF THE CATECHOL-O-METHYLTRANS-FERASE GENE ASSOCIATED WITH INCREASED RISK FOR SCHIZOPHRENIA

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Current thinking is that environmental influences interact with vulnerabilities in some individuals to trigger the onset of certain illnesses, such as schizophrenia. Literature on the subject supports cannabis use, and to some extent, the COMT Val allele, as risk factors for schizophrenia. Recently, adolescent cannabis use was found to interact with COMT genotype, increasing the risk for schizophrenia (Caspi et al., 2005). However, few cases were found, greatly reducing subjects in each cell, and cannabis use was dichotomized into use and non-use. Because the literature suggests a dose-response relationship between cannabis use and schizophrenia, and because onset of use has to precede the prodrome to accommodate a causal model of cannabis, we believed greater methodological precision could increase internal validity. Prodrome onset was carefully dated, and total premorbid cannabis use was estimated in 72 schizophrenia patients and 63 controls. Logistic regressions, to explain the risk of being a patient, showed a significant interaction between the Val allele (Val/Val, Val/Met) and cannabis use: greater cannabis use increasing significantly the risk of being a patient in Val allele carriers compared to homozygous Met allele carriers. No effect of cannabis use on schizophrenia was found for the Met/Met genotype. These results support the hypothesis of a genetic vulnerability working in combination with environmental influences to increase the risk for schizophrenia.
ID: 551843

CANNABIS USE IN YOUNG PEOPLE AT HIGH RISK OF DEVELOPING PSYCHOSIS

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Strong evidence exists to show that cannabis use is associated with psychosis and, as cannabis is the most widely used of illicit substances, this constitutes a serious public health concern. The nature of the association between cannabis and psychosis has been the topic of much discussion and it has been tempting to assume a causal relationship. In order to understand better the role of cannabis in the development of psychotic symptoms and disorder, it is important to investigate cannabis use in people who are at high risk of developing psychosis. Information about lifetime cannabis and other substance use was obtained from 122 participants at 'ultra high' risk of developing psychosis. This information was used to investigate the relationship between cannabis use and symptom severity, level of functioning, and the subsequent onset of psychosis. The rate of cannabis use was high: 78.7% of participants reported having tried it at least once. Only 18.5% of the sample was currently using cannabis, but the majority of those that had tried it reported a past period of regular use. Lifetime or current cannabis use was not associated with positive symptoms scores. However, those that had used cannabis heavily, even in the past, presented with higher scores on the PANSS positive subscale item for suspiciousness and persecution (median score 3 vs 1; $P = .026$). No significant differences were found in the rate of transition to psychosis between cannabis users and non-users. However, early-onset cannabis users who also used drugs such as amphetamine and ecstasy tended to be more likely to become psychotic ($P = .064$). The results show that heavy cannabis use is associated with greater levels of persecutory ideation in people at high risk of developing psychosis. However, cannabis use alone does not appear to increase further the risk psychosis within this population. It might be that cannabis use in the context of other substance use, particularly stimulants, is more important.
ID: 551830

DO FIRST- AND SECOND-GENERATION MIGRANTS HAVE A SIMILARLY ELEVATED RISK OF DEVELOPING PSYCHOTIC DISORDERS? A SYSTEMATIC REVIEW

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Background: It has been replicated that migration is a risk factor for psychotic disorders such as schizophrenia. However, it is not clear yet whether the risk increase found among first-generation immigrants persists or even increases among second-generation migrants. This determination is crucial to provide viable explanations for the correlation between migration and psychotic disorders, and to provide insights into potential social causation mechanisms. Objectives: a) to examine the magnitude of risk of developing psychotic disorders among second-generation migrants in comparison with first-generation migrants and reference groups; b) to explore potential mechanisms underlying these findings. Methods: Four databases were searched for relevant articles between 1977 and 2008. Potential studies were screened by two independent reviewers in a two-fold process. Studies were included if they reported numerators and denominators from a defined area, differentiated first- and second-generation migrants, and provided age-corrected data. Data extraction and quality analysis was performed on included studies. Mean weighted relative risk for psychotic disorders was computed for both first- and second-generation migrants, first using all available effect sizes, then using only those studies reporting rates for both migrant generations in order to reduce heterogeneity. Results: The preliminary analysis of the selected studies suggest that the increased risk for psychotic disorders observed among first-generation migrants is also present among second-generation migrants, with a trend toward a further risk increase. However, there remains significant heterogeneity across studies.

Conclusion: The persistence of an elevated risk among second-generation migrants suggests that post-migration factors have likely more impact than the migratory process per se or pre-migration factors, thus supporting social causation mechanisms. Urbanicity, childhood adversity, discrimination and social defeat are among the proposed social factors of relevance to both first- and second-generation migrants.
ID: 551796

CHANGES IN INCIDENCE OF PSYCHOSIS IN A LOCALITY OVER TIME—CLUES TO SOCIOENVIRONMENTAL AETIOLOGY

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Since the earliest research into psychosis, positive associations have been repeatedly found between social adversity and incidence rates of schizophrenia. It has been difficult however to completely exclude the possibility of reverse causality. Natural experiments provide such an opportunity and have produced some evidence that hostility towards minority groups in Israel and Canada is linked to increased rates of psychosis. The social context in which people live changes in response to political and economic events. This can then be investigated as a natural experiment. 9/11 and subsequent events in Europe including Islamophobia were such major events. If social hostility is a factor in the aetiology of psychosis in the short term, it would be predicted that rates of psychosis in Europe would drop amongst people of Caribbean descent (who are overwhelmingly Christian) and rise amongst people who identify themselves as Muslims. The Camberwell Case Register has collected every incidence case of psychosis from a geographically defined area of South East London for over four decades up to 2004. The Black Caribbean and Black African populations who have very high rates of schizophrenia and other psychoses, are overwhelmingly Christian. The purpose of this study was to test whether rates fell amongst Black Caribbean and Black African people after 2001. A binary variable was created to distinguish cases as presenting from 1993 up to and including 2001 or from 2002 to 2004. Poisson regression modelling was carried out to estimate the effect of this variable on incidence and adjust for age, gender and ethnicity if these improved the model. First the cases were stratified into the two ethnic group categories and the Poisson regression modelling repeated for each stratum. The analysis then proceeded to test for an interaction between ethnicity (as the binary variable white and black ethnic minority) and date of presentation, adjusting for age and gender. The results for the overwhelmingly Christian Black Minority Ethnic population show protective effects for onset post-2001 (IRR = 0.54, 95% CI = 0.33–0.87, $P = .012$), age, and to a lesser extent, gender. Thus, the incidence of psychosis in the Black Minority Ethnic population in South-East London was significantly lower in the years 2002 to 2004 inclusive compared to the years 1993 to 2001. This lends support to the theory of social hostility although other explanations are possible.
ID: 551793

NEIGHBORHOOD SOCIAL CHARACTERISTICS AND THE INCIDENCE OF PSYCHOTIC DISORDERS

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One of the most consistent findings in the epidemiology of schizophrenia is that those who live in cities are at greater risk. It is less clear which risk factors drive this increased risk, because few attempts have been made

to move beyond the crude measure of urbanicity. Social factors across different levels of organization may be involved, in particular those involving availability of and access to social capital. We conducted a first contact incidence study of psychotic disorders between 1997 and 2005 in the city of The Hague, the Netherlands (n = 618) and investigated associations between individual and neighborhood characteristics and incidence of psychotic disorders, using multilevel Poisson regression analysis. First, after adjustment for individual level age, sex, marital status and ethnic minority status, measures of neighborhood socioeconomic level, residential mobility, population density, voter turnout at local elections and crime level were all significantly associated with the incidence of psychotic disorders in a dose-response fashion. We calculated a cumulative score of neighborhood social disadvantage, based on these five indicators and divided it into tertiles (low, medium and high social disadvantage). The individual level adjusted incidence rate ratio (IRR) of psychotic disorders was 1.89 (95% Confidence Interval, 1.38–2.60) for individuals living in the socially most disadvantaged neighborhoods and was 1.35 (95% CI = 0.95–1.92) for those living in moderately disadvantaged neighborhoods compared to those living in the most advantaged areas (Wald x2 [df = 2], 18.19, P < .0005). Second, we investigated the effect of the ethnic composition of neighborhoods on the incidence of psychotic disorders, not only among ethnic minorities, but also among native Dutch. In neighborhoods with a very high proportion of non-Western ethnic minorities, the incidence rate for native Dutch was 35.4 per 100 000 (95% CI = 18.2–62.1), indirectly standardized to age, sex and neighborhood socioeconomic level. In neighborhoods with a relatively low proportion of ethnic minorities, the incidence rate for native Dutch was 21.1 (18.4–24.2). Among ethnic minorities, the pattern was opposite. These results are suggestive for an ethnic density effect both in ethnic minorities and in native Dutch. Thus, neighborhood social characteristics strongly influence the incidence of psychotic disorders within an urban environment in interplay with individual factors.
ID: 551769

EXPOSURE TO PRENATAL MATERNAL STRESS PREDICTS DEVELOPMENT RESEMBLING THAT OF HIGH RISK AND PRE-SCHIZOPHRENIC CHILDREN

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Because retrospective studies suggest that stress to the pregnant mother increases risk for schizophrenia, our goal was to determine whether prenatal maternal stress explains variance in childhood characteristics seen in pre-schizophrenic and high risk populations using a prospective approach. We have followed more than 150 children whose mothers were pregnant during the January 1998 Quebec ice storm crisis, contacting families up to 10 times since shortly after the disaster to determine if effects could be seen on the children's cognitive, behavioural, or physical development. Ice storm stress was separated into objective aspects of exposure (eg, days without power, financial loss) and subjective reaction (PTSD-like symptoms rated from the Impact of Event Scale—Revised). At the 2005 ICOSR we reported that greater prenatal maternal stress from the ice storm was associated with poorer IQ and language at 2 years, more behavioural problems at 3 years, and greater dermatoglyphic asymmetry. Here, we report results through age 5 years of age. Results indicate significant effects of the severity of maternal objective stress from the ice storm on cognitive and language development at age 5 years: WPPSI IQ scores were significantly lower for the high stress group than for the low stress group, especially in verbal IQ; and the high pre-

natal stress group had significantly lower Peabody Picture Vocabulary Test scores than the low stress group. Also at 5 years, children from the high objective stress group exhibited significantly more severe autistic-like symptoms, whether rated by parents or teachers, than those in the low stress group. Effects of exposure are also seen on physical markers. The ratio of the 2nd (index) to 4th (ring) fingers (the 2D:4D ratio) is a sexually dimorphic trait, with women having lower ratios than men. Our results show that prenatal stress from the ice storm predicted this ratio in 5 year olds. Results also show that exposure to the ice storm was associated with a feminization of the ratio; other studies show that schizophrenic men and women tend to have more feminine ratios than controls. In conclusion, we find that prenatal stress from a natural disaster is associated with many traits seen in pre-schizophrenic or high risk children. Supported by grants from the Stairs Memorial Fund (McGill University), Canadian Psychiatric Research Foundation, and Canadian Institutes of Health Research.
ID: 551765

THE SOCIAL DETERMINANTS OF HIGH RATES OF PSYCHOSIS IN THE UK BLACK CARIBBEAN AND BLACK AFRICAN POPULATIONS: A SYNTHESIS OF FINDINGS FROM THE AESOP STUDY

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The incidence of schizophrenia and other psychoses is elevated in migrant and ethnic minority groups. The ÆSOP study was established to test hypotheses concerning social and biological factors that might explain the increased incidence of these disorders in the UK Black Caribbean and Black African populations. ÆSOP is a multi-centre incidence and case-control study of first-episode psychosis. Cases were all individuals presenting to specialist mental health services for a first time with a psychotic disorder over a two-year period. Controls were a group of randomly selected, population-based volunteers recruited over the same time period. We collected data on clinical presentation, ethnicity and a range of potential social and biological risk factors. ICD-10 and DSM-IV diagnoses were determined by consensus, blind to the subject's ethnicity. Over the study period, 535 incident cases and 391 controls were identified. Compared with the White British population, the incidence of all psychoses was significantly higher in both Black Caribbean (Rate Ratio (RR) 6.7) and Black African (RR 4.1) populations. Broadly, Black Caribbean and Black African cases had more manic and positive symptoms and fewer negative symptoms. We investigated the potential contribution of social and biological factors by testing whether the effect, or prevalence, of risk indicators was higher in the Black populations. For indicators of childhood and adult social adversity, we found a similarly increased odds of psychosis in all ethnic groups. However, all indicators of social adversity (eg, separation from a parent before the age of 16, index of adult social disadvantage) were more common in the Black Caribbean and, to a lesser degree, Black African populations, compared with White British. In addition, in area level analyses, we replicated the finding that rates of schizophrenia in Black groups are highest in areas of low ethnic density. For biological indicators (eg, minor physical anomalies, neurological soft-signs), there was no evidence either that effects were higher, or the variables more common, in the Black groups. Our findings provide strong evidence that the high rates of psychosis in the UK Black

Caribbean and Black African populations are, in part at least, a consequence of greater exposure to individual and area level social risk factors over the life course. This further supports a role for social adversity in the aetiology of psychosis in general.
ID: 551726

EFFECTS OF PRENATAL INFECTION ON NEUROPSYCHOLOGICAL AND NEUROANATOMIC OUTCOMES IN SCHIZOPHRENIA

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In previous work, our research group and other investigators have identified associations between several prospectively identified in utero infectious and inflammatory exposures and risk of schizophrenia. In the present study, we sought to examine whether in utero exposure to herpes simplex viruses [herpes simplex virus type 1 (HSV1), herpes simplex virus type 2 (HSV2), and cytomegalovirus (CMV)], and interleukin-8 (IL-8) are related to neuropsychological and neuroanatomic abnormalities that have been associated with schizophrenia in previous studies. In the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, archived maternal serum specimens were assayed for each of these herpesviruses and for IL-8 among cases of schizophrenia from a large birth cohort. Cases were assessed in adulthood with comprehensive neuropsychological testing and magnetic resonance imaging in order to relate these infections and IL-8 to measures of executive function/working memory and to neuromorphologic outcomes. In utero exposure to HSV1, HSV2, and CMV were each associated with diminished performance on the auditory N-back (2-back condition) and exposure to HSV1 was related to an increase in errors on the Wisconsin Card Sort Test, suggesting deficits in working memory and executive function in exposed cases. Prenatal exposure to HSV-2 and CMV were related to diminished thalamic volume. Elevated IL-8 in utero was associated with an increase in ventricular cerebrospinal fluid (CSF) and decreases in volumes of the right caudate, left entorhinal cortex, and right posterior cingulate. These findings suggest that prenatal exposure to infection and cytokine activation disrupt the development of neural circuitry essential to the performance of executive function and working memory tasks among patients with schizophrenia, and impair the genesis of neuroanatomic structures associated with this disorder. This suggests pathogenic mechanisms by which in utero infection contributes to risk of schizophrenia, and provides further validation for a role of these exposures in the etiology of this disorder.
ID: 551699

A SYSTEMATIC REVIEW OF GENE-URBANICITY INTERACTIONS IN PSYCHOSIS

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The finding that the rate of psychotic disorder is higher in children and adolescents growing up in an urban environment is well replicated and unlikely to be confounded entirely by gene-environment correlation due to selective drift to urban areas in those at genetic risk for psychosis. "Urbanicity" is a proxy for an as yet unidentified environmental factor (s) prevalent in urban areas, and, if causal, may contribute to up to 20%–30% of the incidence of psychotic disorder in some countries. For this reason, urbanicity is an interesting factor to study in the context of GxE. We conducted a systematic review of the literature and identified four studies in the Netherlands, Germany, Israel and Denmark that attempted to examine gene-urbanicity interactions using epidemiological designs and indirect measures of genetic risk. All studies found evidence for gene-urbanicity interaction. The Dutch and Danish studies reported that the increase in incidence associated with urbanicity in individuals without a family history of psychosis was much smaller than in those with a family history. The German study found an effect of urbanicity on psychosis rates only in individuals with a psychometric psychosis liability. The study from Israel used cognitive impairment as indicator for genetic risk and found a nearly tenfold difference in increase in incidence associated with urbanicity between the cognitively non-vulnerable group and the cognitively vulnerable group. Clearly, the possibility of interaction between an environmental exposure in urban areas and genetic risk is in need of further study, focusing on (i) the precise nature of the urban exposure, for example growing up in an area lacking in trust and cohesion, (ii) the psychological and neurobiological mechanism of the environmental exposure in order to develop rational hypotheses about gene-environment interaction, (iii) the nature of the genetic variation involved and ultimately (iv) the mechanism of the gene-environment interactions.
ID: 551690

META-ANALYSIS OF PATERNAL AGE AND SCHIZOPHRENIA RISK IN THE OFFSPRING

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Advancing paternal age (APA) is a well-replicated and relatively robust risk factor for schizophrenia in the offspring. In regards to autism risk in the offspring, paternal age has a sexually dimorphic effect, with a much greater impact on risk of autism in females than in males. A recent meta-analysis of paternal age and schizophrenia risk in the offspring did not adjust for gender and study design effects, and did not use the same age classes across studies. We calculated pooled estimates using meta-analysis, adjusting for these factors and including data from additional studies. Articles were identified by PubMed searches and review of references. We attempted to contact authors of all studies published after 1992 to request summary data stratified by gender and the same five-year paternal age groups. Studies where greater than 80% of cases had a diagnosis of non-affective psychosis, and who provided data in the requested format were included. Data from the Northern Finland 1966 Birth Cohort, which have not been previously published, were also included. A total of 8 studies met our criteria including 5 cohort and 3 case-control studies. Within the cohort studies, males and females were considered separately. In both cohort and case-control studies, we found a J-shaped association between paternal age and schizophrenia risk in the offspring (reference paternal age of 25–29). Effect sizes were similar between cohort and case-control studies. There was no evidence of sexual dimorphism for the paternal age effect. Further studies are needed to investigate mechanisms for this association, including the increased risk in offspring of fathers under age 25.

Table. Risk of schizophrenia by paternal age for cohort and case-control studies

Paternal Age (years)	Cohort Studies				Case-Control Studies			
	Cases (n)	Total (n)	Crude RR	95% CI	Cases (n)	Controls (n)	Crude OR	95% CI
<20	313	49826	1.41	1.26–1.59	179	3398	1.37	1.17–1.60
20–24	2862	561986	1.15	1.09–1.20	1491	38032	0.99	0.92–1.08
25–29	4554	1025448	1.00	Reference	2420	62752	1.00	Reference
30–34	3415	754591	1.02	0.97–1.07	1812	43505	1.20	1.10–1.31
35–39	1902	366779	1.17	1.11–1.23	952	22697	1.11	1.02–1.20
40–44	927	154443	1.35	1.26–1.45	477	10121	1.24	1.12–1.38
45–49	348	55829	1.40	1.26–1.56	182	3806	1.23	1.06–1.44
50–54	136	17260	1.77	1.50–2.10	67	1160	1.48	1.16–1.90
>54	71	6858	2.33	1.85–2.94	36	322	2.87	2.03–4.06
Total	14528	2993020			7616	185793		

ID: 551689

CHILDREN OF PARENTS WITH AFFECTIVE AND NON-AFFECTIVE PSYCHOSES: A PROSPECTIVE STUDY OF CHILDHOOD INTERNALIZING AND EXTERNALIZING BEHAVIOR

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It is generally accepted that children of parents with schizophrenia or other forms of psychosis are at heightened risk for a range of behavioral problems. However, it remains unclear whether offspring of parents with different forms of psychosis (eg, schizophrenia, other non-affective psychoses, and affective psychoses) have distinct forms of behavioral problems (ie, internalizing and externalizing). This investigation examined behavioral observations at ages 4 and 7 years of children of psychotic (n = 281) and non-psychotic parents (n = 188). There were no significant differences between groups in behavior observed at age 4. At age 7, compared to children of unaffected parents, children of parents with psychosis had a significantly elevated risk for externalizing problems {adjusted odds ratio (aOR) 2.8 (95% CI = 1.5–5.6)}, in particular for offspring of parents with schizophrenia (aOR = 4.4; 95% CI = 1.7, 12.5). This increase in risk for externalizing problems was observed for females only (aOR = 8.1; 95% CI = 2.5–26.3). In contrast, male children were at increased risk for internalizing problems (aOR = 3.6; 95% CI = 1.6–8.3). Additional analyses examined rates of individual symptoms of internalizing and externalizing behavioral problems in relation to parental psychosis. Male high-risk offspring had higher rates of shyness and withdrawal compared to low-risk male offspring. Female high-risk offspring exhibited more variable mood or unstable emotional responses compared to low-risk female offspring.

Implications for treatment of parents with psychotic disorders and high-risk children are discussed.
ID: 551664

MATERNAL IRON DEFICIENCY AND RISK OF SCHIZOPHRENIA IN OFFSPRING

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Iron is essential for brain development and functioning. Iron deficiency in early life leads to long-lasting neural and behavioral deficits in infants and children, and disruptions in myelination and dopamine function. Hence, we examined the effects of early iron deficiency on the risk of schizophrenia in adulthood. We hypothesized that maternal iron deficiency, assessed by maternal hemoglobin concentration ascertained during pregnancy, increases the susceptibility to schizophrenia in the offspring. The data were drawn from a large, population-based birth cohort. Hemoglobin was prospectively assayed in virtually all pregnancies. Mean hemoglobin concentration over pregnancy was the primary exposure. Mean maternal hemoglobin $\leq$ 10.0g/dl was associated with a nearly fourfold, statistically significant increased rate of schizophrenia (adjusted rate ratio, 3.73; 95% CI = 1.41–9.81, P = .008), adjusting for maternal education and ethnicity. For every one g/dl increase in mean maternal hemoglobin, a twenty-seven percent decrease in the rate of schizophrenia was observed (95% CI = 0.55–0.96; P = .024). Further analysis revealed that the effect was specific to the third trimester. These novel findings suggest that maternal iron deficiency may be a risk factor for schizophrenia in the offspring. Since iron deficiency anemia occurs commonly in pregnancy, these findings may have important implications for prevention of schizophrenia in the population.
ID: 551659

CNS INFECTIONS DURING CHILDHOOD AND RISK FOR SCHIZOPHRENIA: A CASE CONTROL STUDY

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Some studies found a positive association between viral or bacterial CNS infections during childhood and risk for later schizophrenia, psychotic disorder or mood disorder with psychotic symptoms (1,2). A large, recently published Swedish study found a slightly increased risk for nonaffective psychotic illness and schizophrenia with previous viral CNS infections, but no increased risk with bacterial infections (2). The aim of this study was to assess the risk for schizophrenia in early adulthood after viral or bacterial CNS infection during childhood. The association between CNS infections in childhood and hospitalization for schizophrenia was examined by identifying 3500 persons who had been hospitalized as children for meningitis. Controls were 6400 persons who as children had been hospitalized for gastroenteritis. They were followed for later hospitalization for schizophrenia using the National Psychiatric Hospitalization Case Registry in Israel. Cox Regression analysis was used to assess risk for later schizophrenia. Among the 9970 individuals who were included in the study, 6371 (63.9%) were diagnosed with gastroenteritis and 3599 (36.1%) were diagnosed with CNS infections. Overall, no association was found between

Table. Risk for hospitalization for schizophrenia among individuals hospitalized for CNS infections in childhood (by type) compared to individuals hospitalized for Gastroenteritis in childhood, by age groups.

Age of Childhood Hospitalization		Not later hospitalized (N = 9,898)	Later Hospitalized (N = 72)	Unadjusted HR (95% CI)	Adjusted[*] HR (95% CI)
<1	Gastroenteritis	3436	28	1	1
	CNS infections- bacterial	224	3	1.58 (0.48–5.19)	1.57 (0.48–5.15)
	CNS infections- viral	748	3	0.49 (0.15–1.6)	0.46 (0.14–1.51)
1–4	Gastroenteritis	1616	8	1	1
	CNS infections- bacterial	103	3	5.26 (1.39–19.88)	5.27 (1.4–19.93)
	CNS infections- viral	936	3	0.64 (0.17–2.4)	0.65 (0.17–2.46)
>4	Gastroenteritis	1271	12	1	1
	CNS infections- bacterial	80	0	–	–
	CNS infections- viral	1484	12	0.88 (0.39–1.95)	0.72 (0.32–1.6)

*Adjusted for gender

CNS infections during childhood and risk of later hospitalization for schizophrenia. Post hoc analyses found that children hospitalized for a bacterial CNS infection between the ages of 1–4 years were at increased risk of later hospitalization for schizophrenia (adjusted HR = 5.27, 95% CI: 1.4–19.93) (table). However this finding is based on 3 cases. Bacterial CNS infections at an early age could be associated with a slightly increased risk for schizophrenia later in life.
ID: 551584

THE RELATIONSHIP BETWEEN NEURODEVELOPMENTAL AND SOCIAL FACTORS IN FIRST EPISODE PSYCHOSIS

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Introduction: Previous work has demonstrated an association between a) markers of neurodevelopmental impairment, and b) markers of early and later social adversity and psychosis. We sought to explore, in an epidemiological sample of first episode psychosis cases, whether there was a relationship between specific markers of neurodevelopmental impairment and social adversity, or whether these factors comprised entirely distinct pathways to the disorders. Methods: All cases from the UK MRC AESOP study with complete social and biological data ($N = 213$: M = 113; $F = 100$) were included in this analysis. Two markers of neurodevelopmental impairment (total Neurological Soft Sign (NSS) score and total Minor Physical Anomaly (MPA) score) and two markers of early (prolonged parental separation in childhood) and later (cumulative index of long term social disadvantage prior to onset) social disadvantage were chosen. Correlations between each neurodevelopmental and each social item were calculated, firstly in the whole sample, and then stratified by gender and by diagnosis. Results: We found no evidence of any correlation between NSS scores for any social variable, or for parental separation and any neurodevelopmental variable. However, there was evidence of a significant and consistent positive correlation between higher MPA scores and greater later social adversity (Spearman's Rho 0.204; $P = .003$) in the whole sample. This finding held for both men (0.214; $P = .02$) and women (0.208; $P = .04$). In terms of diagnosis, this held true only for schizophrenia (0.22; $P = .01$) but not for either manic psychosis or depressive psychosis. Conclusion: Our findings suggest a specific relationship between the presence of higher scores of MPAs and higher levels of long term social disadvantage, in both men and women destined to develop schizophrenia. The precise nature of this relationship, and its apparent diagnostic specificity, remain to be elucidated.
ID: 551558

THE PREVALENCE OF PSYCHOTIC SYMPTOMS IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW

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There is evidence that psychosis exists on a continuum in the population in both adult and child and adolescent samples. A large number of studies have been carried out examining the prevalence rates of psychotic symptoms in adult populations, however studies in child and adolescent samples are more scarce. To date, no systematic review of the literature on psychotic symptoms specifically in childhood and adolescence has been carried out. This review aimed to establish prevalence rates of psychotic symptoms in children and adolescents. A systematic review of all published literature on the prevalence of psychotic symptoms in children and adolescents was conducted using electronic databases Ovid Medline, Pubmed and Psychinfo with an agreed battery of search terms: young people, adolescents, teenagers, child, psychotic symptoms, psychosis, paranoia, delusions, grandiosity, unusual beliefs/ideations, bipolar, positive and negative symptoms, dissociative disorders, prevalence. Reference lists of the relevant papers were examined to identify further articles. We included both clinical and community samples of children and adolescents. We excluded studies reporting prevalence rates of psychotic symptoms in children and adolescents with organic illnesses and in schizophrenic and selected samples at high risk for psychosis.126 papers were located. Twenty nine relevant studies were identified: 14 from clinical and 15 from community settings. Methods used to identify psychotic symptoms included self-report questionnaires, clinical interview, standardised interview instruments and review of patient charts or a combination of methods. Reported prevalence of psychotic symptoms for clinical samples ranged from 0.4% to 81% across ages 2 to 19 years (outpatient samples 0.4 to 28%, inpatient samples 1.1 to 81%). Prevalence rates in community samples varied from 2% to 58.9% spanning ages 7 to 19 years (rates determined by questionnaire 6% to 58.9% and at interview 9% to 50%). Differing methodology across studies is reflected in a wide variation of rates of psychotic symptoms both within and across clinical and community samples. Research in this area would benefit from a standardised developmentally appropriate screening instrument with high sensitivity for identifying psychotic symptoms in children and adolescents. Future studies could employ a two stage process to screen large samples of children and adolescents and determine rates of psychotic symptoms at interview.
ID: 551476

DO NEIGHBOURHOOD CHARACTERISTICS AFFECT THE DURATION OF UNTREATED PSYCHOSES?

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Background: Family involvement in help-seeking has been shown to be associated with a shorter duration of untreated psychoses, but it is unknown whether factors at the neighbourhood-level also affect the duration of untreated psychoses [DUP]. We sought to test this hypothesis. Methods: All cases of first-episode psychoses which occurred over a two-year period in 32 neighbourhoods of Southeast London were included in the study. DUP was estimated for all cases. We fitted a number of multilevel Gaussian (normal) Bayesian models, which adopted different assumptions with regard to spatial variability of DUP to asses whether there was evidence of heterogeneity in DUP by neighbourhood, having accounted for a priori individual-level confounders. Model fit was assessed via the Deviance Information Criterion. Results: 314 subjects with first episode psychoses were included in the analysis. DUP was heavily skewed with a median of 72 days (inter-quartile range: 22–323). The median DUP between wards varied from 19 to 631.5 days. We transformed DUP onto the log scale to normalise the outcome variable in order to fit our Bayesian models. After adjustment for individual differences in age, sex and ethnicity, there was no evidence of significant variation in DUP between neighbourhoods. A Bayesian model with individual-level predictors, but without any hierarchical effects provided the best fit to the data. As previously reported, ethnicity minority status and increased age were significantly associated with longer DUP. Discussion: Neighbourhood factors do not appear to be associated with the duration of untreated psychoses, suggesting that the predictors of DUP are rooted in the individual and family, not at the societal level.
ID: 551448

NEUROPSYCHOLOGICAL FUNCTION AND PATHWAYS TO CARE: FINDINGS FROM THE AESOP FIRST EPISODE PSYCHOSIS STUDY

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Numerous studies have found that patients with psychosis perform poorly on neuropsychological tests compared with healthy controls. We sought to investigate whether there was a relationship between cognitive function and pathways to treatment. We also sought to investigate any differences by demographic factors. 593 Participants, recruited as part of the three centre AESOP study (Aetiology and ethnicity of schizophrenia- a longitudinal epidemiological study of FEP) who made contact with services performed a battery of neuropsychological tests to assess intellectual function (National Adult Reading Test-Nart and the Wechsler Adult Intelligence scale, Revised-WAIS-R). Participants intellectual functioning was compared with their type of admission. Data on pre-morbid and current intellectual function was then compared with data also gathered on clinical presentation. Any correlations in terms of socio-demographic characteristics

(namely ethnicity, age and gender) and socio-economic status were explored. Analysis was undertaken using t-tests and ANOVAs. No Significant differences were found in pre-morbid intellectual function between patients whose admission was compulsory versus non-compulsory. There was however a significant relationship between current intellectual functioning and pathways to care ($P = .014$). Patients who were voluntarily admitted had a mean full scale IQ of 91.38 compared with patients who were compulsorily admitted who had a mean full scale IQ of 86.04. Those with lower cognitive function were more likely to be compulsorily admitted than being voluntarily admitted. There was additionally a trend for lower IQ and those who had police involvement ($P = .043$). There was no significant relationship between Criminal justice or GP referral and GP involvement. These findings suggest poor performance on neuropsychological testing; in this case current low intellectual functioning is associated with being compulsorily admitted and having police involvement. These findings raise the question of what role cognitive function actually plays in enabling people to negotiate a positive pathway to care. There is potentially a need for increased support and information from agencies for those with lower cognitive function who may be less able to communicate with and navigate the mental health system. Funded by the UK Medical Research Council.
ID: 551446

SYMPTOM CHARACTERISTICS IN AFRICAN-AMERICAN AND EUROPEAN-AMERICAN SUBJECTS WITH SCHIZOPHRENIA: PRELIMINARY RESULTS

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The heterogeneous presentation of schizophrenia makes symptom-level analyses particularly important in designing studies exploring the etiology and pathophysiology of this disorder. We used phenotypic data from 1192 African-Americans (AAs) and 1289 European-Americans (EAs) with schizophrenia drawn from the Genetic Association Information Network (GAIN) schizophrenia study. Factor analysis in MPlus yielded five symptom factors in both the AA and EA cohorts: Schneiderian symptoms, auditory hallucinations, delusions, visual hallucinations, and negative symptoms. Additional analyses suggested that the lack of measurement invariance in the five factor structure between the AA and EA samples is largely due to noninvariance of the negative factor loadings and thresholds. Demographic variables such as age of onset, duration of illness, and sex displayed different patterns of correlations with the factors in the AA and EA samples. Earlier age of onset predicted higher scores for all factors except the negative symptom factor in the EA cohort which showed no significant relationship. Duration of illness positively correlated with auditory hallucinations and negative symptoms in both samples but visual hallucinations only in the AA subjects. The only significant sex differences were higher levels of auditory and visual hallucinations in the AA females. The extent to which these populations differ in symptom expression may be a function of differential environmental exposures or genetic predispositions between groups.

Subsequent analyses incorporating genome wide genotypic data will aid in distinguishing these possibilities.
ID: 551416

PREVALENCE RATES AND CORRELATES OF PSYCHOTIC-LIKE SYMPTOMS AMONG ADOLESCENTS REFERRED TO A CHILD AND ADOLESCENT PSYCHIATRIC OUTPATIENT SERVICE

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During the past decade, there has been growing interest in psychotic-like symptoms among young people. For years, such symptoms were not asked about by child and adolescent mental health professionals as it was considered meaningless in the absence of a psychotic diagnosis. However, there is now compelling evidence from population-based cohorts that self reported psychotic symptoms in early adolescence are associated with a higher risk of psychotic illness in adulthood. Prevalence studies of psychotic symptoms among clinical child and adolescent samples are few and to date, have shown prevalence rates of psychotic symptoms ranging from 4.5% to 33%. We wished to investigate the prevalence and correlates of psychotic-like symptoms in a sample of adolescents referred to an Irish child and adolescent mental health outpatient service. Over a one year period consecutive referrals of 12–15 year olds to a child and adolescent mental health service in North Dublin were asked to participate in the 'Welcome' Study. Subjects underwent a comprehensive assessment conducted by a psychiatrist or psychologist. The interview protocol included the K-SADS PL, Clinical Global Assessment Scale, the Clinical Global Impressions scale, the Adolescent Wellbeing scale, the Parental Stress Scale and a psychosis screening questionnaire. The psychosis screening questionnaire is derived from the DIS-C: and comprises the following questions: Q1/ "Have other people ever read your mind?",Q2/ "Have you had messages sent to you via the TV/radio?" Q3/ "Have you ever thought people were spying on you or following you?" and Q4/ Have you ever heard voices that other people can't hear?" Forty-four adolescents have participated in the study so far of whom 48.8% have responded positively to one or more of the psychosis screening questions. Analysis of responses to individual questions was as follows: Q1 "mind-reading"16.3%; Q2 "TV/radio 0%; Q3 "spying" 25.6%; Q4 "voices" 18.6%. Overall 95.4% of participants had a psychiatric diagnosis of whom 56.8% had co-morbid diagnosis and 4.5% (n = 2) were diagnosed with a psychotic disorder .Of note no-one was originally referred to the service with suspected psychosis. We conclude that the prevalence of psychotic-like symptoms are far higher than previously thought among young adolescents referred to a child and adolescent psychiatry service. These symptoms should be routinely enquired about as part of the initial assessment.
ID: 551298

PRENATAL EXPOSURE TO RETINOL (VITAMIN A) AND EXECUTIVE FUNCTIONING IN ADULT OFFSPRING WITH SCHIZOPHRENIA

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The aim of this study is to evaluate evidence for the theory that elevated maternal retinol (vitamin A) exposure levels, particularly during the third trimester, are associated with decreased executive functioning in adult offspring with schizophrenia. Prenatal exposure to excess retinol levels and related compounds (retinoids) has been associated with toxicity to the central nervous system as well as congenital fetal anomalies including hydrocephaly and spina bifida. Several studies have shown that retinoid dysregulation may be an important factor in the etiology of schizophrenia, since congenital anomalies similar to those caused by retinoid dysfunction are found in patients with schizophrenia and their relatives, and numerous schizophrenia candidate genes are regulated by retinoic acid (Goodman, 1998). In the present study, we assessed the relationship between serologically documented prenatal exposure to retinol from archived maternal sera, and a series of measures of executive functioning, in 20 individuals with schizophrenia from a large and well-characterized birth cohort. The cases were derived from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study. Sera were assayed for retinol by an established protocol and cases were administered a standard neuropsychological test battery including measures of executive function. Elevated retinol levels among schizophrenia cases were associated more total errors on the Wisconsin Card Sort Test ($P = .01$), including both perseverative errors ($P = .03$) and non-perseverative errors ($P = .03$), and lower test scores on the Ruff Figural Fluency test ($P = .09$). These findings provide compelling evidence that retinoids, already implicated in the etiology of schizophrenia and congenital malformations, may also lead to executive function deficits in patients with schizophrenia.
ID: 551282

THE RELATIONSHIP BETWEEN ETHNICITY AND PSYCHOTIC SYMPTOMS AS MEASURED BY THE SCAN: PILOT DATA FROM THE GENETICS AND PSYCHOSIS (GAP) STUDY

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Background: The presence of underlying symptom dimensions in the psychopathology of psychosis is well established, and the relationship between ethnicity and psychotic symptoms has been demonstrated in previous studies (Janssen et al. 2003 1, Veling et al. 2007 2). Methods: The Item Group Checklist (IGCL) of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) Version 2.1. was used to derive scores for 59 patients for the SCAN. The symptoms investigated comprised the following IGCL Item Groups: Depressive delusions and hallucinations (Item Group 13) Nonspecific auditory hallucinations (IG 21) Non-affective auditory hallucinations (IG 24) Miscellaneous delusions (IG 28) Delusions of reference (IG 29) Delusions of persecution (IG 30) IGCL scores were dichotomised prior to analysis into present and absent. Subjects: All 59 subjects in the present sample were recruited to the GAP study from the inpatient services of the South London and Maudsley NHS Foundation Trust. All met diagnostic criteria for psychosis (ICD-10). and were recruited during the period May 2005 to June 2006. The mean age of the sample was 27.73 years (sd. 7.82) and the group comprised 40 males and 19 females. The sample was categorised by ethnicity into Black 63%) and White/Other (37%). The Black sample comprised Black African, Black Caribbean, and Black Other. The White/Other sample comprised White British, Mixed, Indian, Bangladeshi and Caucasian. Results: Of the six groups of positive symptoms analysed, a positive rating of presence for one symptom reached significance: There was a trend for several symptom groups to be more common in the

black patients but these did not reach statistical significance. However, depressive delusions and hallucinations (IG13) were found to be associated with ethnicity (P = .025; Pearson's x2(1) = 5.629), being more common in the white/other group. Conclusion: There was a tendency for several groups of symptoms to be rated more commonly in the black patients but these differences were not significant. However, depressive delusions and hallucinations were more common in the white/other patients.
ID: 551188

TIME COURSE OF ILLICIT DRUG USE AMONG FEP PATIENTS: DATA FROM THE PICOS-VENETO STUDY AFTER ONE YEAR OF FOLLOW-UP

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Introduction: Substance misuse prevalence rates are higher among psychotic patients than in the general population. Emerging evidences suggest a casual role of drug exposure in developing psychosis. Of great concern and clinical relevance is whether or not the pattern of substance use among these subjects is changing over time and how it affects the course of illness. This study aims to determine substance misuse prevalence rates variation over 1 year in first episode psychotic (FEP) patients. Methods: The presented data are part of the PICOS-Veneto project, a multi-site study aiming to characterise course and outcome of psychosis from the first contact. Assessments were performed using standardized measures including: clinical evaluation, socio-demographic characteristics and illicit drugs use. Results: 143 FEP patients were evaluated at baseline and at 1 year follow up. At baseline 19.6% was positive for any drug use, 18.4% cannabis, 5.0% cocaine, 5.7% hallucinogens. At one year follow up, 9.1% was positive for drug misuse, 9.1% cannabis, 1.4% cocaine, 0.7% hallucinogens. If compared with the general population, prevalence rates, among FEP subjects, were significantly higher at the baseline: cannabis 18.4% vs 8.0%; cocaine 5.0% vs 1.2% and hallucinogens 5.7% vs 0.3%. After one year drug use prevalence rates are similar to those observed in the general population. Conclusions: Substance misuse prevalence rates are significantly higher among FEP patients than in the general population. A significant reduction in this behaviour is observed one year after the psychosis onset. This finding could help in understanding the meaning of the association between psychosis and drug use.

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ID: 551153

MORTALITY AND SUICIDE IN SCHIZOPHRENIA. FINDINGS FROM THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY

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Our aim was to analyze the mortality and especially suicide rate and predictors in schizophrenia and other psychotic disorders in the Northern Finland 1966 Birth Cohort. The Northern Finland 1966 Birth Cohort Study is based upon 12 068 pregnant women and their 12 058 live-born children. Those who were alive at the age of 16 (n = 10 934) were followed up to the age of 39 years. We used validated hospital diagnoses until 1997 and information on mortality until 2005. Risk ratios (RR) were calculated having healthy subjects as comparison group. Crude and adjusted hazard ratios (HR) and their 95% confidence interval (95% CI) for suicide by school performance were computed using Cox regression which takes the time to the event (suicide) account. RR of death for all cohort members suffering from psychosis (n = 155) was 6.19 (95% CI: 3.96–9.49). For schizophrenia patients (n = 100) RR was 7.07 (4.24–11.42). Due the young age of cohort members leading cause of death was suicide. At the end of year 2005 (age 39) 7 of 100 schizophrenia patients had commit a suicide. Case fatality (CF, number of suicides divided by number of subjects) was 7%. CF for females was 2.9% (1/35) and for males 9.2% (6/65). Suicide risk was high especially for males and in early phase of psychotic disease; two thirds of suicides in schizophrenia occurred within three years after onset of illness. Suicide rate of schizophrenia patients was nearly 2-fold higher six years after first discharge from psychiatric care (P = .005) compared to hospital treated patients with non-psychotic disorder. Among individuals with psychosis predictors of mortality were violent criminality and male gender, while good school performance was a predictor of suicide. For psychotic persons having good school performance (highest 20%), the adjusted hazard ratio (HR) for suicide was 3.56 (0.97–13.05) compared with the remaining 80%. In the non-psychotic population (97% without psychiatric hospitalization), accordingly, adjusted HR was 0.28 (0.07–1.16). Interaction (school performance x psychiatric diagnosis) was significant (P = .01) even when adjusted with gender, social class and age of onset of illness. This is the first study of suicide risk in a prospectively followed population-based cohort of individuals with schizophrenia. The suicide rate for patients with new-onset schizophrenia followed until the age of 39 is high. Great majority of the suicides took place during the first years of the illness.
ID: 551135

A COMPARISON OF SYMPTOM PROFILES BETWEEN DIFFERENT ETHNIC GROUPS IN A FIRST ONSET PSYCHOSIS STUDY

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The aim of the present study was to investigate whether the symptom profile in first onset psychosis patients from various ethnic groups differs from that of their White British counterparts. We recruited 536 patients as part of a multi-centre, population based, incidence study of psychosis, of which 43% were White British, 29% Black Caribbean, and 13% Black African. Psychopathology was assessed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). A Principal Axis Factor analysis was performed on symptom scores, using Varimax rotation. The symptom dimension scores were then compared between different ethnic groups employing regression analyses. Factor analysis gave rise to a five factor solution of manic, reality distortion, negative, depressive, and disorganisation symptom dimensions accounting for 47% of total variance. Regression analyses revealed significant differences between ethnic groups. Specifically, Black Caribbean patients experienced more reality distortion and fewer negative symptoms than White British (P = .045, and P = .010 respectively).

With regards to severity, Black Africans tended to have more severe manic and reality distortion and less severe disorganisation symptoms when compared with White British ($P = .002$, $P = .003$, and $P = .021$ respectively). Our results indicate that there are significant variations in symptom profiles between Black Caribbean, Black African and White patients with first onset psychosis. These may reflect differences in underlying aetiological factors.

ID: 551122

DO CANNABIS AND URBANICITY INTERACT IN CAUSING PSYCHOSIS?

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Background: Cannabis use and the urban environment are risk factors for psychotic illness. It is unknown, however, whether these environmental factors may interact with each other as well on psychosis risk. Method: Prospective data on 2438 adolescents and young adults (aged 14 to 24 years) from the Early Developmental Stages of Psychopathology (EDSP) study were analyzed. Urbanicity was defined at baseline as the German city of Munich (4061 persons per square mile) versus the surroundings of Munich (553 persons per square mile). Cannabis use and psychotic symptoms were assessed by means of the Composite International Diagnostic Interview at baseline, at T2 (four years later), and again at T3 (eight years later). Logistic regression analysis was used to investigate the interaction between urbanicity and T2 cannabis use on psychosis outcome at T3. Results: Cannabis use was associated with an increased risk of expression of psychosis, even after exclusion of individuals with previous experiences of psychotic symptoms at T2 and after adjustment for age, gender, socio-economic status, use of other drugs other, and childhood trauma (OR = 1.61, 95% confidence interval 1.03 to 2.52, $P = .036$). The effect of cannabis on psychosis outcome, however, was much stronger in those who grew up in an urban area compared to those who grew up in a rural area (risk difference 9.6%; test for interaction $\chi^2 = 5.69$, $df = 1$, $P = .02$). Neither urbanicity nor pre-existing psychotic experiences predicted later cannabis use. Discussion: These results show that environmental factors may interact with each other in causing psychosis. The effects of cannabis on psychosis outcome seem to be particularly detrimental for those young adults who are growing up in an urban environment.

ID: 551108

INFECTIONS OF TOXOPLASMA GONDII AND THE LATER DEVELOPMENT OF SCHIZOPHRENIA IN MOTHERS

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Several studies suggest that infectious diseases including Toxoplasma gondii can influence the risk of schizophrenia. Our own previous study (1) showed that children, who were born with high level of Toxoplasma gondii-specific immunoglobulin (IgG), have a slightly increased risk of schizophrenia. The elevated level of IgG in the neonatal samples in our previous study indicates that the mother has a history of T. gondii infection. The aim of this study is to investigate if mothers, to children born with a high level of IgG, suffer an increased risk of schizophrenia. Children born in five counties in Denmark from 1992 to 1995 were screened for T. gondii at 5–10 days post-partum ($N = 53,881$). Their mothers were followed from the day they gave birth until first diagnosis of schizophrenia during 1992 to 2007. Preliminary results indicate a general association between Toxoplasma gondii and later psychiatric illness (RR = 1.21 (95% CI: 1.13; 1.29)). The relative risk for schizophrenia was of similar magnitude but not statistically significant. Final analyses will be presented at the conference. Supported by the Stanley Medical Research Institute.

Reference

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ID: 551087

PSYCHOPATHOLOGY DURING CHILDHOOD AND ADOLESCENCE PREDICTS DELUSIONAL-LIKE EXPERIENCES IN ADULTS: A 21 YEAR BIRTH COHORT STUDY

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Community surveys have shown that many otherwise well individuals report delusional-like experiences. The aim of this study was to examine the association between psychopathology during childhood and adolescence as predictors of subsequent delusional-like experiences in young adults. The study was based on a birth cohort of 3617 young adults born between 1981 and 1984. Psychopathology was assessed at age 5 and 14 by mothers using the Child Behaviour Check List (CBCL), and by the cohort members with the Youth Self Report (YSR) at age 14 delusional-like experiences were measured using the Peters Delusional Inventory at the 21 year follow up. The association between childhood symptoms and later delusional-like experiences was examined using logistic regression adjusted for gender and age at last assessment, as well as drug use and the presence of nonaffective psychotic disorder at age 21. High CBCL scores at 5 and 14 years predicted high levels of adult delusional-like experiences; (Highest versus other quartiles OR and 95% CI: 1.25; 1.00–1.57: 1.85; 1.48−2.30 respectively). Those in the highest quartile of YSR scores at 14 years were nearly four times more likely to have high levels of delusional-like experiences at age 21 (OR and 95% CI: 3.71; 2.92–4.71). Adolescent onset psychopathology and continuous psychopathology through both childhood and adolescence strongly predict delusional-like experiences at age 21. Delusional-like experiences and hallucinations at 14 years were significantly associated with adult delusional-like experiences. The general pattern of associations persisted when adjusted for previous drug use or the presence of nonaffective

psychoses at age 21. Our study found that psychopathology during childhood and adolescence predicts adult delusional-like experiences. Understanding the biological and psychosocial factors that influence this developmental trajectory may provide clues to the pathogenesis of psychotic-like experiences.
ID: 551057

ARE NEURAL TUBE DEFECTS IN SIBLINGS A RISK FACTOR FOR SCHIZOPHRENIA: A POPULATION-BASED TEST OF THE ROLE OF LOW FOLATE DURING PREGNANCY IN RELATION TO SCHIZOPHRENIA RISK

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Mothers with low folate intake and TT homozygote mothers for the methyltetrahydrofolate reductase (MTHFR) gene are at increased risk for having children with neural tube defects. Neural tube defects as well as schizophrenia have been found to occur with increased frequency in cohorts exposed to famine during fetal life, and a meta-analysis examining the polymorphisms in schizophrenics and controls found the odds ratio for TT homozygotes to be 1.48 (95% CI = 1.18–1.86). This supports the hypothesis that folate status may be an important determinant of schizophrenia risk. In order to test this hypothesis in a population-based setting, we used the Danish population-based registers to examine schizophrenia risk in the Danish population using the occurrence of neural tube defects in siblings as a proxy for low folate intake or MTHFR TT homozygosity in the mother. We based our data on the Danish civil registration system. Through this system it is possible to establish links between individuals, their parents, and through the parents with their sibs for persons born in Denmark 1952 or later. Exposure was determined by diagnosed neural tube defects identified through the National Patient Register and the Register of Congenital Malformations. Follow-up was made through the Danish Psychiatric Central Register, covering all psychiatric hospitals and since 1995 all psychiatric outpatient wards. Outcome was schizophrenia, ICD-8 295, ICD-10 F20, 25. We also studied the broader group of non-affective psychoses as a potential outcome. Results will be available at the conference.
ID: 551026

EARLY VIRAL INFECTIONS AS A RISK FACTOR FOR SCHIZOPHRENIA

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Several studies have suggested that exposure to infections in utero or during early childhood is a risk factor for the onset of schizophrenia later in life. Several studies have been based on ecological data or information based upon maternal recall, and only few cohorts exist where it is possible to follow-up individuals for whom there is serological evidence of early infections. We studied the role of Herpes simplex virus 1 and 2 and cytomegalovirus in a nationwide birth cohort in Denmark. We identified all cases in a Danish psychiatric hospital or outpatient clinic. For each case, we selected one control from the same cohort born on the same day as the case and of the same gender, and alive on the data of first admission with schizophrenia for the case. We initially identified 923 schizophrenia patients, but there was only sufficient biological material available from the dried blood spot samples in the neonatal biobank for PKU screening for 602 cases and 602 controls. Those included in the study and those who had to be excluded due to lack of biological material did not differ significantly by established risk factors for schizophrenia including family history of mental illness and urbanicity of place of birth. At the Stanley Neurovirology Laboratory type specific antibodies to the gG2 glycoprotein of viral infection were measured by enzyme immuno assay and an assay value < 0.2 optical density unit was predefined as indicating exposure to viral infection. There was an increased risk associated with HSV2, RR 1.51 (95% CI = 1.08–2.10). There was no general association between CMV and schizophrenia (RR 1.10), but a significant interaction by gender where the risk was increased in males (RR 1.49, 95% CI = 1.05–2.11), contrary to what was found in women (RR 0.76, 95% CI = 0.52–1.11) for HSV1. We only found a weak and non-significant association between HSV1 and schizophrenia (RR 1.12, 95% CI = 0.89–1.40). We did, however find an effect in the group of individuals with foreign born mothers, ie, second generation immigrants (RR 3.72, 95% CI = 1.30–10.61), both compared to HSV1 seronegative second generation immigrants and to seropositive and seronegative native Danes. We identified both general and subgroup specific associations between early viral infections and schizophrenia risk. This may indicate an interaction between early infections and other subgroup specific genetic or environmental risk factors in the etiology of schizophrenia.
ID: 551013

CANNABIS USE AND TRUE INCIDENCE OF PSYCHOTIC SYMPTOMS IN A POPULATION-BASED SAMPLE

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Research has consistently shown that adolescent cannabis use increases the risk for later development of psychotic symptoms or schizophrenia with a factor of two. However, it still remains equivocal whether the relationship between cannabis use and psychosis is causal or follows the so-called self-medication hypothesis. In the current study, prospective data from the Early Developmental Stages of Psychopathology study ($N = 2438$, age at baseline 14 to 24 years) were analyzed. Substance use and psychotic symptoms were assessed at baseline and at follow-up at T2 (four years later) and again at T3 (eight years later), by means of the Composite International Diagnostic Interview. Logistic regression analyses were conducted to investigate the effect of T2 cannabis use on true incidence of psychotic symptoms at T3, by only including individuals who were cannabis naive at baseline and had no sign of psychotic symptoms at T2. Analyses revealed that cannabis use at T2 significantly increased the risk for psychotic symptoms at T3, after adjusting for age, gender, socio-economic status, urbanicity, use of

other drugs, and childhood trauma (OR = 1.57, 95% confidence interval 1.13 to 2.17, P = .007). The effect of T2 cannabis use on T3 psychosis outcome remained both strong and significant when only including individuals who were cannabis naïve at baseline and had no previous psychotic experiences at T2 (OR = 1.88, 95% confidence interval 1.11 to 3.16, P = .018). Testing the reverse association (ie, the effect of psychotic symptoms at T2 on cannabis use at T3) did not reveal significant results (OR = 0.89, 95% confidence interval 0.67 to 1.19, P = .45), speaking against self- medication mechanisms. The data presented here confirm that adolescent cannabis use increases the risk to develop psychotic symptoms later in life. Self-medication mechanisms are very unlikely to explain this association. ID: 551007

BIPOLAR DISORDER, SCHIZOAFFECTIVE DISORDER AND SCHIZOPHRENIA OVERLAP; A NEW COMORBIDITY INDEX

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Objective: Growing evidence of an etiologic overlap between schizophrenia, schizoaffective disorder and bipolar disorder has become increasingly difficult to disregard. We investigated the magnitude of the overlap between the clinical diagnoses of bipolar affective disorder, schizoaffective disorder, and schizophrenia over a 30 year period, based on the entire Danish population. We introduced a new comorbidity index, measuring the magnitude of the overlap between the three disorders, enabling us to make a new contribution to the discussion of whether they are distinct or overlapping disease entities. Method: We established a register-based cohort study of more than 2,5 million persons born in Denmark. Risks for the 3 psychiatric disorders were estimated by survival analysis, using the Aalen-Johansen method. Results: Overall, N = 12 734 were admitted with schizophrenia, N = 4205 with bipolar disorder and N = 1881 with schizoaffective disorder. A female bipolar patient's risk of also being admitted with a schizoaffective disorder, before the age of 45 was approximately 103 times higher than that of a woman at the same age in the general population. Thus, we defined the comorbidity index between schizoaffective disorder and bipolar disorder at age 45 to be 103. The index between schizophrenia and schizoaffective disorder was 80 at age 45, and between schizophrenia and bipolar disorder 20. Similar results were found for men. A strong effect modification by age was present resulting in a higher index for younger patients. Conclusions: The proposed comorbidity index revealed a large overlap between the diagnostic categories of schizophrenia, schizoaffective disorder, and bipolar disorder. There was a large overlap between schizophrenia and schizoaffective disorder as well as a large overlap between bipolar disorder and schizoaffective disorder. But, more surprisingly it was clear that a substantial overlap between bipolar disorder and schizophrenia was present. The study supports the existence of an overlap between bipolar disorder and schizophrenia. ID: 551000

IS THE INCREASED RISK OF SCHIZOPHRENIA IN IMMIGRANTS AN ARTIFACT OF SELECTIVE MIGRATION?

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Background: Many studies have shown that foreign immigrants have an increased risk of developing schizophrenia in their host country as compared to their native counterparts. Although, the factor(s) responsible for the increased risk remain unknown, it has been hypothesized to include environmental factors associated with the process of migration. However, if people migrating from one country to another have a higher liability (genetic and/or environmental) of developing schizophrenia, then an alternative explanation for the increased risk associated with migration could be that immigrants have a higher pre-existing liability of developing schizophrenia, or in other words that migration per se may not increase the risk of schizophrenia, but the increased risk associated with migration is due to selective migration. Objective: The aim of this study was to assess whether risk factors for schizophrenia were also risk factors for emigration. If risk factors for schizophrenia also increase the risk of emigration, we may have evidence that immigrants are a pre-selected group of people who have a higher liability to develop schizophrenia as compared to the native counterparts. Below we focus on the potential association of the degree of urbanization at place of birth on the risk of emigration from Denmark; urban place of birth has consistently been shown to also increase the risk of developing schizophrenia. At the conference results concerning other risk factors for schizophrenia will be presented, including a history of mental illness in a family member. Methods: We followed all people born in Denmark 1971–1991 for the first emigration from Denmark 1971–2006. Results: Among children (0–15 yrs) the greater the degree of urbanization at place of birth, the higher the risk of emigration from Denmark. Conclusion: The higher the degree of urbanization of place of birth, the higher the risk of schizophrenia and emigration from Denmark, suggesting that people migrating from Denmark are expected to carry a higher liability to develop schizophrenia than their native counterparts. Whatever the unknown factor(s) responsible for the urban-rural differences in the risk of schizophrenia, some of these may also be responsible for the increased risk of schizophrenia among immigrants. Supported by the Stanley Medical Research Institute. ID: 550964

EARLY DEVELOPMENTAL RISK FACTORS FOR VOICE-HEARING AMONG 7 AND 8 YEAR OLD CHILDREN

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The accurate identification of children and adolescents who experience hallucinations may allow us to target those at higher risk for psychotic illness in adulthood. In 2002/2003 auditory vocal hallucinations (AVH) were assessed in a population-based sample of 3870 children in the province of Groningen, the Netherlands. Voice-hearing was assessed with the Auditory Vocal Hallucination Rating Scale (AVHRS; Jenner and Van de Willige, 2002). To investigate associations between voice-hearing and pre- and perinatal influences, early development and current behaviour problems, for a case-control sample data were gathered from the Infant Health Service records, and from parental completed Child Behaviour Checklists (CBCL). A 5-year follow-up study is currently being carried out to investigate prevalence, persistence and characteristics of AVH in the case-control sample of now 12 and 13 year old children, and their relationship with social behaviour. At baseline, the one-year prevalence of AVH was 9%. 15% of AVH children reported severe suffering and AVH elicited more anxiety in girls. The prevalence for AVH was higher in rural areas, but AVH were more severe, more often externally attributed and of greater functional impact in the urban environment. There was some evidence for an association with prenatal maternal infection (OR 2.07, 95% CI = 1.04–4.05; P = .04) and slower motor development in early life (OR 1.22, 95% CI = 1.02–1.46; P = .03). Only weak associations were apparent between AVH and current problem behaviour. We conclude that there may be continuity between AVH in childhood and more severe psychotic

outcomes given the severe suffering in a subgroup, associations with early developmental deviance and evidence for a poorer prognosis in an urban environment.

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ID: 550962

THE ANTECEDENTS OF SCHIZOPHRENIA: A REVIEW OF BIRTH COHORT STUDIES

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Background: Birth cohort studies suggest that individuals who develop schizophrenia differ from the general population on a range of developmental indices. We summarize key findings from birth cohort studies to identify areas of convergence and areas requiring further research. Method: We examined studies based on general population birth cohorts where data are collected prospectively from birth or childhood, and whose outcome is schizophrenia or related disorders. We searched various electronic databases to identify such studies using the search parameters (schizo* OR psych*) AND (birth cohort). We also examined references from relevant articles and previous reviews. Results: We found 10 birth cohorts from 6 countries with studies adopting adult schizophrenia as an outcome. They provide relatively consistent evidence that, as a group, children who develop schizophrenia in adulthood have behavioural disturbances and psychopathology, intellectual and language deficits and early motor delays. Some studies provide evidence of changes in educational performance and physical growth. Birth cohort studies also find evidence of a wide range of putative risk factors for schizophrenia. Conclusions: Birth cohort studies provide important, convergent insights into how the developmental processes of individuals with schizophrenia differ from their peers. Some more recent studies examine developmental trajectories; that is examining individual rather than group measures across development—a particular strength of birth cohort designs. Larger cohorts and new paradigms, together with modern epidemiology and biomedical science, are illuminating the developmental pathways to schizophrenia.
ID: 550905

IMPACT OF GENETIC VULNERABILITY FOR PSYCHOSIS, FETAL INFLAMMATION, AND GENDER ON AGE 7 COGNITIVE AND BEHAVIORAL FUNCTIONING

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Recent work on the etiology of schizophrenia has focused on premorbid and prodromal endophenotypes to characterize early identifiers of risk. This high-risk study assessed the impact of genetic vulnerability, fetal inflammation, and gender on age 7 offspring cognitive and behavioral outcomes. Using data from the longitudinal New England Family Study (NEFS) cohort, we identified 185 parents with psychosis and 126 comparable control parents. There were 169 (87 males, 82 females) offspring among these psychotic parents ('High-Risk') and 247 (125 males, 122 females) among the controls. Fetal inflammation, parental psychosis, their interaction and gender were together modeled as predictors of age 7 cognitive and behavioral functioning in the offspring. Least-squares means, fixed effects and covariance parameters were estimated using mixed linear models accounting for intrafamilial correlation. Cognitive functioning was significantly lower among high-risk offspring and those exposed to fetal inflammatory conditions, operationalized as IQ, academic achievement, and perceptual-motor and verbal-conceptual functions (eg, there was a 5.5 point mean IQ difference between offspring exposed and unexposed to fetal inflammation ($P < .0002$); and there was a 3.5 point mean IQ difference between the high-risk and control offspring ($P < .003$). The fixed-effects parameters for inflammation were significant across all cognitive measures; genetic vulnerability was significant for IQ ($P < .01$), and interactions for verbal/conceptual functioning ($P < .02$) and inhibition ($P < .02$). Both of these interactions were found to be significant for males but not for females. Genetic vulnerability for psychosis and fetal inflammation are independently associated with lower cognitive functioning even by age 7, and together have an interactive effect on both verbal/conceptual cognitive functioning and dysregulation of affective expression primarily in males.
ID: 551933

EVALUATION OF PERINATAL AND PEDIATRIC RISK FACTORS FOR THE DEVELOPMENT OF SCHIZOPHRENIA

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Schizophrenia is a disorder that affects in a significant degree the psicosocial functioning of the pacient in many areas. One of the major risks to have this disorder is related with biological proximity; identical twins (sharing 100% of genetics) do not show a 100% concordance for schizophrenia, which suggests that environmental or epigenetic factors that are not well enough characterized, could have a determinant rol during neurodevelopment phase on the origin of this disorder. Method. This case-control study explored the association between perinatal risk, pediatric risk neurological conditions (seizures on early infancy, cranial traumatism) and the risk for schizophrenia. Case totaled 100 patients with schizophrenia diagnosis, every case was individually matched by gender and nearly age with one sibling without a psychiatric diagnosis in axis 1 (DSM IV criteria). Results: Adjusted analyses showed that the risk of schizophrenia was associated with fetal suffering/distress ($x^2 = 34.0$, 1 gl, $P < .001$ Fisher $P < .001$). The logistic regression model was able to discriminate cases from controls (general efficacy 86.5%, regarding Hosmer y Lemeshow model), being more accurate to predict subjects without schizophrenia (93%). Results suggest

that this perinatal and early childhood conditions are associated with the risk of schizophrenia and seem to act not only independently. Conclusions: The following complications were significantly associated with schizophrenia: Cranial traumatism, seizure on early infancy, complications of delivery (abnormal labor and delivery, fetal suffering or distress and incubator use); even in a isolated way or integrated in a synergistic model. A combination of diverse disciplines and approaches will be needed to elucidate the mechanisms underlying these important associations in order to establish preventive measures. The development and implementation of optimal strategies for recording important events during pregnancy, delivery and early childhood is needed to identify subjects on risk for schizophrenia.

Table. Predictors factors for schizophrenia: logistic regresión model

Independent risk	β	D. E. β	Exp (β)	IC 95% Exp (β)	P
Cranial traumatism	3.7	0.8	39.1	8.3–183.3	<0.001
Seizure on early infancy	3.3	1.1	27.0	3.0–240.9	0.003
Abnormal labor and delivery	2.4	1.2	10.7	1.0–111.3	0.05
Fetal suffering or distress	1.5	0.8	4.6	0.93–22.7	0.06
Incubator use	3.2	1.5	0.04	0.002–0.73	0.03

ID: 555523

ECT USE IN A PUBLIC HOSPITAL IN SYDNEY

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The aim of the study was to determine the use of ECT in a public hospital in Sydney. ECT data over a 5 and a half year period at a public hospital servicing a suburb of 271 710 population (2006 census) in Western Sydney was analysed. The data collected was: the type of ECT given (eg. bilateral / unilateral etc), the indications (diagnoses), gender, age and legal status of patients who received ECT. During this period (January 2003 to August 2008) 916 ECTs were administered of which 483 were right unilateral and, 433 bilateral. None of the patients received bifrontal ECT. 816 ECTs were administered to females whilst only 100 ECTs were given to males ie, F:M ratio was 8:1. This ratio of females: males was strikingly different from the female: male admission ratio of only 3:2. The majority (504) of the patients who received ECT suffered from depression whilst 130 suffered from schizophrenia, 274 suffered from schizoaffective disorder and 8 suffered from mania. Only a quarter (248) of ECTs were given voluntarily while the rest (668) were given to involuntary patients who were under the NSW Mental Health Act 2007. About 10% (90) of the patients were 65 years or over of which 50 ECTs were given to patients over 80 years of age. The use of ECT in this centre is much less when compared to its use in the other centres in the same Area Health Service. Although current practices suggest Bifrontal ECT is preferable to the other types, none of the patients were given bifrontal ECT. In addition only half the patients received Unilateral ECT despite unilateral ECT usually having less side effects and less memory impairment. It has become apparent that the use of ECT in this centre needs further evaluation and implementation of more up-to-date practices.
ID: 554143

7. 7. Genetics, Basic

ASSOCIATION OF THE BRAIN-DERIVED NEURO-TROPHIC FACTOR (BDNF) VAL66MET POLYMORPHISM WITH HIPPOCAMPAL N-ACETYL ASPARTATE (NAA/CHO) LEVEL AND VERBAL MEMORY CAPACITY

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Background: The brain-derived neurotrophic factor (BDNF) is a key regulator of neural plasticity and has been suggested to be involved in the pathophysiology and pathogenesis of schizophrenia and depression, with particular emphasis on dysfunctions of the hippocampal formation. In the present study, we investigated the impact of the val66met polymorphism in the BDNF gene on hippocampal functioning, in particular on hippocampal n-acetyl aspartate, a biochemical marker of neuronal integrity, as well as on verbal memory capacity, which depends on the functional integrity of the hippocampus. Methods: 192 subjects gave written informed consent to participate in the study (67 schizophrenic, 45 bipolar and 33 OCD patients, and 47 healthy subjects). Proton magnetic resonance spectroscopy was performed in the left hippocampus according to a standardized algorithm, verbal memory was assessed using the VLMT, and the subjects were genotyped with regard to the val66met polymorphism (rs6265) of the BDNF gene. Results: Met allele carriers showed lower relative n-acetyl aspartate (NAA/Cho) levels (-6.2%; $F_{1,117} = 3.9$, $P = .05$) and worse verbal memory performance (-6.6%; $F_{1,141} = 3.8$, $P = .05$) as compared to homozygous val/val carriers. The effect on verbal memory capacity was most pronounced in the schizophrenic patients (-17.0%). Conclusions: These findings provide further evidence for a crucial role of BDNF in hippocampal functions, particularly in hippocampus-mediated verbal short-term memory. Although association studies between the BDNF gene and schizophrenia have been inconclusive, our results are consistent with the assumption that changes in BDNF functioning may contribute to the development of schizophrenia.
ID: 546112

A CHROMOSOME 15Q13–14 2-BASE PAIR POLYMORPHISM IN THE PARTIAL DUPLICATION OF THE ALPHA 7 NICOTINIC ACETYLCHOLINE GENE IS ASSOCIATED WITH SCHIZOPHRENIA

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Multiple genetic linkage studies support the hypothesis that the 15q13–14 chromosomal region contributes to the etiology of schizophrenia. Among the putative candidate genes in this area are the alpha 7 nicotinic acetylcholine gene (CHRNA7) and a partial duplication of alpha 7 (CHRFAM7A). We have previously reported that a large chromosomal segment including the CHRFAM7A gene locus, but not the CHRNA7 locus, is deleted in some individuals. In addition, the CHRFAM7A gene locus also contains a polymorphism consisting of a 2 base pair (2-bp) deletion at position 497–498 of exon 6. The purpose of this study was to determine whether the 2-bp polymorphism or the segmental deletion of CHRFAM7A is associated with schizophrenia. We have employed a PCR-based method to quantify the copy number of CHRFAM7A and the presence of the 2-bp polymorphism in a large, multi-ethnic population of Caucasian, African-American and Hispanic descent for association of this locus with schizophrenia. The presence of the 2-bp polymorphism was associated with schizophrenia (allele frequency $P = .014$, genotype $P = .055$). Association of the 2-bp polymorphism with schizophrenia was highest in the African-American population (genotype $P = .018$, allele frequency $P = .028$). Association of the 2-bp deletion with schizophrenia also reached statistical significance in the Caucasian population (genotype $P = .028$, allele frequency $P = .033$). The association of the 2-bp deletion with schizophrenia did not reach significance in the Hispanic population. Comparison of P50 auditory gating test-to-conditioning (T/C) ratios in controls revealed no significant difference in the T/C ratio in those individuals with the 2-bp deletion (18.3 ± 2.3 vs 27.4 ± 6.7, $P = .213$). CHRFAM7A copy number was not associated with schizophrenia or with P50 auditory gating in any of the ethnicities or in the group as a whole. The 2-bp deletion polymorphism is in strong linkage disequilibrium with an inversion of the entire duplicate gene and surrounding loci. We conclude that the presence of the 2 bp deletion at the CHRFAM7A locus may therefore represent larger genomic rearrangements that may contribute an increased risk for developing schizophrenia by epistatic influences, perhaps involving CHRNA7.
ID: 550808

DIFFERENTIAL REGULATION OF THE *CHRNA7* GENE IN SCHIZOPHRENIC SMOKERS

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The α7 neuronal nicotinic receptor gene (*CHRNA7*) has been implicated in the pathophysiology of schizophrenia by genetic and pharmacological studies. A mutation 1831bp upstream of exon one in the *CHRNA7* gene is associated with schizophrenia, after correction for multiple testing (Caucasians, $P = .003$; African Americans, $P = .001$). Genotype for this SNP predicts a positive response to the α7* receptor agonist, DMXB-A. Expression of the α7* receptor, as measured by [125I]α-bungarotoxin binding is decreased in post-mortem hippocampus, cortex and reticular nucleus of the thalamus in schizophrenic subjects compared to non-mentally ill controls. Most schizophrenic patients are heavy smokers. Smoking changes the expression of multiple genes and differentially regulates gene expression in schizophrenic hippocampus. This differential regulation is in specific patterns; expression is either lower or higher in schizophrenic non-smokers, compared to control non-smokers, and is brought to control levels or normalized in schizophrenic smokers. Several schizophrenia candidate genes are differentially regulated by smoking in schizophrenia, including *CHRNA7*. We have examined the effects of smoking on *CHRNA7* in additional subjects by qRT-PCR and western blot, finding that smoking differentially regulates expression of both mRNA and protein. *CHRNA7* mRNA and protein levels are significantly lower in schizophrenic non-smokers, compared to control non-smokers ($P < .05$). Core promoter polymorphisms in the *CHRNA7* gene, associated with both the P50 deficit and with schizophrenia, are significantly more abundant in the schizophrenic non-smokers with low levels of

CHRNA7 mRNA (*P* < .01). In schizophrenic smokers, both mRNA and protein and are brought to control levels. Although α7 subunit levels are adequate in schizophrenic smokers, low surface expression of the α7* receptor suggests aberrant assembly or trafficking of the receptor. We analyzed the expression of the nicotinic receptor chaperone gene, *RIC3* in hippocampus. *RIC3* expression, though not different in schizophrenic postmortem hippocampus was decreased in smokers.
ID: 550768

MITOCHONDRIAL VARIANTS IN SCHIZOPHRENIA, BIPOLAR DISORDER, AND MAJOR DEPRESSIVE DISORDER

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An increasing number of brain studies implicate mitochondrial dysfunction in psychiatric disorders. The present study evaluated mtDNA variants in brain tissue including substitutions, synonymous and non-synonymous, and rare variants, which could predispose to bipolar disorder (BD), schizophrenia (SZ) and major depressive disorder (MDD). Genomic DNA from dorsolateral prefrontal cortex (DLPFC) from a total of 77 subjects (12 with BD, 14 with SZ, 15 with MDD, and 36 controls) was studied for mtDNA sequence variations using Affymetrix GeneChip Mitochondrial Resequencing Arrays 2.0. The microarray resequencing of mtDNA was 100% concordant with conventional capillary electrophoresis sequencing results for 103 mtDNA variants. There was 99.997% concordance for 3 individuals that were completely resequenced using both methods. In 45 000 sequences there was 1 discordant base call. The mitochondrial microarray however showed a large N call rate, which may be improved by using similar PCR conditions as the National Institute of Standards and Technology. DLPFC from subjects with schizophrenia had an increased rate (22% higher compared to the control rate (*P* = .0017)) of synonymous base substitutions in mtDNA. A novel risk factor for BD and MDD was found in the ND4L gene at T10652C. In addition, there was a significant increase of the mtDNA common deletion in brain DLPFC in the ND4L T10652C carriers. Postmortem brain pH, used as a quantitative trait, showed significant association (*P* = .004) with three mtDNA SNPs (tRNA Leu, ND4, and ND5). These 3 mtDNA SNPs are ethnic-specific haplotype-defining polymorphisms for the super haplogroup cluster (U, K, UK). This super-haplogroup showed a significantly increased postmortem pH (mean 7.0 ± 0.18 SD) compared to the other haplogroups combined. Focusing on haplogroup susceptibility factors in psychiatric disorders and considering mtDNA variants in brain may lead to innovative treatments that improve mitochondrial health and brain function.
ID: 550673

A SUSCEPTIBILITY GENE FOR PSYCHIATRIC DISORDERS INCLUDING SCHIZOPHRENIA, BIPOLAR DISORDER AND GILLES DE LA TOURETTE IN 13Q14

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The idea that schizophrenia (SZ) and bipolar disorder (BP) share a common genetic ethiology has emerged from the fact that several vulnerability loci or genes may be common to the two disorders. Moreover, the nosology of major psychoses is challenged by the findings that SZ and BP share several neurobiological, neuropsychological and clinical phenotypic characteristics. A genome-scan in a sample of 48 SZ and BP families from Eastern Quebec was carried out with one of the main objective to test this hypothesis. Model-based and model-free linkage analysis were performed in this sample and provided a nonparametric linkage (NPL) value of 5.21 at marker D13S1247, a score which clearly suggests that 13q14, where lies D13S1247 locus, contains one or several genes underlying both mood disorders and schizophrenia. Our data thus suggest a susceptibility locus in 13q13-q14 that may be shared by schizophrenia and mood disorder. That locus would be additional to another well documented and more distal 13q locus where the G72/G30 gene is mapped. In a parallel project on the genetic study of Gilles de la Tourette (TS), we recently completed a full genome scan in a large Eastern Quebec family (127 members) in which 20 family members were definitely affected by Gilles de la Tourette (TS) and 20 others showed tic disorders. One of the most striking features of the results from this linkage study is that the best finding was also obtained in 13q14 with the exact same marker (D13S1247) that yielded the best significant evidence for linkage with SZ and BP. Indeed, in 13q14, we observed 3 markers linked to TS with a maximum parametric lod score (Z_{max}) above 1, including a Z_{max} of 3.01 at marker D13S1247. Moreover, the nonparametric linkage analysis (NPL) was consistent with the parametric one and yielded a maximum NPL entropy score of 3.58 again at D13S1247. Given our actual results obtained with TS, we can now expand on our previous conclusion and stipulate that 13q14 may harbor a more general susceptibility gene for psychiatric disorders including SZ, BP and now TS.
ID: 550663

ASSOCIATION WITH SCHIZOPHRENIA OF THE BIPOLAR DISORDER GENE PURINERGIC RECEPTOR P2X, LIGAND-GATED ION CHANNEL, 7 LOCATED AT 12Q24

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Purpose of the study: The purinergic receptor P2X, ligand-gated ion channel, 7 (P2RX7) gene is a positional candidate for bipolar disorder (BP) since its location at 12q24 where strong linkages with BP were reported (Morissette et al., 1999; Shink et al., 2005a,b). In fact, P2RX7 showed a strong association in French-Canadian bipolar families at the P2RX7 non-synonymous single nucleotide polymorphism (SNP) rs2230912 (*P*-value .0007), which results from an over-transmission of the mutant G-allele to affected offspring (Barden et al. 2006). Numerous convergences are observed between BP and schizophrenia (SZ) for phenotypic and genetic characteristics. For instance, we observed a linkage at 12q23.1 with a mixed phenotype (CL) including both BP and SZ (Maziade et al. 2005). We aimed to evaluate if P2RX7 could also be associated to SZ. Methods: We analyzed 23 SNPs located within P2RX7, including rs2230912, in 247 unrelated SZ and 150 unrelated controls. A Chi2 analysis was used to evaluate the Hardy-Weinberg equilibrium within SZ and controls, and to compare genotypic and allelic

frequencies between them. We aimed to confirm some of these results in our multigenerational families densely affected by SZ and BP using Family-based association test (FBAT). Results: We observed differences between genotypic frequencies at four SNPs ($.0017 \leq P \leq .035$), and differences between allelic frequencies at 8 SNPs ($.0003 \leq P \leq .04$), including rs2230912 previously associated to BP. Using FBAT in families, we observed no association with BP, while a weak association between rs2230912 and our composite phenotype CL was detected, and between a second SNP and SZ ($P = .03$ for both). However, the power of our multigenerational families to test for association is relatively low, more particularly for BP, and for so we cannot confirm or infirm previous association reported with BP. Conclusion: We concluded that P2RX7 is also associated to SZ in French-Canadians.
ID: 550584

A TRANSLATIONAL APPROACH TO PRIORITIZE CANDIDATE GENES FOR SCHIZOPHRENIA: CONVERGENCE OF ASSOCIATION AND GENE EXPRESSION ANALYSES

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Background: We have reported gene expression values in the nucleus accumbens (NAC) of two rat strains that exhibit differential sensitivity to the prepulse inhibition-disruptive effects of the dopamine (DA) agonist, apomorphine (APO) (Shilling et al., Biol Psych 2008). In the present study, we used this database to prioritize a list of 29 genes that had been identified using the custom COGS/UCSD SNP chip, based on their associations with schizophrenia and/or at least one of the following potential endophenotypes for this disorder: prepulse inhibition (PPI), startle magnitude, startle habituation, P50 S1 amplitude, or P50 suppression (Greenwood et al. 2008). Because schizophrenia patients exhibit PPI deficits compared to normal comparison subjects, genes associated with strain differences in sensitivity to APO-induced PPI deficits in this animal model provide a rationale to prioritize specific schizophrenia-associated genes for further investigation. Methods: Affymetrix 230 2.0 chips were used to measure gene expression in the NAC. Twenty-seven of the 29 genes identified by association analysis in human subjects were represented on this gene chip. Gene expression of these 27 genes in the NAC was analyzed based on data collected from this animal model of differential PPI sensitivity to apomorphine in Long Evans (LE) vs. Sprague Dawley (SD) rats. Statistical analysis of microarrays (SAM) was employed to identify significant between strain differences in expression using a false discovery rate (FDR) $< 5 \%$. Results: SAM analyses revealed that 10 of the genes associated with at least one of the potential schizophrenia endophenotypes also exhibited significant gene expression differences in the NAC at a FDR $<5\%$. Interestingly, all 10 genes were upregulated in the LE compared to SD rats. These genes include COMT, NRG1, GRIN2B and GRID2. Gene expression/behavioral correlations will also be presented. Discussion: Specific genes that were associated with endophenotypes for schizophrenia were also differentially expressed across strains exhibiting differences in PPI sensitivity to a DA agonist. This convergent translational approach provides a potentially powerful means to prioritize candidate genes for investigation in future studies, and ultimately might facilitate the identification of genes that contribute to the development of schizophrenia. Supported by MH42228 and MH68366.
ID: 550558

UNDERSTANDING NEUROCHEMISTRY OF SCHIZOPHRENIA ENDOPHENOTYPES: GENETIC ANIMAL MODELS OF HYPERDOPAMINERGIA AND HYPOGLUTAMATERGIA

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There is growing understanding that abnormalities in multiple neurotransmitter systems can be involved in the pathophysiology of schizophrenia. Based on pharmacological observations, two major neurochemical hypotheses have been proposed to explain schizophrenia. The dopamine hypothesis suggests that either an excess of dopamine or an increased sensitivity to the neurotransmitter is the underlying pathological mechanism. A competing notion, the hypoglutamatergic hypothesis of schizophrenia, suggests that decreased glutamatergic transmission underlies schizophrenia, based on the ability of NMDA receptor antagonists to recapitulate certain endophenotypes of schizophrenia. In an attempt to understand the potential contribution of various neurotransmitter systems to particular endophenotypes of schizophrenia several genetically modified animal models have been investigated. A mouse in which the dopamine transporter gene (DAT-KO) has been inactivated provides a model of hyperdopaminergia. This mouse displays hyperactivity, perseverations in cognitive tasks and deficient sensorimotor gating. These behavioral deficits can be corrected by antipsychotic drugs and as such recapitulate particular endophenotypes of schizophrenia related to positive symptoms. A mouse, which carries a hypomorphic allele of the NR1 subunit of the NMDA receptor provides a model for a hypofunctioning glutamate system. NR1 mutant mice display more complex set of behavioral abnormalities that include mild hyperactivity, social dysfunctions, deficient sensorimotor gating and cognitive impairment. These aberrant behaviors can be ameliorated more effectively by atypical rather than typical antipsychotics and thus NR1 deficient mice may have translational value to understand endophenotypes of schizophrenia related to negative symptomatology. Here I will discuss how these and other recent genetic animal models of aberrant neurotransmission may be instrumental to decipher the contribution of specific neurochemical abnormalities to certain endophenotypes of schizophrenia.
ID: 550503

ANALYSIS OF GENE EXPRESSION IN TWO LARGE SCHIZOPHRENIA COHORTS IDENTIFIES MULTIPLE EXPRESSION CHANGES ASSOCIATED WITH NERVE TERMINAL FUNCTION

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Schizophrenia is a severe psychiatric disorder with a world wide prevalence of 1%. The pathophysiology of the illness is not understood, but is thought to have a strong genetic component with some environmental influences on aetiology. To gain further insight into disease mechanism, we used microarray technology to determine the expression of over 30 000 mRNA transcripts in post-mortem tissue from a brain region associated with the pathophysiology of the disease- Brodmann Area 10 (anterior prefrontal cortex) in 28 schizophrenic and 25 control patients. We then compared our study (Charing Cross Hospital Prospective Collection: CCHPC) with that of an independent prefrontal cortex dataset from the Harvard Brain Bank (HBB). We report the first direct comparison between two

independent studies in which 51 genes have been identified that are common between the schizophrenia cohorts and of these, 49 show the same direction of disease-associated regulation. In particular, changes were observed in gene sets associated with synaptic vesicle recycling/ transmitter release and cytoskeletal dynamics. This strongly suggests multiple, small but synergistic changes in gene expression that affect nerve terminal function.
ID: 550256

ALTERATION OF MICRORNA BIOGENESIS IN SCHIZOPHRENIA AND ITS IMPLICATIONS FOR SYNAPTIC STRUCTURE AND FUNCTION

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Our analysis of cortical microRNA (miRNA) expression in postmortem tissue from the superior temporal gyrus (STG) and the dorsolateral prefrontal cortex (DLPFC) has shown that there is a broadly based schizophrenia-associated increase. The scope of this anomaly was suggestive of an alteration to miRNA processing and we can confirm that we have identified a corresponding increase in the expression of mRNA for the DiGeorge Critical Region 8 (DGCR8) gene in both regions of the brain. This gene encodes a major component of the microprocessor complex, which is thought to be a rate-limiting step in the miRNA biogenesis pathway. The link between altered miRNA expression and biogenesis in schizophrenia was even stronger in the DLPFC, with a statistically significant, increase in mRNA for Drosha, also part of the microprocessor, and Dicer another RNase III synonymous with post-transcriptional gene silencing. Quantitative real-time RT-PCR analysis supported the view that there was a schizophrenia-associated increase in mature miRNA expression in both cortical regions and that many of the altered miRNAs were also common to both regions. The biological significance of these findings are profound as each miRNA has the capacity to regulate the expression hundreds of target genes. This was exemplified by upregulation of the entire miR-15 family including miR-15a, miR-15b, miR16 and miR-195. This functionally convergent group is predicted to have many target genes involved in synaptic structure and function and many are also associated with schizophrenia. We have substantiated some of these target gene relationships through luciferase reporter gene assays and gene expression profiling in cells transfected with synthetic miRNA and miRNA inhibitors.
ID: 550221

DIFFERENTIAL NEUROBEHAVIOURAL EFFECTS OF ACUTE AND CHRONIC CANNABINOID TREATMENT ON HETEROZYGOUS NEUREGULIN 1 MUTANT MICE

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The human neuregulin 1 (NRG1) gene is a schizophrenia candidate gene and mice mutant for transmembrane domain (TM) Nrg1 exhibit a marked schizophrenia-related behavioural phenotype. Schizophrenia with its multifactorial aetiology has a concordance rate of 30–50% for monozygotic twins highlighting the fact that neither environment nor genetics alone are sufficient to cause schizophrenia but a combined action is likely. Cannabis use may increase the risk of developing schizophrenia by unmasking the disorder in genetically vulnerable individuals. Using a multi-factorial animal model strategy, we investigated the neurobehavioural phenotype of male heterozygous TM Nrg1 mutant mice (Nrg1 HET) and their wild type-like (WT) littermates, which were treated acutely and chronically with either vehicle or cannabinoids [acute: 5 and 10 mg/kg delta-9-tetrahydrocannabinol (THC) / chronic: 0.4 mg/kg CP 55 490 (CP)]. All mice were tested in a variety of tasks for locomotion, exploration, anxiety and sensorimotor gating [ie, prepulse inhibition (PPI)]. Fos B/deltaFos B as well as c-Fos expression analyses determined neuronal correlates for the behavioural effects of acute and chronic cannabinoid treatment. Acutely, Nrg1 HETs were more sensitive to the locomotor suppressant actions of THC and expressed a greater THC-induced enhancement in %PPI compared to WT mice. Mutants were also more susceptible to the anxiogenic effects of THC. THC selectively increased c-Fos expression in the ventrolateral septum (LSV), the central nucleus of the amygdala and the paraventricular nucleus of Nrg1 HETs. Chronically, Nrg1 HET mice developed more rapidly tolerance to CP-induced hypothermia and locomotor suppression compared to WTs. Conversely, tolerance to the anxiogenic effect of CP was only observed in WT mice. In addition, a selective increase in Fos B/deltaFos B expression was detected in the LSV of Nrg1 HET mice following chronic CP exposure, with no corresponding effect seen in WT mice. Acute but not chronic CP treatment facilitated PPI in Nrg1 HET mice and decreased it in WT mice. These data suggest that a variation in the Nrg1 gene alters the sensitivity to the neurobehavioural effects of cannabinoids and results in differential adaptive processes to repeated cannabinoid exposure. Overall, our findings support the idea of an interactive relationship between neuregulin and the cannabinoid system.
ID: 548541

PILOT STUDY OF THE PERCEPTIONS OF GENETIC RISK ESTIMATION AND ASSOCIATED REPRODUCTIVE DECISIONS IN CHINESE

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Background: Schizophrenia is a polygenic illness affecting about 1% of the population across different countries. First-degree relatives of schizophrenia are more prone to be affected. However, relatively few studies have been launched to examine the relationships between risk perception, reproductive decisions and attitudes towards predictive testing in a Chinese sample. Aim: to investigate relationships between risk perception, reproductive decisions and attitudes towards predictive testing, for patients with schizophrenia and their first-degree nonpsychotic relatives, respectively Method: A Chinese version of a tailor-made questionnaire (Austin et al., 2006) capturing specific questions on perceptions of psychotic disorders was administered to 57 patients with schizophrenia and 25 corresponding first-degree nonpsychotic relatives in an outpatient clinic in Shantou. Results: Only a quarter of nonpsychotic relatives of patients with schizophrenia perceived risk accurately and more than half of the relatives overestimated/underestimated the genetic risk. For the patients, only 12.3% perceived genetic risk

accurately. 32% of the relatives and 28.1% of the patients reported that family history had affected reproductive decisions. Majority of the relative supported prenatal genetic testing for psychosis as well as genetic testing in general, while no more than half patients agreed with the prenatal and general genetic testing. Conclusions: Most of the first-degree nonpsychotic relatives estimated the risk inaccurately among the current Chinese sample. Facilitating accurate risk perception through genetic counseling could significantly impact reproductive decisions, and the appropriate impact reproductive decisions, and the appropriate use of genetic tests in the future in China.
ID: 546390

MICRORNA CHANGES IN THE PREFRONTAL AND TEMPORAL CORTICES IN SCHIZOPHRENIA

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microRNA (miRNA) are small RNA molecules that are expressed in a developmental and tissue-specific manner, and are thought to regulate at least a third of all human genes through the sequence-specific base pairing with the 3'-UTR of specific target mRNAs. Expression profiling experiments have shown that many mammalian miRNAs appear to be crucial to the development of the brain and the nervous system. It has been suggested that abnormalities in the miRNA system could potentially alter brain structure and function, and may contribute to the development of disorders such as schizophrenia. Gene expression studies in our laboratory have identified a general trend toward gene down-regulation in schizophrenia, and it is possible that this could in part be a consequence of post-transcriptional gene silencing. To investigate this hypothesis, miRNA expression was analysed in postmortem cortical grey matter of the superior temporal gyrus (STG) and dorsolateral prefrontal cortex (BA9; DLPFC); from both schizophrenia and control subjects using a high throughput microarray platform. This study identified a global up-regulation of miRNA expression in the STG and DLPFC and many expression changes were validated using a custom-designed real-time RT-PCR method. Investigation of primary and precursor miRNA transcripts as well as genes involved in the miRNA biogenesis pathway suggest that altered mature miRNA expression may be a consequence of aberrant miRNA processing. Using in silico target gene analysis, numerous schizophrenia candidate genes were found to have putative miRNA binding sites for these altered miRNA within their 3'-UTR (eg, BDNF, RELN, HTR2A, DRD1, DLG4, VSNL1, GRIN3A, GRM7, CHRM1 and PLEXNA2). A luciferase reporter gene assay was established and many miRNA recognition elements were functionally validated. This data suggests that alterations in post-transcriptional gene silencing may play a significant role in schizophrenia-associated changes in gene expression.
ID: 550907

TIMING OF PRENATAL DEVELOPMENTAL PERTURBATIONS INDUCED BY MUTANT DISC1 RESULTING IN SCHIZOPHRENIA-LIKE BEHAVIORAL AND PATHOLOGICAL ALTERATIONS

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Data from neuropathologic, neuroimaging, neuropsychological and epidemiologic studies suggest that early neurodevelopmental alterations may contribute to the dysfunction in schizophrenia and related disorders. We used a genetic mouse model as an experimental system to demonstrate the contribution of neurodevelopmental insult on adult pathology. Previously, we have generated an inducible mouse model of the human mutation of Disrupted-In Schizophrenia 1 (mhDISC1), using a Tet-off system. The expression of mhDISC1 is restricted to forebrain neurons. Although the existence of mhDISC1 results in schizophrenia-like alterations, such as enlarged ventricles, the timing for the generation of these alterations remains incompletely understood. To evaluate the critical time points for adult pathological alterations, we generated three groups of mice with expression of mhDISC1 prenatally and postnatally; prenatally only; or without expression. The expression of the mhDISC1 was regulated by feeding mice with doxycycline-containing food. Prenatal but not postnatal expression of mhDISC1 was associated with decreased social interaction and increased aggressiveness. Mutant mice with prenatal expression displayed enhanced sensitivity to a NMDA antagonist, MK-801, or amphetamine. Prenatal expression was also associated with depressive features as indicated by increased immobilization time and decreased latency to immobility in Porsolt Forced Swim Test. In addition, prenatal but not postnatal expression of the mutant protein produced decreased total cortical volume, reduced parvalbumin immunoreactivity, and increased dendritic spine density in granule cells of the dentate gyrus. We believe these results provide experimental support for neurodevelopmental hypothesis of schizophrenia and related disorders.
ID: 551899

DISC-1 PROTEINS ENCODED BY LEU607PHE ALLELES SHOW A DIFFERENTIAL SUB-CELLULAR LOCALISATION AND DIFFERENTIALLY MODULATE NEUROTRANSMITTER RELEASE

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Like other putative schizophrenia susceptibility genes, disrupted-in-schizophrenia 1 (DISC-1) may impact on synaptic functioning, in part through effects on microtubules. The Leu607Phe substitution is one of the few polymorphisms in DISC-1 which is coding, and which has been associated to a schizophrenia spectrum phenotype. The latter property increases the prior probability that is a functional variant, but direct evidence for this is lacking. Given the links between DISC-1, microtubules, and synapses, we have used an in vitro model system to examine whether the polymorphism affects neurotransmitter release, microtubule dynamics, or the sub-cellular localisation of the encoded DISC-1 protein. SH-SY5Y cells were chosen for this study as they are human and have a neuronal phenotype. Undifferentiated SH-SY5Y cells were transfected with constructs containing either V5-tagged Leu607 or Phe607 DISC-1. Twenty four after transfection, [3H] noradrenaline neurotransmitter release from the cells was examined using an established assay. Perfusate was collected after basal (5mM K+) and stimulated (100 mM K+) release, the adherent cells solubilized, and the quantities of released and non-released [3H] noradrenaline determined by liquid scintillation counting. Western blots were used to quantify tyrosinated and detyrosinated alpha-tubulin, markers of dynamic and stable microtubules respectively. SH-SY5Y cells were also grown on slides, transfected with V5-tagged Leu607 or Phe607 DISC-1 and anti-V5 immunofluorescence performed to characterise their sub-cellular distribution. Consistent with prior observations, Leu607- and Phe607-DISC-1 were differentially distributed, with only Leu607 DISC-1 showing localisation to the centrosome, an organelle important in microtubule organization. Transfection of Phe607 DISC-1 decreased basal noradrenaline release, whilst Leu607 DISC-1 had no effect. The results reveal that the Leu607Phe polymorphism affects the subcellular localisation of DISC1 and basal neurotransmitter release by SH-SY5Y cells. The latter finding suggests that modulation of neurotransmitter release may be added to

the many roles that DISC-1 plays in the brain, and that may contribute to its role in genetic pathophysiology. Ongoing studies are being conducted to determine if the variants are associated with differences in the proportion of stable to dynamic microtubules and with other evidence for altered microtubular and synaptic functioning.
ID: 551792

HOW DISC1 MOUSE MODEL CAN HELP ADDRESS THE COMPLEX PATHOGENESIS OF SCHIZOPHRENIA

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Animal models are instrumental in elucidating the neurobiology of schizophrenia. Despite of significant advances, heterogeneity of etiological factors and the complex pathogenic mechanisms of this psychiatric disease call for further development of animal models. Recent discoveries in human genetics have provides a new framework for developing models with strong etiological and neurobiological validity. In addition, a better elucidation of environmental factors that contribute to the disease allows for modeling gene-environment interactions using relevant genetic risk factors and identified environmental challenges. I will describe new findings with our mouse models based on inducible expression of mutant human Disrupted-In-Schizophrenia (DISC1). Two main directions in using this models will be overviewed, ie, the timing of the effects of mutant DISC1 on neurodevelopment and interactions of mutant DISC1 with an environmental factor that induces strong immune response during pregnancy. For the first project, I will evaluate the new data to indicate that majority of subtle schizophrenia-like neurobehavioral alterations in mutant mice, such as enhanced sensitivity to a NMDA antagonist, MK-801, or amphetamine as well as the decreased total cortical volume and reduced numbers of parvalbumin-positive cells, are due to prenatal expression of mutant DISC1. For the second project, I will discuss the new findings about possible synergistic interactions between mutant DISC1 and prenatal poly IC treatment to activate immune response in pregnant mouse dams. Compared to saline-treated DISC1 mice, poly IC-challenged DISC1 mice exhibited increased anxiety-like and depression-like responses associated with the decreased density of dendritic spines in the dentate gyrus of the hippocampus. I will argue that DISC1 mouse model provides new avenues for advancing mechanistic studies of the complex pathogenesis of schizophrenia and related neurodevelopmental disorders.
ID: 551678

THE ROLE FOR THE CIRCADIAN TIMING SYSTEM AND THE GENE CLOCK IN INFORMATION PROCESSING

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Background: The precision of the circadian timing system is in large part dictated by endogenous molecular clocks and the expression of circadian genes. There is recent scientific evidence that suggests an association between variations in circadian genes, bipolar disorder, and schizophrenia. The circadian genes have been shown to be important in the processing of somatosensory signals and in systems that affect information processing, such as the dopaminergic system. Both neuranatomical and behavioral similarities have been reported between circadian gene knockout mice and patients who are diagnosed with schizophrenia. Similarities include reduced hippocampal volume, enlarged ventricles as well as impairments in PPI and memory. The Clock 3111 T/C SNP has been associated with variations of activation patterns in the go no go task in bipolar depressed patients. An

increased frequency of the C allele has been reported in patients with schizophrenia, particularly in disorganized and residual sub-groups. These findings suggest that endogenous clocks can process sensory stimuli and play a key role on sensory driven adaptive behavior as well as information processing. Aim: To test the associations between Clock 3111 T/C genotype and both clinical and neuropsychiatric measures of information processing in subjects with psychotic illnesses. Methods: Subjects: Subjects with a SCID-IV confirmed diagnosis of Bipolar type I with psychosis, Schizophrenia, and schizoaffective disorder enrolled in a phenotyping study at the University of Texas Southwestern Medical Center at Dallas Department of Psychiatry's Division of Translational Research. Genotyping: All Subjects will be genotyped for the Clock 3111 T/C SNP (rs1801260). Measures of Working Memory: (1) WAIS-III Digital Symbol Coding, (2) WAIS-III Letter-Number-Sequencing, (3) WMS-III Spatial Span. Measures of Executive Functioning: (1) Wisconsin Card Sorting Test, (2) Trails B Trail Making Test. Measures of Neuropsychiatric Functioning: (1) PPI, (2) Eye Tracking Statistical Analyses: We will test for associations between Clock 3111 T/C genotype (T/T, T/C, C/C) and both clinical and biologic measures of cognitive functioning. Significance: Circadian genes may serve a more varied purpose as a component of a central integrator system and therefore be important in information processing in psychotic illnesses.
ID: 551598

ASSOCIATIONS AND INTERACTIONS BETWEEN A NETWORK OF DOPAMINERGIC GENE POLYMORPHISMS IN SCHIZOPHRENIA: A - FOLLOW-UP IN AN INDIAN SAMPLE

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We have earlier evaluated the hypothesis that dopaminergic polymorphisms are risk factors for schizophrenia (SZ) in Caucasian samples from the USA and Bulgaria (Talkowski, et al. Hum. Mol. Genet. 2008). The most promising associations are detected with SLC6A3 (alias DAT), DRD3, COMT and SLC18A2 (alias VMAT2). Here we present the follow-up analyses in the collaborative Indian trio sample ($n = 601$ families). Unscreened cord blood samples ($n = 520$) were collected from live birth at Lok Nayak Hospital, New Delhi. The SZ diagnoses were based on DSM IV criteria, similar to the US sample. Informed consent was obtained from the probands and family members at Ram Manohar Lohia Hospital, New Delhi. Snplex and SnapSHOT assay methods were employed for SNP genotyping. Our goals were, a) to seek replication at SNP level based on our earlier work in the US and Bulgarian sample, b) to understand the linkage disequilibrium (LD) patterns in the Indian sub-population and c) to test the epistatic interactions reported. We have evaluated a total of 41 SNPs. Suggestive associations were detected in the same direction reported earlier at SLC18A2 (rs363338, trends test $P = .075$). At DRD3 and SLC6A3, trends were noted with the opposite alleles (respectively, rs324030, $P = .084$; rs403636, $P = .058$). We also observed additional SNPs with suggestive associations at SLC18A2 (rs363399, rs10082463 and rs363285, $P < .1$). The LD patterns were similar to the US and Bulgarian samples. Earlier reported epistatic SNP interactions at all four genes between seven locus pairs ($p \leq 0.05$), were not noted. However, we observed other epistatic interactions, the majority being between SNPs at SLC6A3 and COMT. They need to be explored further at a functional level. Overall, we suggest the importance of DA genes and their interaction, as risk factors for SZ in the Indian sample.
ID: 551488

DISC1 EXPRESSION AND FUNCTION IN THE HIPPOCAMPUS

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Disrupted In Schizophrenia-1 (DISC1) is a highly promising schizophrenia susceptibility gene which is involved in several processes important to neurodevelopment, such as neurite outgrowth and neuronal migration. DISC1 is expressed in several brain areas implicated in schizophrenia, with particularly strong expression in the hippocampus. Immunohistochemical analysis of Disc1 expression in the mouse hippocampus reveals strong expression in areas CA1-CA3 and the dentate gyrus throughout development, with expression becoming more well-defined as these structures mature. We have also discovered that Disc1 is expressed by precursors migrating toward the dentate gyrus in early development. Given that functional and anatomical abnormalities in the hippocampus are consistently observed in the schizophrenic brain, there is an intriguing possibility that DISC1 abnormalities confer an increased risk for schizophrenia by disrupting the development of the hippocampus. To investigate this possibility, we have performed functional studies in the mouse hippocampus that indicate a role for Disc1 in its development.
ID: 551367

ALTERNATIVE SPLICING OF A NOVEL CASSETTE EXON IN THE DOPAMINE TRANSPORTER IS ASSOCIATED WITH SCHIZOPHRENIA

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We aimed to refine previously detected, replicable associations and epistatic interactions between intronic variations within the dopamine transporter (SLC6A3, "DAT") and schizophrenia. In fine-mapping analyses, we obtained near complete common variation information within these regions. To date, 375 variations have been catalogued, including 164 common variants which we captured at r2 < 0.95 using 88 'tag' SNPs. Significant associations with schizophrenia were replicated with several linkage disequilibrium (LD) clusters spanning introns 3 and 4 of the gene between two Caucasian cohorts (494 cases / 540 controls from the U.S., 659 trios from Bulgaria). A primate-specific computational model predicted a novel 108 base pair cassette exon defined by a potential recursive splice site and a standard 5' splice site motif within intron 3. The predicted exon was flanked within 600 nucleotides by schizophrenia-associated SNPs which fell within predicted splicing regulatory signals. Alternative transcripts have not been previously identified at DAT. We detected alternative splicing of the cassette exon (E3b) in cell transfection experiments and verified the inclusion of E3b in endogenous DAT transcripts in human substantia nigra tissue using RT-PCR assays. Differential inclusion of E3b was observed between constructs bearing schizophrenia risk alleles in this region and a construct with non-risk alleles. Using tag SNPs to represent all plausible risk alleles spanning the cassette exon and predicted regulatory sequences, we detected a significant association between schizophrenia and a common haplotype in both cohorts. E3b introduces multiple in-frame stop codons into the mRNA which truncates the DAT open reading frame

and may serve as a mechanism to negatively regulate DAT production. Exon E3b is conserved among primates and many other placental mammals but appears to have been lost in the Glires clade. We conclude that alternative splicing of a novel cassette exon could alter DAT function in the human brain and confer risk for schizophrenia.
ID: 551264

SCHIZOPHRENIA GENETICS: NUMBER OF GENES, ENVIRONMENTAL INFLUENCES AND DISEASE PENETRANCE UNDER EPISTATIC MODELS

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Schizophrenia is a complex disease with a prevalence of about 1% in the general population. Little is known about the genetics underlying schizophrenia, the number of genes and the interplay between genes. We aim to get insight into the genetics of schizophrenia by investigating a range of genetic models and their fit to empirical data. In particular, we consider additive, multiplicative and network models as well as combinations of additive and network models. These models are evaluated by calculating a likelihood-based score of how well they fit observed prevalences from pooled epidemiological studies of families where at least one member suffers from schizophrenia. (1) Our models are functions of number of genes, allele frequencies and environmental influence where the disease penetrance is determined as a function of the particular genetic model and environmental influence. The data are best explained by models containing few genes in epistasis, and furthermore, models with recessive genes are generally superior. Particularly, best fits are obtained under a one-gene additive model combined with network models with recessive genes, which is in keeping with recent findings on a de novo copy number variant expressing a rare chromosomal deletion. (2) Another striking result is that the percentage of individuals in the general population predisposed to schizophrenia is between 5% and 7% in the best fit model. Compared to a prevalence of 1%, this indicates that the environment has an important influence on the development of schizophrenia: only one in six (five to seven) predisposed individuals develops schizophrenia.

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ID: 551137

CONVERGING EVIDENCE FOR *DPYSL2* AS A RISK FACTOR FOR SCHIZOPHRENIA

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The genetic basis of schizophrenia is not clearly understood and no causative mutations have been definitively identified. It is highly heritable and involves the interaction of multiple genes of small effect and their interplay with the environment. Understanding the number of genes and their role and interaction in the pathophysiology, susceptibility to the disease or particular clinical symptoms and antipsychotic metabolism remains a crucial

issue in understanding the disease and developing novel drug strategies. We identified DPYSL2 as a candidate gene for schizophrenia from a transcriptome screen of the prefrontal cortex of a rodent phencyclidine (PCP) model of schizophrenia developed in our laboratory 1,2. This PCP model produces a pattern of metabolic hypofunction, neurochemical changes and behavioural deficits in the prefrontal cortex that closely mirror the cognitive deficits of schizophrenia 1,2. DPYSL2 is an intriguing candidate gene as it maps to 8p21, a region of the human genome, that has been repeatedly implicated by linkage analyses and association studies. In addtion its role in axonal formation and guidance in the developing nervous system is highly consistent with the neurodevelopmental theory of schizophrenia. To further characterise the function of DPYSL2 we have validated specific siRNAs to knockdown the expression of DPYSL2 in vitro and in vivo. In addition, we have performed a case-control association study of DPYSL2 in DNA samples from 500 UK patients with DSM4 schizophrenia and 500 controls using tag SNPs selected from HapMap3 and the ABI SNPBrowser4. Genotyping of SNPs in several haplotype blocks has been completed and association analysis at both single SNP and haplotype levels is underway. Our initial findings include the observation of a modest association with a 3'-UTR SNP in DPYSL2. In conclusion, combining neurobiological and genetic association studies provides a powerful means to understanding the contribution of individual candidate genes to the pathophysiology of schizophrenia. This work was funded by formerly Mitsubishi Pharma Co. (currently Mitsubishi Tanabe Pharma Co.) and NHS Scotland RandD for Mental Health Research.

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ID: 551097

DISCOVERY AND INITIAL CHARACTERIZATION OF A NOVEL D-AMINO ACID OXIDASE MRNA VARIANT

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D-amino acid oxidase (DAO) degrades D-serine, the endogenous NMDA receptor (NMDAR) co-agonist. Since D-serine levels and NMDAR function may be reduced in schizophrenia DAO is a pathophysiological candidate. This is supported by its genetic associations with and gene expression alterations[1,2] in schizophrenia and its potential benefit as a therapeutic target. We previously showed regional differences in DAO cellular localization and antigenicity between human cerebellum and cortex[1]. One potential explanation may be the regional expression of alternative splice variants. We have described splice variants for other schizophrenia genes[3,4], of interest since they may represent novel therapeutic targets for the disorder. This study therefore investigated novel DAO mRNA variants in human brain. We used exon-exon PCR and primers designed to novel human DAO sequences deposited on the Aceview database. PCR products were purified, sequenced and any novel variants analysed in silico and expressed in mammalian vectors in vitro. A novel variant, denoted DAO_vG, was detected in human cerebellum and lymphoblasts but could not be detected in cortex. Sequencing revealed DAO_vG comprises a portion of Intron8–9 of DAO at its 5' end continuous with exons 9, 10, 11 and the 3' UTR of the DAO gene. PCR experiments with primers flanking Intron8–9 verified that DAO_vG is not the result of retention of the entire Intron8–9 but is likely transcribed from a novel start site. In silico analysis revealed the presence of two single nucleotide polymorphisms (SNPs) in the 5' sequence of DAO_vG and showed that one of them alters binding of 3 transcription factors. Current studies are investigating whether DAO_vG mRNA levels are regulated by these SNPs or are altered in schizophrenia using lymphoblasts from Japanese schizophrenia ($n = 45$) and control ($n = 45$) subjects. A mammalian expression vector containing DAO_vG has been generated and ongoing studies are characterizing the function of DAO_vG transfected into HEK293 cells. In conclusion, we report a novel mRNA variant of DAO, detected in human cerebellum but not cortex. Ongoing studies are investigating its transcriptional regulation, expression in schizophrenia and functional characterization. Supported by Oxford University.

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ID: 551059

POLYMORPHIC VARIANTS OF THE TNXB ASSOCIATED WITH COGNITION AND SCHIZOPHRENIA SUSCEPTIBILITY

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The TNXB is a gene of an extracellular matrix protein tenascin X (TNX) spanning 68.2 kb on 6p21.3 in HLA-III region. TNX is important for the proper deposition of collagen fibers in dermis and its deficiency causes an autosomal recessive form of Ehlers-Danlos syndrome. TNX is also known to be associated with growth of central and peripheral nerves. Recently, an association between two SNPs of the TNXB (rs1009382 and rs204887) and schizophrenia was observed in family trios from the UK. With moderate significance, the results have been replicated in the Japanese but not in the Chinese population. We have genotyped 5 SNPs of the TNXB in 51 schizophrenic patients (SP) + 684 members of 176 European-American families from the CBDB/NIMH 'sibling study'. SNP genotyping was performed on the ABI PRISM 7900HT System by using TaqMan® SNP Genotyping Assays chemistry (ABI). Single SNP and three-marker haplotypes association analyses were calculated using the TDTPHASE (version 2.37) based on 100 000 permutations. The FBAT was used to test for a marker association with the clinical phenotype. Quantitative trait analysis (ie, with cognitive phenotypes) was performed in parent-affected child trios using QTDT (version-2.4.3). TNXB rs2071293 (C/T) and rs185819 (Arg[T/C]His) SNPs were associated with schizophrenia. FBAT analyses showed under-transmission of "C" and "T" alleles of the SNPs to SP ($z = -2.855$; $P < .005$; $z = -2.757$; $P < .004$, respectively). Two combinations of three-marker haplotypes were contributing to schizophrenia as well involving those SNPs (1. rs2269429-rs204887-rs185819: global $P < .009$; [2]rs185819-rs204900-rs2071293: global $P < .008$). As single markers the other rs2269429, rs204887, rs204900 SNPs did not show any difference in the transmission. Healthy subject's data suggested a significant association of the rs185819-rs204900-rs2071293 haplotype of the TNXB with cognitive parameters, eg, verbal (global $P < .01$) and visual memories (global $P < .004$), memory span (global $P < .015$), processing speed (global $P < .04$) and results of Nback (global $P < .04$) and card sorting (global $P < .01$) tests. We have not been able to replicate previous finding in this European-American sample. However, our data have indicated two novel SNPs of TNXB gene in association with schizophrenia either in or out of haplotypes. Strikingly, the haplotype involving those SNPs was also implicating to cognitive functioning. KRM acknowledges the USA Federal Government contract #HHSN271200700340P.
ID: 550921

TIMING OF PRENATAL DEVELOPMENTAL PERTURBATIONS INDUCED BY MUTANT DISC1 RESULTING IN SCHIZOPHRENIA-LIKE BEHAVIORAL AND PATHOLOGICAL ALTERATIONS

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Data from neuropathologic, neuroimaging, neuropsychological and epidemiologic studies suggest that early neurodevelopmental alterations may contribute to the dysfunction in schizophrenia and related disorders. We used a genetic mouse model as an experimental system to demonstrate the contribution of neurodevelopmental insult on adult pathology. Previously, we have generated an inducible mouse model of the human mutation of Disrupted-In Schizophrenia 1 (mhDISC1), using a Tet-off system. The expression of mhDISC1 is restricted to forebrain neurons. Although the existence of mhDISC1 results in schizophrenia-like alterations, such as enlarged ventricles, the timing for the generation of these alterations remains incompletely understood. To evaluate the critical time points for adult pathological alterations, we generated three groups of mice with expression of mhDISC1 prenatally and postnatally; prenatally only; or without expression. The expression of the mhDISC1 was regulated by feeding mice with doxycycline-containing food. Prenatal but not postnatal expression of mhDISC1 was associated with decreased social interaction and increased aggressiveness. Mutant mice with prenatal expression displayed enhanced sensitivity to a NMDA antagonist, MK-801, or amphetamine. Prenatal expression was also associated with depressive features as indicated by increased immobilization time and decreased latency to immobility in Porsolt Forced Swim Test. In addition, prenatal but not postnatal expression of the mutant protein produced decreased total cortical volume, reduced parvalbumin immunoreactivity, and increased dendritic spine density in granule cells of the dentate gyrus. We believe these results provide experimental support for neurodevelopmental hypothesis of schizophrenia and related disorders.
ID: 551930

CONVERGENT PATTERNS OF ASSOCIATION BETWEEN PHENYLALANINE HYDROXYLASE VARIANTS AND SCHIZOPHRENIA IN FOUR INDEPENDENT SAMPLES

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Recessive mutations in the phenylalanine hydroxylase (PAH) gene predispose to phenylketonuria (PKU) in conjunction with dietary exposure to phenylalanine. Previous studies have suggested PAH variations could confer risk for schizophrenia, but comprehensive follow-up has not been reported. We analyzed 15 common PAH "tag" SNPs and three exonic variations that are rare in Caucasians but common in African-Americans among four independent samples (total n = 5414). The samples included two US Caucasian cohorts (260 trios, 230 independent cases, 474 controls), Bulgarian families (659 trios), and an African-American sample (464 families, 401 controls). Analyses of both US Caucasian samples revealed associations with five SNPs; most notably the common allele (G) of rs1522305 from case-control analyses (z = 2.99, P = .006). This SNP was independently replicated in the Bulgarian cohort (z = 2.39, P = .015). A non-significant trend was also observed among African-American families (z = 1.39, P = .165), and combined analysis of all four samples was significant (rs1522305: $x2$ = 23.28, 8 df, P = .003). These results for this SNP met our a priori criteria for statistical significance, namely an association that was robust to multiple testing correction in one sample, a replicated risk allele in multiple samples, and combined analyses that were nominally significant. Case-control results in African-Americans detected an association with L321L (P = .047, OR = 1.46).Our analyses suggest several associations at PAH, with consistent evidence for rs1522305. Further analyses, including additional variations and environmental influences such as phenylalanine exposure are warranted.
ID: 560454

ADVANCES IN STATISTICAL GENETICS: APPLICATION TO SCHIZOPHRENIA AND RELATED NEUROPSYCHIATRIC DISORDERS

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Background: The identification and characterization of genetic factors contributing to common, complex neuropsychiatric diseases such as schizophrenia has been advanced by major breakthroughs in high-throughput, whole-genome genotyping assays and related genetic technologies. With advances in genomics, such as CNV analyses and epigenetics, there causes a burden to "order" and scale these disparate findings. The massive amounts of data these technologies generate require sophisticated data analysis methods for their reliable and compelling use. Methods: Genome Wide Association Studies (GWAS) are typically based on more 500 000 genotype assays performed on each of many thousands of subjects. Such studies require data analysis tools that can accommodate genetic background heterogeneity among the subjects, linkage disequilibrium between genetic variations, missing data, and the fact that many loci–both within and across different genetic regions–may contribute to phenotype expression. Results: We describe in a non-mathematical way, the use of novel data analysis methods for pursing genetic background assessments on the subjects in large-scale genetic study, as well as haplotype-based studies, that accommodate allelic complexities in GWAS contexts. These methods are showcased in actual data and brief discussion of their merits, as well as room for

improvements, is provided. Conclusions: Advances in statistical analysis methods, when coupled with commensurate advances in genetic/genomic technologies and phenotyping technologies, will lead to insights into inherited predisposition to schizophrenia and related neuropsychiatric disorders.
ID: 555087

GENETIC ANALYSES BETWEEN BDNF AND SNAP25 GENES AND STRUCTURAL MRI OF EARLY-PSYCHOSIS PATIENTS

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Background: Schizophrenia and other psychotic disorders are a heterogeneous group of disorders, which share similar clinical and pathophysiological characteristics. The brain-derived neurotrophic factor (BDNF) and synaptosome-associated protein of 25 kDa (SNAP25) genes are considered good candidates for early psychosis due to their significant association with schizophrenia and their importance in the postulated neurodevelopmental model. Hypothesis: The BDNF/SNAP25 gene variant(s) will predict grey matter abnormality in the brain of early psychosis patients when comparing with healthy controls, as measured by magnetic resonance imaging (MRI). Method: Two polymorphisms in the BDNF gene, BDNF(Val-66-Met) and BDNF(HinfI), and 3 polymorphisms in the SNAP25 gene, SNAP25(DdeI), SNAP25(MnlI), and SNAP25(TaiI), were investigated for the possibility of association with total grey matter volume using 62 schizophrenic patients and 28 healthy controls. We compared allelic frequencies and genotype distributions between early psychosis patients and healthy controls, and total grey matter volume between alleles and genotypes of each of these polymorphisms. Results: In our preliminary analysis, we detected significant difference in total grey matter volume within early psychosis patients between genotype distributions of BDNF(Val-66-Met) ($P = .003$) and SNAP25(DdeI) ($P = .015$), as well as with the total sample in BDNF(HinfI) ($P = .033$) and SNAP25(DdeI) ($P = .009$). Conclusion: Our results showed an interesting correlation between genotypes and grey matter volume and required further investigation with larger samples and sub-regional grey matter volumes.
ID: 554760

MNSOD IN TARDIVE DYSKINESIA: GENE ASSOCIATION STUDY AND META-ANALYSIS

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Tardive Dyskinesia (TD) is a potentially irreversible movement side effect that occurs in approximately 25% of patients with long-term typical antipsychotic exposure (Margolese et al. 2005). The motor side effects of TD interfere with normal voluntary movements, and causes discrimination by others, thus these side effects greatly reduce treatment compliance and worsen outcome. Predicting which patients will likely develop TD remains an important issue in treatment prescription. Oxidative stress has been implicated in the pathophysiology of TD. The brain is vulnerable to oxidative stress for several reasons. It uses a great deal of energy. It has large amounts of polyunsaturated fatty acids that are substrates for lipid peroxidation cascades. Further, certain brain regions, the basal ganglia in particular, contain large amounts of transition metals, some of which are involved in the formation of hydroxyl radicals via superoxide dismutase (SOD). Genetic studies have suggested that the manganese superoxide dismutase MnSOD (SOD2) Ala9 allele may be protective against TD (Hori et al. 2000; Galecki et al. 2006), though neither Zhang et al. (2002) nor Thelma et al. (2007) replicated the finding. We analyzed the Ala9Val polymorphism in MnSOD for association with TD is our sample of schizophrenia patients (N = 193 Caucasians and 30 African Americans). We also carried out a meta-analysis of all the studies published previously. We did not a significant association between Ala9Val and TD occurrence or AIMS scores in our sample. We observed a significant association, with TD-positive patients being more likely to carry the ValVal genotype (OR = 1.47; 95% CI: 1.03–2.12; P = .036). In conclusion, the Ala9Val polymorphism in MnSOD is involved in TD pathogenesis, though the effect may be small.
ID: 551950

LACK OF ASSOCIATION OF THE NAD(P)H DEHYDROGENASE, QUINONE 1(NQO1) GENE TO TARDIVE DYSKINESIA IN CHRONIC SCHIZOPHRENIA PATIENTS

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Introduction: Tardive dyskinesia (TD) is a potentially irreversible side effect of chronic antipsychotic medication that arises in approximately 25% of chronically treated schizophrenia patients. Oxidative stress has been one of the proposed mechanisms influencing TD risk. NAD(P)H dehydrogenase, quinone 1 (NQO1; MIM# 125860) is a 35.5 kb gene consisting of 6 exons and is located on chromosome 16q22.1. It codes for a phase II detoxifying homodimeric flavoprotein that catalyzes two-electron reduction of quinones to hydroquinones and is also involved in the detoxification of superoxide radicals to hydrogen peroxide. NQO1 is expressed in the substantia nigra and carries a common functional polymorphism, Pro187Ser (C609T), in exon 6. Individuals carrying variant TT genotype (Ser/Ser) expressed only trace amount of NQO1 protein and exhibit only 2–4% of the quinone reductase activity compared to the wildtype CC genotype (Pro/Pro). Methods: We investigated the role of the NQO1 polymorphism C609T (Pro187Ser) in a group of well-characterized schizophrenia patients (N = 223) who have been assessed for TD. We also performed a meta-analysis of all the previously published TD studies with the C609T polymorphism, including data from our sample (N = 5 studies). Results: We did not observe any allelic or genotypic association of the C609T polymorphism with the occurrence or severity of TD in our Caucasian and

African American samples when analyzed independently. In the meta-analysis, 1071 schizophrenia patients were genotyped for NQO1 C609T and 396 of them were positive for the diagnosis of TD. No significant allelic or genotypic association of the C609T alleles or genotypes with TD occurrence was observed. Conclusions: The NQO1 C609T does not play a major role in TD risk; however, additional polymorphisms should be tested before the role of NQO1 in TD can be completely excluded.
ID: 551938

8. 8. Genetics, Clinical

A NEUREGULIN 1 VARIANT IS ASSOCIATED WITH INCREASED LATERAL VENTRICLE VOLUME IN PATIENTS WITH FIRST EPISODE SCHIZOPHRENIA

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Background: Structural brain abnormalities are already present at early phases of psychosis and might be the consequence of neurodevelopmental deviance. Neuregulin 1 gene (NRG1) is a candidate gene for schizophrenia, and its protein has different roles in nervous system development and plasticity. A polymorphism within NRG1, SNP8NRG243177, has been associated with brain function among healthy and high risk subjects, and with reduced cell migration among patients with schizophrenia. We examined whether variations in this polymorphism influence brain volumes in first episode of schizophrenia subjects. Methods: Ninety-five minimally-medicated patients experiencing their first episode of schizophrenia underwent SNP8NRG243177 genotyping and structural brain MRI. Lobar volumes of grey matter (GM), lateral ventricles volume, and cortical cerebrospinal fluid (CSF) were compared among the groups according to their genotype after controlling for total intracranial volume. Results: The SNP8NRG243177 risk T-allele was significantly associated, in a dose-related fashion, with increased lateral ventricles volume. Genotype explained 7% of the variance of lateral ventricles volume. No significant differences in GM lobar or cortical CSF volumes were found among subgroups. Backgrounds: Our findings suggest that genetic variations of NRG1 gene can contribute to the enlargement of the lateral ventricles described in early phases of schizophrenia. These results suggest novel lines of research into potential mechanisms by which schizophrenia susceptibility genes might exert their effect on brain structure.
ID: 540126

GENETIC AND TRANSCRIPTIONAL VARIATION OF AN RNA EDITING ENZYME IN SCHIZOPHRENIA

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Evidence that RNA editing plays a role in psychiatric disorders is accumulating. The linkage 'hotspot' for schizophrenia at locus 1q21–22 includes the *ADAR1* gene(Adenosine Deaminase Acting on RNA 1), one of three editing enzymes which convert adenosine to inosine in RNA. This process has profound functional consequences within ADAR substrates, which include several glutamate receptor subunits, the GABAα3 receptor subunit and the 5-HT$_{2C}$ receptor. Preliminary data indicate that RNA editing could be reduced in schizophrenia and in addition, we have previously reported genetic association of ADAR1 with positive symptoms in schizophrenia. The current study tested the hypothesis that altered expression of ADAR enzymes occurs in schizophrenia. ADAR transcripts were investigated in the postmortem brain of schizophrenia cases in comparison with normal controls. The thalamus and anterior cingulate cortex (ACC) were tested because evidence suggests that schizophrenia patients have abnormalities in thalamo-cortical networks related to cognitive and sensory processing. To measure gene expression, messenger RNA (mRNA) was extracted from medial dorsal thalamus, the ventral tier region of the thalamus and the ACC from controls ($n = 14$, $n = 11$, $n = 28$ respectively) and schizophrenia subjects ($n = 13$, $n = 9$, $n = 37$ respectively). Quantitative PCR was performed for ADAR1, ADAR2 and ADAR3 transcripts. Data were normalized to the expression of four housekeeping genes (glyceraldehyde 3-phosphate dehydrogenase, beta-2-microglobulin, actin-beta, 18S). Results indicate that ADAR1 transcript levels are reduced in schizophrenia cases compared with controls in the medial dorsal thalamus ($P = .04$)and the ACC ($P = .03$) but not in the ventral thalamus. ADAR1 expression was also associated with ADAR1 genotype ($P = .003$) in cases and controls. No differences in ADAR2 or ADAR3 expression were detected between the groups. These results suggest that genetic variation associated with the reduced expression of ADAR1 is related to the pathophysiological mechanisms of schizophrenia. These findings also suggest that generalized reductions of RNA editing in several ADAR1 substrates could occur in schizophrenia. Extensive screening of ADAR1 is being conducted to clarify and replicate these findings.
ID: 550657

A NEW APPROACH FOR INVESTIGATING THE ROLE OF THE DYSTROBREVIN-BINDING PROTEIN (DTNBP1) IN PSYCHOSIS

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Association studies have been mixed over the role of dysbindin in schizophrenia. Differences in findings may signal that different haplotypes are important in varying populations. The goal of this study was to model the role of dysbindin in psychosis, capitalizing on the idea that different variants may contribute to risk for different people and that dysbindin may more directly effect the endophenotype of cognitive disruption than the full clinical picture of psychosis. Participants were part of a Finnish twin cohort that has been described in detail elsewhere. 298 twins were included in the current analyses; 127 controls and 172 twin pairs where one twin had a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features. Twins were tested using an extensive neurocognitive and clinical battery, completed structural magnetic resonance imaging paradigms and provided blood samples for harvesting genetic data. Four supermarkers were used to look at nine SNPs in the dysbindin gene, creating population specific haplotypes. Successive backwards multiple regressions were conducted to examine the role of haplotypes in cognitive performance. Outcomes were standard scores in cognitive domains known to be impaired in schizophrenia. Six "risk" and three "protective" haplotypes were identified based on their effects on multiple cognitive domains. Risk haplotypes occurred in less than 5% of the population and a new variable was created coding for the presence of any of

the risk haplotypes. The overall risk variable along with the three protective haplotypes, was analyzed for its effects on cognition, clinical symptoms, brain structure and disease status. Chi-squared tests showed patients were marginally more likely to have the risk haplotypes than controls or healthy co-twins ($P = 0.05$). Mixed-models ANOVAs showed risk haplotypes were associated with impaired cognitive performance, increased CSF and sulcal volume, and marginally decreased gray matter volume in patients and co-twins but not controls. They also predicted higher ratings on thought disorder among patients. Protective haplotypes predicted decreased sulcal and CSF volume across all participants and were associated with lower ratings of hallucinations and anhedonia in patients. These findings support the role of dysbindin in psychosis. Multiple variants may contribute to symptom severity and disease risk through common effects on expression of DTNBP1.
ID: 550637

CLINICAL CORRELATES OF OE NEURONS GENE EXPRESSION IN SCHIZOPHRENIA

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Over the last decade, the olfactory system and more specifically the olfactory epithelium (OE) has received growing attention as an alternative model for the study of the neurodevelopmental deficits of schizophrenia. OE is a unique tissue where some key features of neurodevelopment of the central nervous system occur throughout life. OE and its synaptic targets in the olfactory bulb (OB) provide an opportunity for a snapshot of morphologic and molecular neurodevelopmental processes that are ongoing even in late life. We have started a systematic collection of OE tissue in patients with schizophrenia and normal controls with the goal of studying gene expression from OE tissue and ultimately identify biological markers specific to the disease. In this symposium we discuss novel results on the correlation of clinical variables with UPSIT score and neuropsychological testing as well as OE gene expression profile. We have been able to confirm previously described association of negative symptoms with poor performance on the UPSIT in 15 patients with schizophrenia. In a subset of 10 subjects, we found a significant correlation between 5 genes, including RNA-binding protein genes, and UPSIT score. We will discuss correlation between gene expression and neuropsychological testing. Our results further confirm a relationship between negative symptoms of schizophrenia and poor performance on smell identification test. They also indicate that a method to clarify gene expression profile from OE neurons has been established and might be a useful technique to identify genes that correlate with indicators of psychopathology in schizophrenia.
ID: 550626

STRESS-REACTIVITY AS RISK FACTOR FOR THE POSITIVE SYNDROME OF PSYCHOSIS: EVIDENCE FOR A GENETIC CONTRIBUTION.

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Background: Increased stress-reactivity has been reported in subjects who are at increased risk to develop psychosis. Moreover, it has been suggested that stress-reactivity may be specifically related to the develop-

ment of positive symptoms. To add evidence to the hypothesis that stress-reactivity is an endophenotype for psychosis, the present study examined i) whether stress-reactivity clusters within families of psychotic patients, and ii) whether stress-reactivity in the relatives co-segregates with positive symptoms in the patients. Methods: The sample consisted of 47 patients with a diagnosis of psychotic disorder and their siblings ($n = 47$). The Experience Sampling Method (ESM—a structured diary technique) was used to measure stress-reactivity, defined as the increase in negative affect in reaction to stress in daily life. Positive symptoms in the patients were measured with the Brief Psychiatric Rating Scale. Results: Within-trait, cross-sib associations showed a significant association between stress-reactivity in the patient and stress-reactivity in their first-degree relative ($B = 0.15$ (SE = 0.04), $P = .001$). Additionally, significant cross-trait, cross-sib associations were established showing a significant association between the patient's positive symptoms and stress-reactivity in the first-degree relative ($B = 0.30$ (SE = 0.09), $P = .001$). Discussion: This study provided evidence for familial transmission of increased stress-reactivity. Furthermore, increased stress-reactivity levels in the siblings were associated with increased positive symptom intensity in the patients. These results thus suggest a genetic contribution to increased stress-sensitivity, which is specifically underlying the positive dimension of psychosis.
ID: 550461

MICRORNA GENOMIC VARIATIONS IN PSYCHI-ATRIC DISEASES

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MicroRNAs (miRNAs) are short (19~25 nucleotides) single-stranded non-coding RNAs that are generated from endogenous hairpin-shaped transcripts, precursor miRNAs. miRNAs function as guide molecules in post-transcriptional gene silencing by base pairing with target mRNAs, which lead to mRNA cleavage or translational repression. With >400 members in human, miRNAs are one of the largest gene families, accounting for ~1% of the genome.Since miRNAs are abundant in brain and playing important role in brain development and function, and they can regulate the expression of many genes of neurological interest simultaneously, variants in miRNA genes have the potential to play a role in complex psychiatric diseases such as schizophrenia and bipolar disorder. We present here results on the deep resequencing of known human miRNA precursors and variants identification in 281 brain-significant miRNAs. We have sequenced the genomic DNA region of these 281 miRNAs in 282 samples including 94 HapMap (CEU, YRI, JPN and CHB) samples and 188 Stanley Medical Research Institute (SMRI) and NIMH Genetic Initiative Bipolar, Schizophrenia, Major depression and control Caucasian samples. A total of 748 SNPs have been detected, of which 103 SNPs were located in miRNA precursors. Nominally significant associations have been detected for 33 SNPs between disease/control comparison and none of these associations withstood multiple testing corrections. Common variant associations of the identified precursor variants in large schizophrenia and bipolar samples will also be presented.
ID: 550421

THE EUROPEAN NETWORK OF NETWORKS FOR THE STUDY OF GENE-ENVIRONMENT INTERACTION

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The Dutch Schizophrenia Network was funded in 2005 by a large government grant which was matched for 50% by Industry. The model chosen was that of a single large nationwide study (G.R.O.U.P.) focussing on aetiology in the first instance, and evidence-based community psychiatry in the second. To date, more than 1000 families with at least one affected member have been collected, including detailed assessment of genetic variation, environmental exposures, cognition and structural MRI. Data collection, including 3- and 6-year follow-up of all families, is now extended as part of a combined effort of existing schizophrenia networks in Europe, called the European Network of Networks for the Study of Gene-Environment Interaction (EU-GEI). Within EU-GEI, new paradigms have been developed for the study of gene-environment interactions, including novel experimental psychosis paradigms, neuroimaging approaches and studies to assess the impact of gene-environment interactions on transition from prodromal to clinical state, course of illness across the critical period and multiple within-sample replications of GxE findings. In addition, novel genetic approaches towards candidate selection are tested, including GWAS stratified by environmental exposure, E-QTL, mechanism-based gene searches and impact of environmental exposures on common CNVs.
ID: 550328

DYSBINDIN AND D-AMINO-ACID-OXIDASE GENE POLYMORPHISMS ASSOCIATED WITH POSITIVE AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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The purpose of the present study was to investigate whether previously observed genotype-phenotype associations between dystrobrevin-binding protein 1 gene (DTNBP1; dysbindin) and D-amino-acid-oxidase (DAO) gene variants and clinical symptoms in schizophrenia patients could be replicated in a Scandinavian patient sample. In this genotype-phenotype association analysis, we investigated if three dysbindin single nucleotide polymorphisms (SNPs) and three DAO SNPs were associated with symptoms assessed with the Positive and Negative Syndrome Scale (PANSS) in a total of 155 patients with schizophrenia spectrum disorders. The PANSS items were divided into five factors; negative, disorganized, positive, excited and anxiety and depression symptoms. The main finding of the present study was an association between a dysbindin polymorphism and negative symptoms, and between a DAO polymorphism and anxiety and depression. This replicates results of previous studies. In our sample there was an additional association between both genes and total PANSS scores and between a dysbindin SNP and depression and anxiety. Most genetic case-control studies performed so far have focused on the association between dysbindin and DAO and the diagnosis of schizophrenia compared to healthy controls, although there are some indications that clinical phenotypes across diagnoses are associated with certain gene variants. Dysbindin and DAO, both involved in glutamate receptor function, have recently been reported to be associated with positive and negative symptoms in schizophrenia. The present association between dysbindin and DAO SNPs and clinical symptom characteristics further indicates involvement of glutamate abnormalities in schizophrenia pathophysiology as suggested by previous studies. It also indicates that dysbindin and DAO polymorphisms may be associated with subgroups of clinical characteristics in schizophrenia.
ID: 550279

PREMORBID FUNCTION AND PRODROMAL SYMPTOMS IN YOUNG GENETIC HIGH-RISK RELATIVES

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Premorbid deficits are common in schizophrenia and have been shown to predict outcome. Similarly, negative symptoms and subthreshold and brief-lasting intermittent psychotic symptoms are characteristic of the prodromal period before the onset of schizophrenia. The relation between premorbid functioning and prodromal symptoms in high-risk individuals is unclear. We examined premorbid functioning using the Premorbid Adjustment Scale (PMAS; Cannon-Spoor et al., 1982) and prodromal symptoms using the Structured Interview for Prodromal Symptoms (Miller et al., 2003). The PMAS evaluates social, sexual, academic and occupational functioning across four periods of development (childhood, early and late adolescence and adulthood). Fifty-six young relatives, with a first-degree family history of schizophrenia, ages 12 to 24 years were evaluated. Cross-sectional analyses revealed that poorer social and academic function in childhood (up through age 11) correlated with a greater degree of prodromal symptoms (Spearman $r = 0.38$, $P = .004$). In assessing specific clusters of prodromal symptoms, negative (Spearman $r = 0.38$, $P = .004$), disorganization (Spearman $r = 0.38$, $P = .004$) and general prodromal symptoms (Spearman $r = 0.26$, $P = .05$) were significantly correlated with childhood PMAS scores, with a trend for positive symptoms (Spearman $r = 0.23$, $P = .09$) in adolescents and young adults (age 16.8 ± 3.2 years). These analyses survived Bonferroni correction, except positive and general symptoms. Subsequent longitudinal growth curve analyses indicated that childhood social and academic maladjustment was significantly predictive of greater growth in prodromal negative symptoms over time ($\beta = .34$, $P = .001$), but not positive, disorganization, or general prodromal symptoms. These results indicate a significant relationship between measures of social behavior and function and clinical measures of psychopathology. Thus, prodromal symptomatology emerging during adolescence in genetically at-risk individuals may be preceded by poor premorbid social and academic functioning in childhood. Premorbid functioning in high risk individuals is highly relevant and would be an easy marker to target for early identification and intervention. Longitudinal data will help to study the relationship between premorbid maladjustment, prodromal symptoms and eventual conversion to psychosis in genetically vulnerable individuals.
ID: 550278

GENETIC RISK AND OUTCOME OF PSYCHOSIS (GROUP), A MULTI SITE LONGITUDINAL COHORT STUDY: OBJECTIVES, RECRUITMENT AND ASSESSMENT METHODS AND CHARACTERISTICS OF INCLUDED PARTICIPANTS

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Background: Studying both genes and environment in interaction is a fruitful strategy to identify the variations that may give rise to the psychotic vulnerability and variations in its course. A longitudinal study of both clinical and non-clinical populations offers the opportunity to elucidate etiological and pathogenetic factors. The main objective of the GROUP study is to investigate the dynamic interaction over time between genetic and environmental factors that contribute to 1) the expression of psychosis, and 2) the variations in course of psychosis. Methods: A naturalistic cohort study with a 6 year follow-up of 1) patients with non-affective psychotic disorders and 2) their siblings and parents, and (3) healthy controls performed by a consortium of four academic psychiatric centers, with their affiliated mental health care institutions in the Netherlands covering more than 7,5 million inhabitants. Extensive assessment of demographic and diagnostic variables, severity of psychopathology or traits, course, needs and care-consumption, neuropsychological functioning, DNA. Results: Baseline assessment is completed: 3737 subjects have been included: 1045 patients, mean age 27.6, (SD 7.2), 70% with a DSM-IV diagnosis of schizophrenia, 56% in their first psychotic episode, 1123 siblings, mean age 28.5, (SD 8.3), 828 parents mean age 53.7, (SD 6.9) and 641 healthy controls mean age 30.9, (SD 10.6). Part of this sample was used in a recently published study on a genome-wide search for copy number variations associated with schizophrenia (Stefansson et al. 2008) Conclusion: the Genetic Risk and Outcome of Psychoses (GROUP)-project will provide insight in gene-environment vulnerability and resilience factors in the development of a psychotic disorder, and in the variation in the course of the disorder. Acknowledgement: The study is supported by the ZonMW program Geestkracht, the 30 colloabarative Mental Health Organizations, and Astra-Zeneca, Bristol-Myers Squibb, Janssen-Cilag, Lilly.

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ID: 550220

ISSUES AND ADVANTAGES OF STUDYING INTERMEDIATE PHENOTYPES IN MULTICENTER STUDIES: THE GERMAN MOODS EXPERIENCE

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Intermediate phenotypes, especially using imaging genetics, have emerged as a powerful strategy to identify neural mechanisms linked to genetic risk for common mental disorders. In the context of large networks, studying these phenotypes is complicated by issues of scanner and subject heterogeneity and quality control. We present the experience from more than 160 subjects scanned using structural and functional neuroimaging in the German federally funded MooDs network. A reliable battery of neuroimaging tasks and methods for stringent quality control are presented. We show that stringent quality control is necessary to successfully combine data from different sites for imaging genetics. If these procedures are observed and adequate statistical models are used for analysis, neural mechanisms linked to common genetic risk variants for schizophrenia have been identified in the context of the network with a high degree of sensitivity and reliability.
ID: 550212

DEVELOPMENTAL CRITICAL PERIOD IN GENETIC REDOX DYSREGULATION: ANIMAL AND HUMAN STUDIES IN SCHIZOPHRENIA

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Converging evidence favors an abnormal susceptibility to oxidative stress in schizophrenia. Decreased levels of glutathione (GSH), the major cellular antioxidant and redox regulator, was observed in cerebrospinal-fluid and prefrontal cortex of patients. Importantly, abnormal GSH synthesis of genetic origin was observed: Two case-control studies showed an association with a GAG trinucleotide repeat (TNR) polymorphism in the GSH key synthesizing enzyme glutamate-cysteine-ligase (GCL) catalytic subunit (GCLC) gene. The most common TNR genotype 7/7 was more frequent in controls, whereas the rarest TNR genotype 8/8 was three times more frequent in patients. The disease associated genotypes (35% of patients) correlated with decreased GCLC protein, GCL activity and GSH content. Similar GSH system anomalies were observed in early psychosis patients. Such redox dysregulation combined with environmental stressors at specific developmental stages could underlie structural and functional connectivity anomalies. In pharmacological and knock-out (KO) models, GSH deficit induces anomalies analogous to those reported in patients. (a) morphology: spine density and GABA-parvalbumine immunoreactivity (PV-I) were decreased in anterior cingulate cortex. KO mice showed delayed cortical PV-I at PD10. This effect is exacerbated in mice with increased DA from PD5-10. KO mice exhibit cortical impairment in myelin and peri-neuronal net known to modulate PV connectivity. (b) physiology: In cultured neurons, NMDA response are depressed by D2 activation. In hippocampus, NMDA-dependent synaptic plasticity is impaired and kainate induced g-oscillations are reduced in parallel to PV-I. (c) cognition: low GSH models show increased sensitivity to stress, hyperactivity, abnormal object recognition, olfactory integration and social behavior. In a clinical study, GSH precursor N-acetyl cysteine (NAC) as add on therapy, improves the negative symptoms and decreases the side effects of antipsychotics. In an auditory oddball paradigm, NAC improves the mismatched negativity, an evoked potential related to pre-attention and to NMDA receptors function. In summary, clinical and experimental evidence converge to demonstrate that a genetically induced dysregulation of GSH synthesis combined with environmental insults in early development represent a major risk factor contributing to the development of

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ID: 550194

DRD2 VARIATION AND WEIGHT GAIN IN FIRST EPISODE SCHIZOPHRENIA

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Background: All antipsychotics act on the dopamine D2 receptor, and second generation antipsychotics carry a substantial liability for weight gain. The present study extends prior pharmacogenetic investigation of the D2 receptor gene (DRD2) by examining promoter region variation as a predictor of short-term (6-week) weight gain in response to two first-line atypical antipsychotics in first episode (FE) schizophrenia. Methods: Forty-four FE patients enrolled in a randomized trial of risperidone (RIS) vs. olanzapine (OLZ) were genotyped for a common polymorphism in the DRD2 promoter region (−141C Ins/Del) and had baseline and 6-week weight data available for comparison. Carriers of the DRD2 deletion allele ($n = 20$) were compared to C/C homozygotes (non-carriers, $n = 24$). Medication assignment (RIS, $n = 21$; OLZ, $n = 23$) and sex (M/F = 32/12) were also added to the ANOVA model. Results: There were significant main effects ($P < .05$) of both medication assignment (OLZ>RIS) and genotype (carrier>non-carrier), but no interaction of medication and genotype. Carriers of the deletion allele gained ~6 pounds more than non-carriers by the end of 6-weeks, regardless of medication assignment. Results did not appear to be a function of cumulative medication dosage or baseline demographics. Conclusions: DRD2 deletion carriers demonstrate increased liability for antipsychotic-induced weight gain, despite previous evidence that deletion carriers demonstrated reduced symptom response to medication. Additional study of appropriate treatment options for these patients appears warranted.
ID: 550173

OLFACTORY DISCRIMINATION IN YOUNG RELATIVES AT RISK FOR SCHIZOPHRENIA

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Olfactory discrimination deficits are seen in schizophrenia, but it is unclear whether they are related to familial risk and whether they are specific to the predisposition to this illness. We examined the prevalence and clinical correlates of olfactory discrimination abnormalities assessed using the University of Pennsylvania Smell Identification Test (UPSIT) in young relatives at risk for schizophrenia (HR-S) and a small subset of relatives at risk for bipolar disorders (HR-B). UPSIT deficits in the HR-S group were correlated with premorbid maladjustment in late adolescence, prodromal disorganization symptoms, as well as cognitive abnormalities. UPSIT scores were reduced in HR- S and in HR-B subjects compared to the healthy controls, and the HR-B findings survived after covarying the effects of IQ. Olfactory

discrimination deficits may reflect markers of psychopathological vulnerability in young relatives at risk for schizophrenia or bipolar disorder.
ID: 550142

FAMILIAL AGGREGATION OF CLINICAL, NEUROCOGNITIVE AND CEREBRAL STRUCTURAL FEATURES IN SIBLING PAIRS WITH AND WITHOUT SCHIZOPHRENIA

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Clinical, neurocognitive and structural features were found to be heritable in individuals with schizophrenia and their relatives. However, the heritability of neurocognitive measures in families with and without schizophrenia has not been directly compared. In this study, we examined their genetic structure in sibling pairs with and without schizophrenia to test the hypothesis that the familial aggregation of such measures may be altered by having schizophrenia. Patients with schizophrenia and their non-psychotic full siblings, healthy controls, and their full siblings were recruited. Heritability was estimated for positive, negative and disorganization symptoms, working and episodic memory, executive function, attention, volumes of whole brain, amygdale and hippocampus. Negative symptoms, working memory, episodic memory and executive function, but not positive, disorganization symptoms and attention, were found to be significantly heritable in all sibling pairs. However, the heritability of working memory function was significantly decreased in proband sibling pairs as compared to control sibling pairs. Significant genetic correlations were observed between negative symptoms and the cluster of working memory, episodic memory and executive function. Whole brain volume was decreased in individuals with schizophrenia and their siblings. All structural measures were heritable and showed different change patterns across sibling pair types. Most neurocognitive and structural measures were heritable in sibling pairs with and without schizophrenia. However, schizophrenia reduced the heritability of working memory, perhaps due to disease-related environmental or genetic factors. Evidence for pleiotropy will inform future phenotypic studies.

Table. Heritability (h2) for Potential Endophenotypes

	All Sibling Pairs ($N = 278$)			Control Sibling Pairs ($N = 157$)			Proband Sibling Pairs ($N = 121$)		
	h2	S.E.	P value	h2	S.E.	P value	h2	S.E.	P value
positive symptoms	.067	.055	.11	.20	.23	.20	.00	–(a)	.50
negative symptoms	.32	.062	<.001	.67	.20	.0012	.19	.14	.092
disorganization symptoms	.08	.057	.082	.35	.22	.060	.00	–(a)	.50
working memory	.53	.11	<.001	.85	.19	<.001	.38	.23	.052
episodic memory	.57	.11	<.001	.64	.22	.0032	.43	.17	.0070
executive function	.40	.096	<.001	.55	.21	.0064	.27	.12	.015
attention	.039	.16	.40	.055	.31	.43	.00	–(a)	.50
whole brain volume	.97	.17	<.001	.79	.27	.0050	.89	.26	<.001
amygdala volume	.63	.24	.0074	.37	.31	.12	.95	.33	.0037
hippocampal volume	.93	.19	<.001	1.00	–(a)	<.001	.83	.31	.0057

All models adjusted for age, gender, ascertainment bias. –(a):not estimable
ID: 549794

A DATABASE OF COMPREHENSIVE CLINICAL, ENDOPHENOTYPIC AND GENETIC DATA FOR AETIOLOGICAL STUDIES OF SCHIZOPHRENIA

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The Australian Schizophrenia Research Bank is a national database aiming to achieve a sample of 2000 cases of schizophrenia and 2000 healthy controls comprehensively assessed using a structured clinical diagnostic interview and symptom ratings, together with neuropsychological evaluations, structural MRI scans, and genetic analyses of blood samples. Recruitment of cases and controls began in 2007. Clinical assessment includes the Diagnostic Interview for Psychosis, SANS, GAF and measures of childhood adversity, schizotypal traits and personality. The neuropsychological test battery includes Edinburgh Handedness, RBANS, WTAR, WASI, Letter Number Sequencing, COWAT and items from the Neurological Evaluation Scale. Structural MRI scans are conducted at five locations in four states. Blood is stored for genetic analyses at most participating sites with duplicate samples stored separately. Primary genetic analyses will be conducted for the categorical phenotype. Secondary analyses will explore alternative phenotypes derived using empirical methods as well as putative endophenotypes based on neurocognitive and neuroimaging variables. Preliminary data from the first 500 cases will be presented to illustrate the potential of this database to link genetic findings with clinical, neurocognitive and structural brain changes in schizophrenia.
ID: 549548

PROBABILISTIC CATEGORY LEARNING DEFICITS EXIST IN A SUBSET OF UNAFFECTED SIBLINGS OF PATIENTS WITH SCHIZOPHRENIA

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While patients with schizophrenia display normal probabilistic category learning rate in conjunction with an overall performance deficit, the extent to which this deficit occurs in unaffected, first degree relatives of patients with schizophrenia is unknown. A probabilistic category learning test was administered to 128 patients with schizophrenia, 114 unaffected siblings, and 165 healthy participants. There was no significant difference among groups regarding learning rate; however, patients differed significantly from siblings and healthy participants regarding overall performance. Application of a stringent learning definition enabled further classification into good and poor learners. There was no significant difference in learning rate or performance between sibling and healthy good learners. There were significant differences between the percentages of sibling and healthy poor

learners: healthy (16%), siblings (34%), patients (48%), yielding a relative risk of 2.1, χ^2 (1) = 6.5, $P < .01$. Sibling and patient poor learners were significantly different from healthy poor learners during early trials; however, siblings improved during latter trials to the extent that they were significantly different from patients and indistinguishable from healthy participants. Application of a stringent learning criteria revealed that half of the patients with schizophrenia fail to show normal probabilistic category learning rate and performance. One third of unaffected siblings of patients with schizophrenia display probabilistic category learning abnormalities during early learning. This distinction between good and poor learning siblings of patients with schizophrenia, who are otherwise unaffected by illness, may be used to inform genetic studies designed to detect schizophrenia risk alleles.
ID: 548710

THE EFFECT OF COMT VAL158MET POLYMORPHISM ON COGNITION IN EARLY ONSET SCHIZOPHRENIA: A FAMILY-BASED STUDY

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The gene encoding catechol-O-methyltransferase (COMT), an enzyme which regulates prefrontal cortex dopamine, contains a functional single nucleotide polymorphism of the COMT gene (Val158Met, rs4680) which affects performance in working-memory tasks. We sought to investigate its effect on memory and attentional processes in early onset schizophrenia (EOS; onset before the age of 18) using a family-based design. We conducted a comprehensive neuropsychological test battery on 53 EOS probands and 117 of their unaffected first-degree relatives. They were examined on memory (Wechsler Memory Scale-Revised; WMS-R), verbal learning (California Verbal Learning Test; CVLT), visual information processing (SPAN of apprehension test) and sustained attention (degraded-stimulus continuous performance test; DS-CPT). The Structured Clinical Interview for DSM-IV yielded four diagnostic groups: EOS; relatives with Mood Disorders; Other Axis I diagnoses; and no diagnosis (healthy). Analysis of co-variance was performed, with diagnosis and genotype as fixed factors and age as covariate. Results showed that COMT Val158Met genotype was associated with memory and attention. There was a main effect of genotype in which Met158 homozygotes showed better performance on general memory indexes in comparison to Val158 homozygotes [$P = .05$], but not heterozygotes [$P = .47$]. Met158 homozygosity made fewer intrusion errors (CVLT) than Val158 homozygotes [$P = .004$] and heterozygotes [$P = .01$]. Similarly Met158 homozygosity was associated with a higher learning slope compared to Val158 homozygotes [$P = .03$], while heterozygotes were intermediate. Across trials, Met158 homozygotes produced more correct responses (DS-CPT) compared to Val158 homozygotes [$P < .03$] and heterozygotes [$P < .01$]. There was no effect of COMT genotype on SPAN. After applying Bonferroni corrections, a significant genotype by diagnosis interaction on sustained attention [$P = .0004$], showed that the Val158 allele and presence of an Axis I diagnosis was associated with fewer correct responses. Our findings implicate COMT in memory-related processes and sustained attention but not visual processing. The findings suggest that Met158 homozygosity is associated with processes involved in

encoding new information as evidenced by the learning slope, and the executive control of recall (intrusion errors). The COMT polymorphism may increase the risk of a number of Axis I diagnoses in individuals with a family history of schizophrenia.
ID: 548050

GENETIC OVERLAP BETWEEN EXECUTIVE FUNCTION AND SCHIZOPHRENIA—THE MAUDSLEY TWIN STUDY

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Executive functioning impairment is one of the most promising putative endophenotypes for studying the genetics of schizophrenia; however it is not clear to what extent these deficits are genetically linked to the disorder. The study aimed to quantify the genetic and environmental contributions to the variability of verbal fluency and mental flexibility and to estimate the genetic relationship between these and schizophrenia. The twin study design used bivariate genetic model fitting. A total of 335 twins participated in this research: 27 pairs of MZ twins concordant for schizophrenia; 20 pairs of MZ twins discordant for schizophrenia; 69 pairs of MZ twins without schizophrenia; 14 pairs of DZ twins discordant for schizophrenia; 58 pairs of DZ twins without schizophrenia. Verbal fluency was assessed using tests of phonemic and semantic fluency, and mental flexibility was assessed using Trail Making Test (TMT) indices: A, B and B-A. Regression analysis suggested that genetic loading for schizophrenia was positively associated with broader and more severe impairment in executive functioning tasks. Genetic modelling indicated that genetic influences contribute substantially to all of the executive measures, with phonemic fluency being most heritable followed by semantic fluency and TMT B-A. Significant phenotypic correlations with schizophrenia were found for all executive functioning measures. Genetic factors were the main source of the phenotypic correlations, in particular for mental flexibility. For example, shared genetic variance accounted for 91% of the phenotypic correlation (r_{ph} = 0.48; 95% CI = 0.38 to 0.55) between TMT-A and schizophrenia. Environmental effects, although separately linked to neurocognition and schizophrenia, did not generally contribute to their covariance. The strongest genetic correlation with schizophrenia was found for mental flexibility followed by semantic and phonemic verbal fluency. A high genetic correlation suggests that the same genes contribute to individual differences in both executive functioning and to the liability to schizophrenia. Bivariate genetic model fitting suggests that executive functioning is a potentially valid endophenotype for schizophrenia. The inclusion of these phenotypes in linkage or association analysis could improve the power to detect susceptibility genes for schizophrenia.
ID: 548041

ENDOPHENOTYPIC STRATEGY FOR SCHIZO-PHRENIA: AN ILLUSTRATIVE EXAMPLE WITH NEUROLOGICAL SOFT SIGNS

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Incontrovertible evidence for epidemiological genetic influences on schizophrenia has been accumulated since the 1960's (Rosenthal and Kety, 1968; McGuffin, Owen, and Gottesman, 2004). However, the identification of specific genes with large effect sizes that contribute to a susceptibility to schizophrenia has not been successful using conventional molecular genetic approaches. Therefore, researchers have been adopting a new direction that identifies neurobiological and neurobehavioural characteristics associated with schizophrenia, so-called "endophenotypes" (Gottesman and Gould, 2003; Gottesman and Shields, 1972) that may be more closely connected to the expressions of un-named genes (Bray et al. 2008). A substantial number of studies, especially of at-risk offspring, have suggested that neurocognitive dysfunctions are among the most promising of the candidate endophenotypes. On the other hand, the crucial role of neurological indicators in schizophrenia has been recognized as among the "target features" that encompass the idea that genetic and non-genetic processes lead to neurointegrative defects later manifested in neurocognitive systems. In addition, aberrant neurological indicators have also been suggested as potential endophenotypes in schizophrenia. In this presentation, we will argue with substantial evidence for the utility of quantifiable neurological soft signs as potential endophenotypes for schizophrenia spectrum disorders. We start by defining endophenotypes and justifying their utility. We highlight the key criteria that must be met for an endophenotype to be useful and assess the extent to which the manifestations of neurological soft signs meet these criteria. Finally, recommendation for additional research is made in order further elucidate the potential use of neurological soft signs for schizophrenia research.
ID: 546948

ASSOCIATIONS BETWEEN COMT VALMET GENOTYPE AND CLINICAL AND COGNITIVE PHENOTYPES IN MANIC BIPOLAR PATIENTS

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The catechol-o-methyltransferase (COMT) Val158Met polymorphism has been widely studied in relation to cognition in schizophrenia (SCZ), with the preponderance of the literature suggesting that the Valine (Val) allele of this gene is associated with cognitive inflexibility, eg, perseverative behavior. The COMT gene has been studied relatively less in bipolar disorder (BD) and few direct comparisons between BD and SCZ with respect to COMT-phenotype relationships have been reported. There is some evidence that COMT may confer different degrees of liability for clinical presentation and cognitive problems depending on diagnosis. The current study examined symptom presentation, cognitive markers, and genotypes for the COMT Val158Met polymorphism in BD patients hospitalized for a manic episode. Manic BD subjects were genotyped and administered the Brief Psychiatric Rating Scale (BPRS). They were tested in a sensorimotor gating paradigm (prepulse inhibition: PPI) as well as a human open field paradigm designed to quantify exploratory behavior, the human Behavioral Pattern Monitor (BPM). Data collection is ongoing; preliminary results indicate that manic BD Met/Met homozygotes scored higher on BPRS ratings of mania and uncooperativeness than did patients who were Val carriers (heterozygotes or Val homozygotes). Met homozygotes had increased PPI in one of three PPI conditions compared to Val carriers. In the BPM, Val homozygotes showed more perseverative exploratory behavior, as evidenced by more localized, restricted movements during the latter part of the BPM session, than Met carriers (Spearman's rho = .81, P = .02). These initial findings suggest that, in BD, the Met allele

may be associated with greater liability for symptoms of overactivation and agitation and may be protective against the sensorimotor gating deficits that are typically seen in this population. The Val allele, as in SCZ, may confer liability for cognitive inflexibility, perhaps because it contributes to low dopaminergic tone in frontal systems. The identification of genotypic and phenotypic features that are shared by BD and SCZ versus features that are unique to each illness has implications for the development of novel therapeutics for these conditions, and will also contribute to the burgeoning understanding of the overlapping and distinguishing genotype-phenotype relationships in psychopathology. Supported by a NARSAD Young Investigator Award and R01-MH071916.
ID: 546158

ARE INTELLIGENCE AND MEMORY GOOD ENDOPHENOTYPES FOR SCHIZOPHRENIA? GENETIC MODELS IN A HARVARD, IOP, AND NIH COLLABORATION

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Context: Impairments in verbal and visual memory, verbal learning and intelligence are among the most promising indicators of increased risk for schizophrenia making them candidate endophenotypes; however it is not clear to what extent these deficits are genetically linked to the disorder. Objective: To quantify the net genetic relationship between episodic memory, learning, intelligence and schizophrenia in a large multi-site data. Design: Family and twin study. Setting: US and UK Research Institutes. Participants: Data from 2057 individuals were pooled across three sites: 1) Harvard University,USA (2) Institute of Psychiatry,UK and (3) National Institute of Health,USA. Of these individuals 657 were patients, 674 1st degree relatives and 726 were controls. Main outcome measures:The heritabilities of memory, learning and intelligence were estimated and the genetic relationship between each one of these and schizophrenia quantified. Results: Genetic influences contributed to all cognitive domains with intelligence showing the highest heritability ($h2 = 0.69$) and immediate recall of verbal memory the least ($h2 = 0.30$). Significant genetic correlations were found between schizophrenia and 1) immediate (I)/delayed (D) verbal recall (I: -0.96; D: -0.94); 2) I/D verbal learning (I: -0.47; D: -0.30) and 3) I/D visual recall (I: -0.62; D: -0.68) suggesting that schizophrenia and these measures share to some extent the same genes. When the heritabilities of these measures were taken into account, intelligence showed the biggest phenotypic correlation with schizophrenia ($-.49$) with shared genetic influences explaining chiefly the phenotypic co-variance. Conclusion: Unlike molecular genetic approaches which estimate the extent to which allelic variation explains endophenotypic variance, genetic modeling quantifies the net shared genetic influences between the candidate endophenotype and the illness, giving a broader view of the degree of genetic overlap between the two. Supporting our previous work in twins (Toulopoulou et al. 2007) intelligence appears to be the best endophenotype for schizophrenia sharing the greatest genetic variance with the illness. Genome wide searches using a bivariate phenotype such as schizophrenia and intelligence should assist in the search to find quantitative trait loci for schizophrenia.
ID: 546054

Reference

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GENETIC ASSOCIATIONS BETWEEN NEUREGULIN-1 AND COGNITION IN A - MULTIPLEX SCHIZOPHRENIA FAMILY STUDY

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Recent work shows a potentially promising relationship between schizophrenia and variation in the gene Neuregulin-1 (NRG1). A large literature has also found strong familial relationships between schizophrenia and cognitive deficits. Given the role of NRG1 in glutamate regulation, we hypothesize that cognitive deficits may be related to sequence variation within NRG1, thus providing a possible mechanism by which NRG1 could act as a susceptibility gene for schizophrenia. This question was examined using a multigenerational multiplex family sample (419 individuals from 40 families), including 58 affected participants (schizophrenia or schizoaffective disorder, depressed type) and their 361 unaffected and 35 affected relatives. Participants were genotyped using the SNPlex procedure for 38 NRG1 single nucleotide polymorphisms (SNPs) that had previously been reported to be associated with schizophrenia. In addition to diagnostic interviews, participants were administered a previously validated computerized neurocognitive battery that assessed eight cognitive domains, including: abstraction/mental flexibility, attention, verbal/facial/spatial memory, spatial and emotional processing, and sensorimotor dexterity. Pedigree-based variance component quantitative trait analyses using the SOLAR computer program were performed to test for genetic associations between individual NRG1 SNPs and cognitive performance. In the full sample of affected and unaffected individuals, each cognitive domain had at least one significant SNP association, except spatial memory. The average number of significant associations within domains was 5.875. These associations were spread throughout the gene, including intronic and exonic areas, as well as upstream and downstream regions. Of the SNPs with at least one significant association, the range of associations was between one and four. No individual SNP was significant across all domains. When adjusted for multiple comparisons by a very conservative Bonferroni correction ($P < .00016$), two associations remained significant. These findings lend support for several previously reported associations between NRG1 SNPs and schizophrenia and suggest that one of the mechanisms by which NRG1 may contribute to risk for schizophrenia may be via its role in general cognitive function. Future directions include multivariate analyses of cognitive variables and SNPs.
ID: 550835

PSYCHOTIC-LIKE SYMPTOMS IN CHILDREN WITH 22Q11 DELETION SYNDROME

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22q11.2 Deletion Syndrome (22qDS) is associated with a high prevelance of Attention Deficit Hyperactivity Disorder (~40%) and anxiety disorders

(~25%) in childhood and schizophrenia in adulthood (~25%). Previous studies have reported the presence of psychosis or psychotic-like symptoms in some children with 22qDS, but the rates varied. Some clinicians have successfully managed the psychotic-like symptoms with anti-anxiety agents. We systematically assessed 36 Canadian children with 22qDS, and 13 of their unaffected siblings, between the ages of 8 and 12 for presence of psychosis and recurrent psychotic-like symptoms (illusions, paranoia or other overvalued ideas, usual thought form). We found 5 of the 36 (13.9%) 22qDS children had psychotic-like symptoms. This rate however was not significantly different from the 15.4% rate in their siblings. Within the 22qDS group, those with psychotic-like symptoms did not differ in mean IQ, rates of ADHD, or anxiety disorders. However, they are more likely to be reported as "would rather be alone" and be "fearful" on the Childhood Behavioural Checklist than 22qDS subjects without psychotic-like symptoms. Results do not support an increased rate of psychotic-like symptoms in children with 22qDS when compared to their siblings, but those children with psychotic-like symptoms have other symptoms that may be consistent with prodromal symptoms of schizophrenia.

ID: 551886

PHARMACOGENETIC OPPORTUNITIES AND CHALLENGES TO ADDRESS ANTIPSYCHOTIC SIDE EFFECTS

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The variability in the response to antipsychotic agents is a serious challenge in the treatment of patients affected by schizophrenia. Patient response remains unpredictable and the discontinuation rate is high. Antipsychotics are associated, at different degrees, with a risk of various side effects that include movement disorders such as akathisia and EPS, metabolic disorders such as weight gain, dyslipidemia, prolactin elevation, and QT prolongation. These adverse events present specific challenges but also opportunities for pharmacogenetic studies. For each unwanted effect, treatment response is a complex phenomenon resulting from a multitude of elements that may include the severity of the disease, the individual's age, sex, race, concomitant illnesses and therapies, and most likely various genetic factors. It is important to note that these genetic factors may individually contribute to only a small portion of the observed variability in inter-individual response, which makes not only their discovery, but also their clinical application challenging. Furthermore, while certain polymorphisms may play a similar role in the response of various antipsychotics, we must also recognize that differences between drugs in receptor binding profiles, chemical and metabolic characteristics may also lead to the discovery of genetic factors unique to each drug. The field of Pharmacogenetics has rapidly evolved since the completion of the Human Genome Project and is now providing opportunities to identify patients with the greatest chance of benefiting from a particular treatment while minimizing the risk of unwanted side effects. Candidate gene analysis and, most recently, whole genome association studies have been applied to identify DNA variants that affect drug response, and have already identified a number of promising markers. The acceptance of predictive genetic markers in clinical practice will necessitate the validation of their clinical value, as well as the practical utilization of the comprehensive information they provide. Currently, there is no standard approach to determine the effect of multiple genetic markers in the response of a drug treatment. As a result, it has become crucial to develop methods to combine the information gathered from all relevant biomarkers. This will provide a clear interpretation and therefore an easier implementation in clinical practice of the genetic information which may otherwise be viewed as too complex or unpractical.

ID: 551871

TEMPERAMENT AS A DISCRIMINATING MARKER OF GENETIC LIABILITY FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Socio-emotional deficits are among the most debilitating features of both schizophrenia (SCZ) and bipolar disorder (BD). It is well known that both disorders are highly heritable and a growing body of molecular genetics research suggests there may be some overlap in genetic liability for them (Ivleva et al. 2008). However, few investigations into whether socio-emotional processing deficits may confer genetic liability for these disorders, as well as the nature of the phenotypic overlap between them, have been conducted to date. To address this, we examined similarities in temperament between SCZ and BD probands, their discordant co-twins, and healthy control twin pairs. Research indicates that temperament is largely heritable, with individuals differences present very early in life and remaining relatively stable over time (eg, Goldsmith et al. 1997). Our aim was to examine whether certain inherited temperaments confer increased risk for development of these disorders. We also sought to develop a statistical model which identifies which specific temperament dimensions discriminate between patient groups and which (if any) are common to both. Through factor analysis we identified two temperament factors by which to compare the groups: schizotypy/dysthymia (Factor 1) and cyclothymia/impulsivity (Factor 2). We hypothesized that individuals with SCZ would score high on Factor 1 and that scores of their non-affected co-twins and healthy controls would decrease in step-wise fashion as genetic liability for the disorder decreased between those groups. We predicted the same pattern of results for BD on Factor 2. Consistent with our predictions, individuals with SCZ scored significantly higher than healthy controls on Factor 1 ($P < .05$) and the scores of their co-twins fell in-between scores of those two groups. On Factor 2 a similar trend in the data was seen (BD > controls; $P < .01$, unaffected co-twins in-between). Unlike Factor 1, scores on Factor 2 were significantly higher for both patient groups compared to healthy controls. Taken together, these findings indicate that a schizotypal, depressive temperament is associated with increased genetic liability for SCZ, and that such a temperament tends to discriminate between SCZ and BD. On the other hand, a cyclothymic, impulsive temperament is associated with increased genetic liability for BD, and this temperament may constitute an example of phenotypic overlap between the two disorders.

ID: 551861

A CANNABINOID-1 (CB-1) RECEPTOR GENE VARIANT IS ASSOCIATED WITH CLOZAPINE AND OLANZAPINE INDUCED WEIGHT GAIN IN SCHIZOPHRENIA

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Introduction: Clozapine and olanzapine have been associated with substantial weight gain in many patients. However, an individual's propensity to develop weight gain largely depends on genetic factors. A possible mechanism may involve the endocannabinoid system which has been implicated in the regulation of appetite signalling and food intake through the dorsal vagal complex (DVC) of the brainstem. Animal models have shown that olanzapine significantly decreased cannabinoid receptor binding in the DVC (Weston-Green et al. 2008). Furthermore, the cannabinoid-1 (CB-1) receptor antagonist rimonabant has been shown to induce weight loss. The purpose of this study has been to analyze whether variants (SNPs) of the CB-1 receptor gene potentially modulating the endocannabinoid system were associated with antipsychotic induced weight gain. Methods: We have been genotyping several SNPs in a larger sample of antipsychotic induced weight gain using three different samples from the US (A, B and C; total $n = 139$) and one sample from Germany (D; $n = 70$; total $n = 209$), mainly treated with clozapine and olanzapine on average for 11 weeks. Mean weight gain was compared across the genotypic categories using ANOVA as well as ANCOVA including baseline weight or sex as covariate. Results: Mean weight gain in the sample was + 4.01 kg ($\pm$ 4.77 kg). In the sample of Europeans ($n = 123$), carriers of the C/C genotype of the promoter region SNP rs806378 gained only +2.3 kg as compared to C/T and T/T carriers who gained on average 4.2 kg. This association was significant when corrected for baseline weight ($P = .049$). We then excluded those patients who received medications other than clozapine or olanzapine and found a more significant association ($F_{2,72} = 4.48$, $P = .01$ where homozygotes for T/T gained 6.25 kg as compared to 1.93 kg in homozygotes for C/C carriers. The most significant finding was then obtained when examining only patients treated with clozapine $F_{2,61} = 7.49$, $P = .001$. Results remained unaltered when including covariates such as baseline weight or sex. Summary: In conclusion, our studies suggest that a promoter variant of the CB-1 receptor gene is associated with clozapine and olanzapine induced weight gain. We are currently expanding our analyses with including a total of 10 tag SNPs spanning the entire CB-1 gene. These findings may have important implications for discovery of novel antipsychotic drug targets that do not result in weight gain side effects.
ID: 551853

FAMILIAL AND CAS-CONSTROL ASSOCIATION STUDIES OF POSITIONAL CANDIDATE GENES AT 6P23-P22 FOLLOWING FURTHER LINKAGE EVIDENCE FROM EASTERN QUÉBEC POINTS TO MYLIP

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Objectives: To test for linkage to schizophrenia (SZ) in the 6p23-p22 region while taking into account heterogeneity with the 13q13-q14 locus, and to follow-up with an association study of single nucleotide polymorphisms (SNPs) across the region. Methods: A sample of 31 extended pedigrees informative for SZ and a sample of 247 unrelated SZ cases and 207 controls, all from the Eastern Quebec population. Parametric two-point linkage analysis of microsatellite markers was performed on the kindred sample, using an ordered subset analysis to take into account heterogeneity with our former linkage finding at 13q13-q14. Pearson χ^2 tests of allelic and genotypic association and score tests of haplotypic association were performed on 279 SNPs from an expanded Illumina HumanHap 300 SNP array and 10 candidate SNPs in the case-control sample. A subset of these SNPs were typed in the family sample and analyzed with family-based association tests (FBATs). Results: A maximum lod score of 4.03 was obtained with marker SCA1 in a sub-sample of 16 families showing no linkage with to 13q13-q14. The strongest association signals in the case-control sample were observed for SNPs rs2876407 and rs2142672 near the MYLIP gene with false discovery rate (FDR) of 0.17. Consistent association of SZ to the A/A genotype of rs9370867, a Ser342Asn amino-acid change in the MYLIP protein, was observed in the case-control sample ($P = .02$, FDR = 0.29) and to a lesser extent in the 16-kindred sub-sample ($P = .10$). Association to a 5-SNP haplotype in DTNBP1 was also observed in the full kindred sample (FDR = 0.03). Conclusions: In our kindred sample, evidence of linkage to 6p23-p22 is stronger in kindreds not linked to 13q13-q14 suggesting genetic heterogeneity. Association to DTNBP1 may not fully explain the linkage signal, and another gene is likely involved. Our association results do not conclusively identify that possible other gene, but consistency of association between the case-control and family samples points to MYLIP, evidence from the latter sample stemming principally from families yielding linkage at 6p.
ID: 551852

ZNF804A, THE TOP HIT IN THE LARGEST GWAS TO DATE, INFLUENCES PERFORMANCE IQ IN SCHIZOPHRENIA CASES AND HEALTHY CONTROLS

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The ZNF804A locus (rs1344706) exhibited the strongest evidence for association in the largest Genome Wide Association study to date (O'Donovan et al. Molecular Genetics of Schizophrenia Collaboration, 2008). The encoded protein of ZNF804A is unknown and has no known function. This study sets out to examine the influence of the ZNF804A SNP, the top hit in the GWAS, on IQ tests in schizophrenia cases and healthy controls. 251 schizophrenia cases and 1473 healthy controls were assessed using the 11 subtests of the WAIS-R and verbal, performance and full scale IQ scores calculated. The top hit SNP of ZNF804A from the GWAS (rs1344706) was used to determine genotype groups (T = risk allele). MANOVA using genotype and case/control status as fixed factors was used to analyse the IQ results. Bonferonni correction was employed to adjust for the use of the multiple IQ measures. MANOVA indicated an effect of genotype on tests of digit symbol coding ($F = 6.18$, $P = .002$ (adjusted $P = .028$)), performance IQ ($F = 6.31$, $P = .0018$(adjusted $P = .025$)) and full scale IQ ($F = 5.95$, $P = .003$(adjusted $P = .042$)). Post hoc analysis showed homozygous carriers of the T risk allele at rs1344706 performed significantly better than homozygous carriers of the G allele on all 3 of these tests. In separate case and control analysis the results hold for digit symbol coding in cases ($F = 3.12$, $P = .04$) and controls ($F = 3.63$, $P = .03$) and for performance IQ in cases ($F = 3.73$, $P = .025$) and controls ($F = 4.0$, $P = .018$) all in the same direction of effect. The risk allele at the ZNF804A locus seems to be protective for cognitive deficits in performance IQ measures in cases and controls. In the original GWAS the ZNF804A signal was strengthened by inclusion of cases with bipolar disorder. Taken with the results of this study this could indicate that this gene confers risk to a form of psychosis which spares cognitive function.
ID: 551802

NIACIN RECEPTOR VARIANTS INFLUENCE NIACIN SKIN SENSITIVITY

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Introduction: Attenuated flush response to local methylnicotinate (AMN, niacin) skin stimulation represents one of the most commonly replicated peripheral biological parameters in schizophrenia. Skin response is mediated by a pathway involving G protein-coupled nicotinic acid receptors (GPR109A and GPR109B) at epidermal Langerhans cells, Ca2±dependent expression of prostaglandin synthetases, and formation of vasodilatory prostaglandins acting on skin arterioles. The "precursor deficiency hypothesis" posits that deficient flush response in schizophrenia relates to an innate depletion of polyunsaturated fatty acids and disturbed prostaglandin signalling. AMN challenge may thus serve as a surrogate marker of phospholipid repair and remodelling processes, anti-oxidative defense and inflammatory response. The present investigation addresses polymorphisms of GPR109A and GPR109B niacin receptor genes and their impact on skin phenotype to assess functionally relevant DNA variants as contributing co-variate. Method: AMN (0.1M, 0.01M, 0.001M) was applied to the skin of the volar forearm in 31 neuroleptic-naïve first-episode schizophrenia patients (SCH) and 31 healthy controls matched for age and gender. Skin colour response was recorded at three min intervals over 15 min using optical reflection spectroscopy. Buccal swabs were obtained for amplification of genes encoding the high-affinity GPR109A and the low-affinity GPR109B niacin receptor by a PCR-based assay. Results: 20 SNPs were identified in 2 kb of genomic sequence. Two rare missense variants of GPR109B (T173P and F198L) were detected for the first time in SCH. Exonic SNPs modulated niacin sensitivity with attenuated skin response in homocygotic carriers of rare alleles. Conclusion: These results suggest a contributory role of GPR109 gene variants to in niacin sensitivity, and call for further investigation of these markers' role in schizophrenia.
ID: 551784

MICROARRAY GENE EXPRESSION ANALYSES IN THE HIPPOCAMPUS AND PREFRONTAL CORTEX OF PATIENTS WITH SCHIZOPHRENIA

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Schizophrenia is a complex genetic disorder and may involve many genes. Most microarray studies have examined changes in gene expression in postmortem brain samples by comparing matched pairs of patients with schizophrenia and controls. We applied a different approach. We compared approximately 27 000 genes and ESTs in postmortem brain samples from specific brain regions (hippocampus and prefrontal cortex) in control subjects and patients with schizophrenia to a pooled brain sample. For each microarray experiment, fluorescence ratios of Cy5/Cy3 were derived by comparing samples (control and schizophrenic) to the common pooled brain reference. By comparing each sample to the pooled brain RNA, it was possible to compare differences in ratio measurements in gene expression profiles between control and patient brains. A roster of cDNAs that exhibited more than 2-fold expression level changes was generated. Three approaches were used to analyze the fluorescence intensity data. First, the actual lists of differentially expressed genes identified in each data set was examined, and a list of genes determined to be differentially expressed in that data set was defined. A given gene was considered to be differentially expressed if the absolute value of the log2 of its average fluorescence ratio was greater than 1.0. In the second approach, all genes in each list was ranked according to the absolute value of its fold-change measurement by comparing normal brain region to schizophrenic brain region. Finally, overlap in the lists of differentially expressed genes in the two brain regions (hippocampus and cortex) between normal and schizophrenic individuals was generated. In the hippocampus eighty seven genes/ESTs were downregulated and seventy four genes/ESTs were upregulated in subjects with schizophrenia compared to controls. In the schizophrenic prefrontal cortical region, nineteen genes/ESTs were upregulated and twenty genes/ESTs were downregulated. Six genes/ESTs were upregulated and eleven genes/ESTs were downregulated in both brain regions from patients compared to controls. Currently, studies are in progress for more detailed follow up analyses of genes of interest.
ID: 551749

RETHINKING PSYCHOSIS

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It has been conventional for psychiatric research, including the search for predisposing genes, to proceed under the assumption that schizophrenia and bipolar disorder are separate disease entities with different underlying etiologies. These represent the traditional dichotomous classification of the so-called "functional" psychoses and form the basis of modern psychiatric diagnostic practice. Recently positive findings have been emerging in molecular genetic studies of psychoses. However, the pattern of findings shows increasing evidence for an overlap in genetic susceptibility across the traditional classification categories—including association findings at DISC1 and NRG1. Genome-wide association studies (GWAS) now provide greater power to explore the relationship between mood and psychotic illness. We have undertaken molecular genetic studies in large samples of UK individuals with bipolar disorder and schizophrenia, including intensive study of individual candidate genes and, most recently, genome-wide association studies (500 000 SNPs) in 2700 mood-psychosis cases and 3000 controls. This latter study was conducted within the context of the Wellcome Trust Case Control Consortium (WTCCC), a genome-wide association study of 17 000 UK individuals for 7 common diseases. The emerging evidence suggests the existence of relatively specific relationships between genotype and psychopathology. For example, in our dataset variation at GABAA receptor genes is associated with susceptibility to a form of illness with mixed features of schizophrenia and bipolar disorder. Genome-wide significant associations at CACNA1C in bipolar disorder and ZNF804A in schizophrenia show evidence for a contribution to susceptibility across the traditional diagnostic boundaries. The elucidation of genotype-phenotype relationships is at an early stage, but current findings highlight the need to consider alternative approaches to classification and conceptualization for psychiatric research rather than continuing to rely heavily on the traditional dichotomy. As psychosis susceptibility genes are identified and characterized over the next few years, this will have a major impact on our understanding of disease pathophysiology and will lead to changes in classification and the clinical practice of psychiatry.
ID: 551721

ASSOCIATION BETWEEN A POLYMORPHISM IN THE DYSBINDIN GENE AND BRAIN VOLUME MEASURES IN SCHIZOPHRENIA

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Polymorhisms in the dysbindin gene (DTNBP1) have been associated with cognition and symptoms of schizophrenia, however, little is known regarding the contribution of these variants to brain morphology. In this study, the single nucleotide polymorphism (SNP) rs1018381 (C/T) in DTNBP1 was genotyped in a sample of 241 individuals with schizophrenia spectrum disorders and 100 healthy controls with available brain MRI data. The T allele of this intronic SNP has evidence for association with schizophrenia and is also contained within a schizophrenia-associated haplotype, although no significant differences in genotype or allele frequencies at rs1018381 were observed in this sample. Cortical brain gray and white matter MRI volumes (total, frontal, temporal, parietal, and occipital) were measured using automated methods. Analysis of covariance was used to test the hypothesis that variation of this SNP is associated with differences in cortical brain volumes, with volume measurement as the independent variable and genotype as the dependent variable. Covariates included gender, age, total intracranial volume, and diagnostic category. An additional MRI scan protocol covariate was included in the analyses as two different image acquisition protocols were used during the time that MRI scans were obtained. Genotype and allele frequencies were not significantly different between patient and healthy control groups. A significant genotype by diagnosis effect was observed for frontal gray matter ($F = 3.94$, $P < .05$). In healthy controls, T allele carriers had larger frontal gray matter volumes compared to CC homozygotes, however, the opposite result was found in schizophrenia patients: carriers of the T allele had smaller frontal gray matter volumes than CC homozygotes. A similar trend was observed for total cortical gray matter ($F = 3.46$, $P = .06$) as well as in temporal and parietal gray matter measures. No significant effects were observed for white matter volumes. These results are consistent with the involvement of a variant in dysbindin contributing to differences in cortical brain volumes in schizophrenia. Smaller frontal gray matter volumes in T allele carriers at rs1018381 may indicate that this variant is not only associated with increased schizophrenia risk, but also has a negative impact on a brain region involved in the pathophysiology of the disorder.
ID: 551715

NEUROCOGNITIVE IMPAIRMENTS ARE EVIDENT AT AGE EIGHTEEN IN YOUTHS AT GENETIC RISK FOR SCHIZOPHRENIA

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Accumulating evidence suggests that neurodevelopmental abnormalities preceding clinical manifestation of illness are present in youths at-risk for developing psychosis. Neurocognitive abilities, especially executive, attention and memory dysfunction, are implicated as candidate endophenotypes of schizophrenia, including through evidence of impairment in adult relatives. Impaired endophenotype performance in youths deemed at-risk for schizophrenia bears directly on the endophenotype's ability to serve as a marker for early identification and treatment, but the developmental profile of impairments is unclear. As one method of addressing this question, we evaluated neurocognitive performance across the age span of 18–30 in a large sample of young relatives of schizophrenia patients. Youths ($n = 1082$, age 18–30) completed a comprehensive diagnostic assessment and the University of Pennsylvania Computerized Neurocognitive Battery (CNB) in the context of NIMH funded multi-site genetics collaborations (MGI, PAARTNERS, COGS) and local studies. Groups included Genetic Risk (GR; first-degree relative with schizophrenia, $n = 309$); schizophrenia (SCZ; $n = 371$); and community comparison subjects (CCS; $n = 402$); mean age, all groups = 24 yrs. Each group was subdivided into 4 age groups: 18–21, 22–24, 25–27, 28–30 yrs (n range for each subgroup within group = 70–122). Collapsed across age groups, SCZ and GR showed significant (all P's < 0.05) impairments in accuracy of abstraction/flexibility, attention, memory (verbal, face, spatial, working), language, spatial ability, and emotion processing. Fewer differences between GR and CCS were observed in response speed. Especially for accuracy, 18–21 yr olds exhibited the most prominent differences between GR and CCS. However, GR across age groups did not differ from each other except in sensorimotor speed, where 28–30 yr olds were slower than younger groups. The results suggest that candidate neurocognitive endophenotypes reported in adult relatives are also observable in GR adolescents by age 18–21, and are not substantially different from those observed in young GR adults aged 22–30. Thus, they may reflect pathophysiological abnormalities involved in schizophrenia development, and may ultimately facilitate early identification of at-risk youths. As our local longitudinal program grows, we will investigate neurocognition in younger at-risk participants, heritability in at-risk groups, and prediction of conversion to psychosis.
ID: 551709

THE PREVALENCE OF RISK FACTORS FOR SCHIZOPHRENIA: IMPLICATIONS FOR STUDY DESIGN AND PREVENTION

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Many risk factors have been postulated to be contributors (not necessarily causes) to the development of schizophrenia including genes, birth and pregnancy complications, season of birth, low SES, inflammatory process, immigrant status, anoxia, parental age, and head injury to name a few. Starting with estimates of the base rate of schizophrenia in the general population, mathematical methods are used to develop estimates of the population frequency of etiological agents (genetic and environmental) as a function of estimates of the number of factors implicated for any one case. The results indicate that population base rate for each risk factor is likely to be as high as 30%– 60%. Assuming that contributing factors are several to many for any one case, and that the contributing factors are common in the general population, supports the concept of etiologic heterogeneity among cases—different cases will be the product of different combinations of common risk factors. The high rates of contributing factors in the general population will hinder research designs comparing 'sick' vs. 'well' since many 'well' will also have been exposed to the risk factor under investigation. Similarly, the high rate of risk factors in the general population will guarantee that these risk factors will be found in non-schizophrenic psychopathologies in a manner that could be causal or co-incidental. Sample sizes required to generate adequate power to test group differences (null hypothesis designs) will need to be in the range of thousands; odds ratios in the range of tens to hundreds. Alternate research strategies that can mitigate these problems, including various forms of family designs that capitalize on the observed nearly three fold differences in risk for schizophrenia observed among various classes of first degree relatives of people with schizophrenia. There is much potential in shifting emphasis from strategies focused on many and varied and non-specific causal agents (ie, identifying risk factors) to strategies exploring plausible final common pathways that lead to clinical syndromes. Treatment and prevention at the level of risk factors face many roadblocks since many of the risk factors may not be readily modifiable—we cannot change the season in which a person is born and cannot undo a prenatal infection. However, we may be able to

intervene 'downstream' from such events if we understand the final common pathways through which we these events operate.
ID: 551707

A COMMON NEUROCOGNITIVE ENDOPHENO-TYPE FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Although genetic influences on schizophrenia and bipolar disorder are well established, localization of the genes responsible for these illnesses has proven difficult. Given evidence that genes predisposing to psychotic illnesses may be transmitted without expression of the clinical phenotype, efforts have focused on developing endophenotypes. While several neuropsychological measures have been proposed to be endophenotypes for either schizophrenia or bipolar disorder, few studies have systematically assessed neurocognitive tests to determine which tests are sensitive to these illnesses. Here, we will discuss two of our recent studies designed to adjudicate neurocognitive endophenotypes for schizophrenia and bipolar disorder, respectively. For the schizophrenia study, 269 Latino individuals were administered a standard neuropsychological battery. 214 of these were members of families with at least two siblings diagnosed with schizophrenia or schizoaffective disorder. The bipolar study utilized a comparable design and included 708 Latino individuals from pedigrees with a sibling pair diagnosed with bipolar I disorder or schizoaffective disorder. Although five measures were found to uniquely model genetic liability for schizophrenia, digit symbol coding and spatial working memory were the most sensitive. To assess the specificity of these endophenotypes, performance on these measures were compared to family members with bipolar and unipolar affective disorders. These markers clearly distinguished between individuals with psychotic illnesses and those with major depression. A group of partially overlapping neurocognitive tests was found to be sensitive to genetic liability for bipolar disorder in the independent bipolar sample, including the digit symbol coding task and measures of declarative memory. Using two samples of extended pedigrees, one selected for schizophrenia and the other for bipolar disorder, we find that neurocognitive tests are sensitive to genetic risk for these illnesses. Furthermore, some of these neuropsychological tests appear to be markers for both schizophrenia and bipolar disorder, while others are somewhat more specific for one illness or the other. Together these data suggest that both common and unique biological mechanisms are involved in schizophrenia and bipolar disorder.
ID: 551672

miRNA EXPRESSION AND FUNCTION IN THE BRAIN

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In recent years small (about 18–22 nucleotide) RNA molecules have become recognized as important regulators of gene expression. The importance of microRNAs in brain development and function is indicated by their high level of brain expression and by their marked regional and developmental expression patterns. microRNAs are now implicated in the regulation of neurodevelopment, synaptogenesis, and synaptic function, as well as in stem cell proliferation and differentiation, immunologic function, latent viral infection, cell cycle control, and other gene regulation systems. In point of fact, microRNAs seem to be fine-tuning controls for the general management of protein production. The purpose of this presentation will be to discuss the unifying concepts and pathways discovered by microRNA researchers. This presentation will include an overview of microRNA function. Special emphasis will be afforded to microRNA mechanisms in neurogenesis and neural differentiation, synaptic plasticity, and the potential role of microRNA gene regulation systems implicated in schizophrenia.
ID: 551658

AN ASSOCIATION BETWEEN BDNF GENE POLYMORPHISM (VAL66MET) AND COGNITIVE IMPAIRMENTS IN SUBJECTS DIAGNOSED WITH SCHIZOPHRENIA, AND BIPOLAR I WITH PSYCHOTIC FEATURES

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Background: BDNF (Brain-Derived Neurotrophic Factor) plays an important role in plasticity in the CNS. There is evidence that BDNF can induce the transformation of early to late-phase LTP (long-term potentiation), and inhibition of BDNF signaling impairs LTM (long-term memory). Recent findings suggest that BDNF single nucleotide polymorphism is involved in pathogenesis of different psychiatric diseases including schizophrenia. Recently, a single nucleotide polymorphism in BDNF gene (Val66Met), has been associated with memory impairment, and susceptibility to psychiatric diseases. Hypothesis and specific aim: This preliminary study will test the associations between Val66Met genotype and neuropsychiatric measures of information processing in subjects diagnosed with psychotic illnesses (BP I with psychosis, SZ, and schizoaffective D/O). We hypothesize that the Met allele will be associated with worse performance in measures of working memory and executive functioning; PPI, eye tracking. Methods: Study Description: Subjects were enrolled in an ongoing phenotyping study at the UTSW Department of Psychiatry's Division of Translational Research. Subjects: All subjects have a SCID DSM-IV-TR diagnosis of SZ, BP me with psychosis, or Schizoaffective D /O. Genotyping: All subjects included in study will be genotyped for the Val66Met BDNF polymorphism (rs) Measures of Working Memory: Digital Symbol Coding, Letter-Number-Sequencing, Spatial Span, Measures of Executive, Functioning: Wisconsin Card Sorting Test, Trails B Trail Making Test, Measures of Neuropsychiatric Functioning: PPI Eye Tracking, Statistical Analyses: We will test for associations between BDNF genotype (Val/Val, Val/Met, Met/Met) and both clinical and biologic measures of cognitive functioning. One-way ANOVA will be utilized if the assumptions for parametric analyses are met and Kruskal-Wallis test if not. All tests of associations will be conducted collectively among all subjects as well as BP I and schizophrenic separately in order to ascertain if associations identified are particular to one group or another or if the associations are noted in both groups. Statement of significance: Although the genetic transmission of SZ and BP D/O has been hypothesized, no single gene or genes have been definitively implicated. A possible candidate gene is BDNF. Also there are some reports of connection between SZ and BP with polymorphism BDNF gene.
ID: 551655

GENOME-WIDE HIGH-DENSITY SNP ANALYSES USING SPEM ENDOPHENOTYPE SUPPORTS NRXN3 AS A CANDIDATE GENE FOR SCHIZOPHRENIA

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Neurexins are transmembrane neuronal proteins that function as cell adhesion molecules during synaptogenesis and as receptors for intracellular signaling. α-Neurexins are essential for the localization and function of Ca2+ channels and NMDA receptors. The proteins are encoded by several genes, including neurexin 3 gene (NRXN3), which is one of the largest human genes. Previous association and gene expression studies implicate sequence variation in NRXN3 in nicotine, alcohol, and opioid dependence, conditions with substantial co-occurrence in schizophrenia. Using the highly heritable smooth pursuit eye movement (SPEM) endophenotype as a between groups variable, we performed a genome wide association study in schizophrenia subjects with SPEM deficits compared to healthy controls with no SPEM deficits ($n = 45$ in each group). NRXN3 rs12050287 ($P = .05 \times 10\text{--}7$) and rs8007461 ($P = .07 \times 10\text{--}7$) were significantly associated with schizophrenia (OR = 6.96 and 5.64, respectively). First we sought to confirm both SNPs in a larger sample of 370 subjects (186 with schizophrenia) using schizophrenia as a phenotype and then, the SPEM phenotype. NRXN3 rs8007461 was significantly associated with schizophrenia ($\chi^2 = 7.99$, $P < .02$). In addition, there was a significant SNP by diagnosis interaction effect on SPEM ($P < .03$); the NRXN3 genotype significantly affected SPEM in healthy control ($P < .03$) but not in schizophrenia subjects. Analyses of NRXN3 rs12050287 were not significant in the larger sample. Additional analyses were performed in 10 neighboring SNPs and these were not significant. Furthermore, we screened microarray gene expression profiles of NRXN3 transcripts in a separate sample of 32 postmortem cortical specimens (16 schizophrenia and 16 non-schizophrenia controls) obtained from the human frontal eye fields (FEF), a region associated with SPEM deficits in schizophrenia. Schizophrenia patients had 1.25-fold lower expression of NRXN3 mRNA compared to non-schizophrenia controls ($P = .007$). Our results provide the first evidence implicating sequence variation in NRXN3 gene in the etiopathophysiology of schizophrenia and NRXN3 mRNA expression in frontal cortex of schizophrenia patients. These results suggest that NRXN3 might be a candidate gene for neuropsychiatric diseases other than substance use disorders.
ID: 551644

THE PHYSIOLOGICAL ROLE OF DOPAMINE D2 RECEPTORS UNRAVELED BY USING KNOCK-OUT MICE

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Dopamine (DA) is a major neuromodulator of the central nervous system, where it regulates very diverse physiological functions ranging from the control of locomotion to hormone synthesis and release. Consequently, dysfunctions of the dopaminergic system underlie major neurological and psychiatric human disorders, such as Parkinson's disease and schizophrenia. DA elicits its control through the binding to membrane receptors, which belong to the family of seven transmembrane domain G-protein coupled receptors. Our research focuses on dopamine D2 receptors, one of the leading actors of the dopaminergic system. Importantly, D2 receptors are the major target of antipsychotics, this feature together with the major role of D2 receptors in regulating dopamine synthesis and release, makes this receptor a strong candidate gene involved in the etiology of schizophrenia. D2 receptors in vivo have multiple roles. In fact these receptors are present presynaptically on dopaminergic, cortical and thalamic neurons as well as on interneurons. The presynaptic localization of D2 has been shown to modulate release not only of dopamine, but also of other neurotransmitter such as GABA, acetylcholine or glutamate. At the same time, D2 receptors have also major postsynaptic functions. In addition, two isoforms of dopamine D2 receptors are present in the brain, D2L and D2S, both isoforms are generated from the same gene by a mechanism of alternative splicing. Thus, addressing the function of D2 receptors in vivo is very complex. We have approached this study by generating genetically engineered mice in which the expression of the dopamine D2 receptors is either abolished or modified. The biochemical, molecular and behavioral analyses of these mice are clarifying the physiological role of these proteins in specific D2-mediated functions. In particular, we have been able to demonstrate that the two isoforms, D2L and D2S, have different functions in vivo. D2L appears to have mainly post-synaptic activities while D2S has preponderant presynaptic release-modulating functions. More recently, we have started in vivo studies to clearly identify the involvement of pre- versus post-synaptic D2 mediated effects on animal physiology.
ID: 551620

COMT AND MTHFR GENOTYPES ARE ASSOCIATED WITH NEUROCOGNITIVE ABNORMALITIES DURING REAL-WORLD COMPREHENSION IN SCHIZOPHRENIA

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Deficits in adaptive goal-directed behavior contribute to disability in schizophrenia and are linked to a heritable dysfunction in the prefrontal cortex. Execution and comprehension of behavior may be guided by common neural systems subserving real-world knowledge. In an ecologically valid, novel paradigm that assays comprehension of goal-directed behaviors, we have previously described an electrophysiological correlate of abnormal utilization of specific knowledge critical for adaptive integration of means in relation to behavioral goals in schizophrenia. The present study investigated the molecular genetic basis of this abnormality by examining how it is influenced by COMT and MTHFR genes, known to regulate prefrontal function, possibly starting during an individual's development. Event-related electrophysiological potentials (ERPs) were recorded while 16 medicated schizophrenia patients and 16 healthy controls viewed video clips presenting congruous or incongruous target objects in real-world activities. All incongruous objects lacked required properties to complete the conveyed actions, but the incongruous scenes varied in comprehensibility (eg, 'using an electric iron in place of a knife in the context of cutting bread' might be interpreted as 'warming the bread up', but, given the properties of the engaged target object, it was harder to understand the goal of a scene 'a dinner fork is used in place of an electric iron in the context of ironing pants'). This was assumed to place progressively heightened demands on the prefrontal mechanisms mediating adaptive integration of means in relation to behavioral goals. The results revealed that modulation of the P600 ERP response to target scenes (less comprehensible incongruous > more comprehensible incongruous > congruous) was larger in controls than patients. The amplitude of this effect in patients was larger for those with the Met/Met genotype, relative to other genotypes of the COMT Val108/158Met polymorphism, and the C/C genotype, relative to other genotypes of the MTHFR C677T polymorphism. We conclude that in schizophrenia, the COMT 108Val and MTHFR 677T alleles, both of which have been linked to down-regulation of dopamine signaling in the prefrontal cortex, may disrupt neurocognitive mechanisms crucial for flexible integration

of objects and actions necessary for the attainment of behavioral goals. Support: NARSAD and NIH.
ID: 551554

RARE GENE COPY NUMBER VARIATIONS ARE ASSOCIATED WITH SPECIFIC ENDOPHENOTYPES IN SCHIZOPHRENIA

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We performed genome-wide scans for copy number variations (CNVs) to assess whether rare CNVs were associated with specific schizophrenia-related endophenotypes. CNVs were assayed using ROMA at a 35kb-resolution analysis of DNA copy number. Eye-tracking dysfunction (ETD) and craniofacial dysmorphology were measured using objective, quantitative methods. ETD assessed impairment of smooth-pursuit eye movement, and craniofacial dysmorphology analysis focused on an embryologically-derived measure: the junction of the frontonasal-maxillary prominence derivatives. Because the brain and face are developmentally linked, it is plausible that psychopathology and craniofacial dysmorphology are causally linked. Both of these endophenotypes are statistically over-represented among probands with schizophrenia and their first-degree relatives — even among those relatives who were determined to be psychiatrically normal. All probands in the study ($N = 144$) met DSM-IV criteria for schizophrenia or schizoaffective disorder. It was predicted that rare CNVs would be associated with increased dysmorphology since genomic disorders often feature craniofacial anomalies. We differentiate here between "loss" CNVs (deletions), which often cause abnormalities in the heterozygous state, and "gain" CNVs (duplications), which may maintain partial or complete genetic function. Of these probands, 35 had rare CNVs: 14 of them deletions and 21 duplications. There was a marked excess of dysmorphology among probands with deletions (42.9%), three times the rate among probands with duplications (14.3%). The converse of the dysmorphology findings emerged for ETD. Eye-tracking dysfunction was over-represented among probands with no CNVs (58.7%) compared to those with rare CNVs (34.4%). This pattern is consistent with previous findings of the independence of the ETD and craniofacial dysmorphology endophenotypes among schizophrenic probands and their relatives. ROMA methods with yet higher resolution are also currently being applied, and these may reveal previously undetected associations with endophenotypes. It is important to note that the CNVs observed in this study have not yet been established as de novo or inherited, a factor that is relevant to models of transmission in schizophrenia. The results presented here provide the first evidence among neuropsychiatric disorders that biologically interpretable endophenotypes are associated with rare CNVs.
ID: 551529

COGNITIVE AND PERSONALITY STYLES IN TWINS DISCORDANT FOR BIPOLAR DISORDER

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Cognitive and personality styles have been implicated in the symptomatic and euthymic phases of bipolar I disorders, but their role as genetic or environmental influences on the disorder has not been clearly delineated. The present study employed a twin study design to examine whether specific cognitive and personality indices represent state-dependent characteristics or trait vulnerability markers of Bipolar I disorder. The study included 24 twin pairs discordant for Bipolar I disorder (16 MZ pairs, 8 DZ pairs), and 84 Healthy Controls (57 MZ, 27 DZ). The analysis was also carried out the total sample of 54 Bipolar I patients and the MZ subgroup ($n = 16$ twin pairs). The subjects were administered the following self-report measures: Rosenberg self-esteem scale, Dysfunctional Attitudes Scale-24 items, Eysenck Personality Questionnaire, BIS/BAS scale, and Positive and Negative Affect Scale. Differences in mean scores on these measures were investigated in patients, high-risk co-twins, and healthy controls across four comparison analyses, using regression analyses for clustered observations. Correlations between scores on these self-report measures and mood ratings were also tabulated. None of the cognitive and personality style measures demonstrated any viability as endophenotypes of Bipolar I disorder. Instead, the findings suggest that low self-esteem, higher levels of dysfunctional attitudes, elevated psychoticism and neuroticism levels, high BIS activity, and high negative affect may be inferred as disorder-related, environmental factors. This study has implications for clinical research purposes, suggesting that future studies can focus on identifying how combinations of cognitive and personality patterns predispose individuals to, and subsequently maintain, bipolar affective states. Psychotherapeutic interventions may thus target to modify these specific thinking styles, since they do not seem to be unchangeable or genetically inherited.
ID: 551527

KCNH2 AND DOPAMINE RELATED CORTICAL EFFICIENCY

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HERG K+ channels regulate DA neuronal excitability and HERG1a, encoded by KCNH2, are targets for antipsychotic drugs, accounting for the long QT syndrome side affect. In a meta-analysis of 5 independent samples constituting a total of 367 families, 1158 unrelated cases, and 1704 controls, we found significant and consistent association of SNPs in a 3kb region of KCNH2 with schizophrenia. Because of the potential role of this gene in regulating DA activity, we explored the relationship of risk associated SNPs on cortical physiology related to DA activity in normal subjects. Three of the positive SNPs from the meta-analysis were evaluated in fMRI paradigms related to prefrontal cortical function (the N back working memory task, $N = 176$) and to temporal lobe function (incidental neutral encoding memory task, $N = 74$). Risk associated alleles in DA related genes have previously been associated with inefficient cortical processing during these tasks. We observed significantly greater activation (FWE correction $P = .05$) of the HF within normal risk associated allele carriers of KCNH2. Normal subjects carrying risk associated alleles also demonstrated significantly increased activity in an allele load pattern within the DLPFC during the N back despite the lack of a significant difference in overall task performance (ie, inefficient cortical processing). These data suggest a consistent association between risk alleles and impairments in the efficiency of information processing within two areas of the brain implicated in the pathophysiology of schizophrenia. The pattern of inefficient processing linked to risk alleles suggests that DA related function may be the effector of these physiologic associations. We will present data related to testing interactions of KCNH2 and other DA related genes, COMT, DAARP, DRD2, and AKT1.
ID: 551507

GENETIC OVERLAP BETWEEN MEMORY AND SCHIZOPHRENIA—THE MAUDSLEY TWIN STUDY.

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Episodic memory deficits, both in the visual and verbal modalities, are a putative endophenotypes for studying the genetics of schizophrenia; however it is not clear to what extent these deficits are genetically linked to the disorder. The study aimed to quantify the genetic and environmental contributions to the variability of several memory domains and to estimate the genetic relationship between these and schizophrenia. This was a twin design using genetic model fitting. A total of 259 twins participated in this research: 18 pairs of MZ twins concordant for schizophrenia; 14 pairs of MZ twins discordant for schizophrenia; 56 pairs of MZ twins without schizophrenia; 9 pairs of DZ twins discordant for schizophrenia; and 39 pairs of DZ twin pairs without schizophrenia. Episodic memory was assessed using Wechsler Memory Scale-R. Genetic influences contributed substantially to several of the memory tasks; with logical memory-immediate recall and visual paired associates-immediate recall being the most heritable. Significant phenotypic correlations with schizophrenia were found for each of the memory measures. Genetic factors were the main source of the phenotypic correlations, for example shared genetic variance accounted for 97% of the phenotypic correlation ($r_{ph} = -0.46$; 95% CI, -0.56 to -0.34) between visual paired associates-immediate recall and schizophrenia. The strongest genetic correlation with schizophrenia was found for delayed logical memory, followed by visual paired associates and immediate logical memory. Bivariate genetic twin modeling suggests that all three are potentially valid endophenotypes for schizophrenia. Research into the neuroanatomical correlates of memory deficits may illuminate the pathophysiology of schizophrenia. The inclusion of these phenotypes in linkage or association analysis could improve the power to detect susceptibility genes for schizophrenia.

ID: 551501

ASSOCIATION BETWEEN GRM3 AND GRIN2B GENE VARIANTS AND SYMPTOMS IN TREATMENT REFRACTORY SCHIZOPHRENIA

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Purpose: Polymorphisms in the type-three metabotropic glutamate receptor gene (GRM3) and the glutamate receptor ionotropic N-methly-D-aspartate subunit-2B gene (GRIN2B) have been associated with the pathogenesis of schizophrenia as well as treatment response. The purpose of this study was to determine whether the nature of residual psychiatric symptoms in antipsychotic non-responders is related to polymorphisms in these two genes. Methods: Ninety-five subjects meeting DSM-IV criteria for schizophrenia who were treatment refractory (Kane criteria $n = 93$ or at least two previous agents $n = 2$) were enrolled in an IRB approved study where they were eventually treated with either clozapine or olanzapine. Prior to medication switch, residual symptoms were assessed using the

BPRS and SANS scales to examine global psychopathology and negative symptoms, respectively. Participants were 89% Caucasian, 64% male, and 37.9 ± 10.1 years of age. These subjects were genotyped for seven markers in GRM3 (rs274622, rs274226, rs917071, rs6465084, rs1468412, rs1989796, and rs1476455) and three markers in GRIN2B (rs7301328, rs1806201, and rs1805247). Allelic and genotype associations with symptoms was assessed using permutated ($n = 1000$) and Bonferroni adjusted P-values. Results: Genotypes for GRM3 and GRIN2B markers did not deviate from Hardy-Weinberg Equilibrium, with the exception of rs1468412 ($P = 0.023$), which has been previously associated with risk for schizophrenia. Two markers in GRM3 (rs1989796 and rs1476455) that were in moderate linkage disequilibrium (D' = 0.75), were associated with the presence of residual global symptoms as measured by the BPRS total score (Bonferroni-adjusted $P = .038$ and 0.05 respectively) with a false discovery rate of 0.064 for each. Participants with an rs1476455_CC genotype ($n = 73$) had significantly higher BPRS scores than A-carriers (55.1 ± 10.4 vs. 48.3 ± 9.2; $F = 7.6$, $P = .0071$). Additionally, participants with the rs1989796_CC genotype had significantly higher BPRS scores than T-carriers (50.1 ± 5.7 vs. 55.8 ± 10.5, $F = 7.1$, $P = .0091$). No evidence for significant associations with negative symptoms was observed with markers in either gene. Conclusions: These data suggest that polymorphisms in the GRM3 gene may be associated with refractory global psychopathology but not negative symptoms in persons with schizophrenia.

ID: 551467

GENETICALLY DETERMINED CONTRIBUTION OF D2 AND DAT SIGNALING TO HUMAN WORKING MEMORY PHYSIOLOGY

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Dopamine transmission has long been implicated in the pathophysiology of schizophrenia and of its associated working memory deficits. Dopamine signaling involves several proteins, including D2 receptors (encoded by the DRD2 gene) and dopamine transporters (DAT) which are critically implicated in prefronto-striatal physiology. In these brain regions, dopamine modulation of neuronal activity during memory tasks identifies a non-linear inverted-U shaped function. Moreover, in vitro studies have demonstrated that DAT and D2 proteins reciprocally regulate each other presynaptically. In recent studies we have identified novel functional variants of DRD2 which modify the distribution of D2 receptor isoforms in the synaptic environment affecting the physiology of working memory performance and of its related prefronto-striatal activity in healthy subjects and in patients with schizophrenia. Therefore, we have evaluated the genetic interaction between a DRD2 polymorphism (rs1076560) causing reduced presynaptic D2 receptor expression and the DAT 3'-VNTR variant (affecting DAT expression) in a large sample of healthy subjects undergoing BOLD—fMRI during memory tasks and structural MRI. Results indicated a significant DRD2/DAT interaction in prefrontal cortex and striatum BOLD activity during both working memory and encoding of recognition memory. The differential effect on BOLD activity of the DAT variant was mostly manifest in the context of the DRD2 allele associated with lower presynaptic expression. Similar results were also evident for gray matter content in caudate. These interactions describe a non-linear relationship between compound genotypes and brain activity or gray matter content. Complementary data from striatal protein extracts from wild-type and D2 knock-out animals (D2R-/-) indicate that DAT and D2 proteins physically interact in vivo. Taken together,

our results demonstrate that the interaction between genetic variants in DRD2 and DAT critically modulates the non-linear relationship between dopamine and neuronal activity during memory processing. These results may have implications for modulation of prefronto-striatal pathways during working memory in schizophrenia.
ID: 551465

PREMATURE DEATH IN ADULTS WITH 22Q11.2 DELETION SYNDROME AND SCHIZOPHRENIA

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Background: 22q11.2 Deletion Syndrome (22q11.2DS) is a common but under-recognized microdeletion syndrome with multisystem expression including schizophrenia in one of four adults. About 1 in 100 patients with schizophrenia have 22q11.2DS. Little is known about longevity in adults with the syndrome. Methods: We prospectively followed 264 subjects: 102 adults (> 17 years) with 22q11.2DS (44 M, 58 F; mean age 33.6 SD 10.9 years) and their 162 unaffected siblings (77 M, 85 F; mean age 36.1, SD 12.2 years). 46 subjects with 22q11.2DS and 2 siblings had schizophrenia. We compared survival between groups using Kaplan-Meier estimates. Findings: Twelve (11.8%; 4 M, 8 F) individuals with 22q11.2DS died at median age 41.5 (range 18.1–68.6) years. No siblings died ($P < .0001$). Seven of the deaths were in patients with schizophrenia (median age 44.8, range18.1–56.2 y); only one, a suicide (age 38.2 y), could be attributed directly to the psychiatric disease. Only 50% of patients had autopsies. Six (50%) deaths were sudden and unexpected, in patients with schizophrenia ($n = 3$), major CHD ($n = 2$), and neither of these diseases ($n = 1$). There was no evidence of coronary artery disease or cancer, or family history of sudden death, in any of the 12 patients who died. Survival to ages 40 and 50 years was 89.9% and 73.9%, respectively. Survival curves showed non-significant findings when stratified by sex ($P = .48$), major CHD ($P = .25$) or schizophrenia ($P = .60$). Interpretation: Adults with 22q11.2DS have diminished life expectancy and increased risk of sudden death. Further studies, including detailed post mortem examinations, are needed into pathophysiological mechanisms that may help identify preventive strategies. Some of the premature natural deaths in schizophrenia may represent undiagnosed individuals with 22q11.2DS.
ID: 551460

HIGH FREQUENCY OF RARE GENOMIC VARIANTS IN SCHIZOPHRENIA

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Copy number variation (CNV) is a major source of genetic diversity among individuals and is an important risk factor in susceptibility to disease. Recent work has shown that a substantial proportion of sporadic autism is associated with rare de novo (ie, spontaneously occurring) CNVs. Work by our group and others have also found that rare CNVs are significantly enriched among patients with schizophrenia. Here we examine the association between rare CNVs and schizophrenia. We used a 2 100 000-probe microarray platform to analyze DNA from 150 Caucasian patients who met criteria for a DSM-IV diagnosis of schizophrenia, 90 of their first-degree biological relatives and 300 controls. Important findings include the identification of de novo and inherited rare variants, including many that affect the integrity of genes. Interestingly, several of the CNVs identified overlap with mutations previously implicated in autism. Some of the individual genes contained within these CNVs are involved in aspects of CNS development, including synaptic plasticity, neuronal differentiation, and signal transduction.
ID: 551458

GENETIC LINKAGE FOR SCHIZOPHRENIA AND BIPOLAR DISORDER CONFIRMS SHARED AND SPECIFIC SUSCEPTIBILITY LOCI: THE IMPLICATIONS FOR REDEFINING PHENOTYPES

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We have previously published a genome scan (Maziade et al. 2005) on 21 kindreds (Sample 1) for schizophrenia (SZ), bipolar disorder (BP) and a Common Locus phenotype (CL) which encompasses both SZ and BP. We performed a nonparametric linkage analysis of a second sample of 27 kindreds (Sample 2) from the same population in the regions where Sample 1 had given genome-wide suggestive or significant signals. In addition to the analysis in Sample 2, we assessed the overall linkage evidence in the total sample of the 48 kindreds combining Samples 1 and 2. We have recently reported replication results (Merette et al. 2008) in 16p13.11–p12.3 with a NPL_{all} score of 3.70 obtained in Sample 2 at marker D16S3060, 3.2 Mb proximal to our initial BP finding in Sample 1. The combined sample yielded a NPL_{all} score of 3.90, maximized for a subphenotype restricting BP to those with psychotic symptoms. We now report strong replication results in 13q14.11 for the CL phenotype. Sample 2 yielded a NPL_{pair} score of 3.36 at D13S1272 (44.0 Mb), just 2.1 Mb telomeric to D13S1247 (41.9 Mb) where the initial finding had been obtained. The analysis of the combined sample enhanced the evidence with a NPL_{pair} score reaching 5.21 at D13S1297 (42.1 Mb), suggesting a strong concordance in phenotype definition and linkage peak across samples. Thus our study raises the relevance for redefining phenotypes given the possibility of two types of genes for major psychoses: one that confers a general susceptibility shared by SZ and BP, while the other a specific susceptibility to a subphenotype within BP. This research was supported by a Canada Research Chair (#950-200810), the Canadian Institute on Health Research (CIHR; #MOP-57919) and the Fonds de la recherche en santé du Québec (FRSQ).

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ID: 551365

SCHIZOTYPAL DEFICITS AND GENETIC LIABILITY TO SCHIZOPHRENIA: A MULTIPLEX FAMILY STUDY

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The development of quantitative scales that maximize sensitivity of schizotypal deficits to genetic liability to schizophrenia is a crucial step in utilizing schizotypal features in bivariate genetic linkage analyses to identify schizophrenia risk genes. The 671 participants in this study included 43 European-American, multigenerational multiplex pedigrees with 103 affected individuals (schizophrenia or schizoaffective disorder, depressed type) and 480 non-psychotic, first- through fourth-degree index relatives, and an additional 88 non-psychotic control individuals. Social-interpersonal, disorganized, and cognitive-perceptual symptoms of Schizotypal Personality Disorder (SPD) were assessed in the non-psychotic relatives and controls with a modified version of the Structured Interview for Schizotypy (SIS) (Kendler et al. 1989). Genetic correlations between schizophrenia and the SIS subscales (R_g) were obtained using pedigree-based, variance component analyses as implemented in the computer program, SOLAR. Subscales were highly heritable (range 0.17–0.65). A positive genetic correlation with schizophrenia was found for the majority of Social-Interpersonal subscales (range: 0.03–0.54) and both Disorganization subscales (.08 and .63), whereas all Cognitive-Perceptual subscales were negatively genetically correlated with schizophrenia (range: –0.10 – –0.35). The subscales most strongly correlated with schizophrenia were Organization of Speech/Thought, Irritability, and Suspiciousness/Guardedness (R_g = .63, .54, and .41 respectively). Subscale genetic correlations were used to derive weighted, aggregate SIS scale scores for each SPD symptom dimension and across all 21 subscales. Weighted aggregation of the Social-Interpersonal dimension resulted in a significant, positive genetic correlation with schizophrenia (R_g = .46, $P < .001$) and a non-significant trend was found for the Cognitive-Perceptual dimension (R_g = .27, $P = .079$). The Disorganization dimension was not significantly correlated with schizophrenia (R_g = .24, $P = .248$). Weighted aggregation across all subscales was also significant (R_g = .60, $P = .001$). The results argue for the advantage of weighted aggregation using genetic correlation with schizophrenia to maximize sensitivity of SPD symptoms to schizophrenia liability. These optimal combinations of SIS subscales should be most useful as supplementary phenotypes in linkage analyses, although the specific weights reported in this study require replication.
ID: 551330

CATECHOL-O-METHYLTRANSFERASE (COMT) GENE AND RESPONSE TO COGNITIVE REMEDIATION IN SCHIZOPHRENIA: PRELIMINARY FINDINGS

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Genetic variation in the Catechol-O-Methyltransferase (COMT) gene may affect the susceptibility to schizophrenia and impairment on certain types of neurocognitive tasks. The authors aimed to evaluate the effect of the association of COMT Val108/158 Met genotype with the response to a computerized cognitive rehabilitation (CRT) in chronic schizophrenia. Method: Inpatients with DSM-IV schizophrenia, randomly assigned to CRT for 3 hours/wk for 12 wks were genotyped. Patients were evaluated on neuropsychological assessments, functional skills, and clinical symptoms (PANSS) at baseline and at Week 12. Response definition: $> = 20\%$ performance improvement on the Trail Making tests and WCST test at baseline and Week 12 was used as a cut-off criterion to categorize patients into two groups : (1) Responders (those who had normal or below normal performance at baseline and increased performance at endpoint), and (2) Non-responders (those who had below-normal performance at baseline and endpoint, and those with normal performance at baseline, but below-normal performance at endpoint). We combined Met carriers (Met/Val = 17) and Met homozygotes (Met/Met = 2) and compared them to Val homozygotes (Val/Val n = 19). We then divided our sample in four subgroups on the basis of genotype ((Val/Val) versus (Met/Val + Met/Met)) and (Responders versus Non-Responders). Results: We present results on 38 subjects of a planned enrollment of 142. Significantly greater improvement was observed for the global cognitive index ($P = .050$), Trail Making Test ($P = .011$) and working memory tasks ($P = .049$) for the (Met/Val + Met/Met) group who were Responders to CRT in comparison to the Val/Val group who were Non-Responders to CRT. A significant association was observed between higher scores on the PANSS scale and genotypes Val/Val ($P = .044$) for rs4680. The correlation between effect sizes of improvement (higher global cognitive index score and lower PANSS scores) was significant ($P = .038$). Conclusions: These preliminary findings support the hypothesis that COMT polymorphism may influence cognitive functioning through CRT, with the caveat because of the small sample size, positive findings could be due to type I error. The presence of Met allele was associated with significantly greater improvements in overall neurocognition. As we accrue a larger sample size we may be able to determine if the two effects (ie, improvement from CRT and COMT polymorphism) act at different levels.
ID: 551258

miRNA EXPRESSION IN PREFRONTAL CORTICAL BRAIN FROM SCHIZOPHRENIA AND UNAFFECTED INDIVIDUALS

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microRNA profiles have recently revealed consistent patterns of up- or down-regulation in association with a number of human diseases. In 2007 we reported a statistically significant derivation of downregulation of 14 microRNAs and upregulation of one as the outcome of a spotted microRNA microarray testing post-mortem prefrontal samples from 29 schizophrenia patients and 15 unaffected comparison subjects. In this presentation we will describe the results of a follow-up study conducted in a new cohort of 35 schizophrenia, 35 unaffected, and 35 bipolar subjects. microRNA profiles were evaluated with a commercially available microRNA microarray platform (Agilent). We did not replicate the originally reported findings in this new cohort of subjects. However, when we grouped microRNAs by their bioactive "seed" regions we found similar differences in expression patterns between schizophrenia and unaffected subjects in both cohorts. We discuss implications of these results, including that these findings may point to a system of control agents that are dysregulated in schizophrenia. Whether they are etiological causes or responses to dysregulation elsewhere remains unknown, however.
ID: 551241

SEX-SPECIFIC TRANSMISSION OF PSYCHOSIS SUGGESTS X-LINKAGE: IMPLICATIONS FOR SEX DIFFERENCES IN MEMORY DYSFUNCTION IN SCHIZOPHRENIA

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Recent molecular genetic studies demonstrated X-chromosome abnormalities that we predict are important in understanding sex effects identified in previous studies of schizophrenia (SCZ), with men at greater risk for chronicity. Sex differences in brain abnormalities and cognitive deficits associated with memory dysfunction have also been identified, abnormalities present in X-linked disorders. Few studies have systematically evaluated sex-specific transmission risk and even fewer related this to sex differences in cognitive deficits. We tested the hypothesis of sex-specific transmission of psychoses in a recently completed high risk study, the New England Family Studies of Schizophrenia. We hypothesized sex-specific transmission and that it will be significantly associated with sex differences in memory deficits in adulthood. We identified 195 parents with psychoses (non-affective (NP), primarily SCZ, and affective (AP)) and 131 comparable control parents. 188 high risk (HR) and 147 control offspring were diagnostically assessed (185 females; 165 males). Relative risks for psychosis and sex-specific transmission were estimated using generalized estimating equations models to account for intrafamilial correlation. Adult offspring were also cognitively evaluated, including memory function (CVLT) and verbal fluency (FAS). There was a significantly higher risk for psychosis in HR offspring dependent on sex of parent and sex of offspring. 19% of male offspring of mothers with psychosis developed psychosis compared to 3.1% of male offspring of ill fathers. In contrast, 15.2% of female offspring of ill fathers developed psychosis versus 9.5% of female offspring of ill mothers. This pattern held for NP and AP. In case-control analyses, there was a significant interaction effect of group by sex on verbal memory function (unaccounted for by verbal fluency deficits) with male cases having significantly lower verbal memory scores than female cases ($F = 14.75$, $P = .0002$), with effect sizes reaching a 4.8 standard deviation (SD) sex difference between cases versus a .8SD sex difference among controls. Results demonstrate sex-specific (X-linked) transmission regardless of psychosis-type and that it is associated with sex differences in memory dysfunction. Results have important implications for molecular genetic studies of SCZ and other psychoses suggesting the importance of one's gender in understanding gene-brain-behavior SCZ phenotypes.
ID: 551169

ASSOCIATION BETWEEN THE TRYPTOPHAN HYDROXYLASE 1 (TPH1) GENE, SCHIZOPHRENIA SUSCEPTIBILITY, AND SUICIDAL BEHAVIOR

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Serotonin (5-hydroxytryptamin; 5-HT) alternations has since long been suspected in the pathophysiology of schizophrenia. Tryptophan hydroxylase (tryptophan 5-monooxygenas; TPH) is the rate-limiting enzyme in the biosynthesis of 5-HT, and sequence variation in intron 7 of the TPH1 gene has consistently been associated with schizophrenia across studies. In addition, this polymorphism is more frequent in suicide attempters and completers, than in individuals unaffected with any psychiatric disorder. In the present study we have tried to replicate previous findings in a combined Scandinavian case-control sample. Five single nucleotide polymorphisms (SNPs) were genotyped in 837 individuals affected with schizophrenia and 1473 controls. Three SNPs spanning introns 6 and 7, including the A779C/A218C polymorphisms, were associated with increased schizophrenia susceptibility (odds ratio = 1.17, $P = .019$, corrected for multiple testing). However there were no differences in allele frequencies between affected individuals having attempted suicide at least once and patients with no history of suicide attempts ($P = .48$), and heterogeneity between countries was evident ($P = .02$). A systematic review and meta-analysis of the literature on suicidal attempts (SA) showed a large between study heterogeneity (I2 = 0.59, $P = .003$, fixed model), and gave little support for the A779C/A218C polymorphism being a SA susceptibility locus within individuals diagnosed with psychiatric disorders (OR = 0.98, $P = .84$, mixed model). We conclude that the TPH1 A779C/A218C locus increases the susceptibility of schizophrenia in the Scandinavian population, which is in agreement with previous findings in Asian and Caucasian populations. The data at hand suggest that the locus contributes to the liability of psychiatric disorders characterized by elevated suicidal rates, rather than affecting suicidal behavior in individuals suffering from a disorder.
ID: 551145

TELOMERE LENGTH IN DRUG-NAÏVE FIRST EPISODE OF NON AFFECTIVE PSYCHOSIS PATIENTS

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Background: People with schizophrenia have a marked increase in mortality rate compared to the general population. Cardiovascular disease accounts much of this increased mortality. We tested the hypothesis that schizophrenia and related disorders are associated with a shorter telomere length. Telomere length is correlated with metabolic and cardiovascular abnormalities in general population. Methods: Telomere content, which is

a proxy for the telomere length, was measured to newly diagnosed, drug-naïve patients ($n = 32$) with schizophrenia and related psychotic disorders, and control subjects ($n = 32$). Subjects were matched for gender, age, body mass index and smoking status. Findings: The psychosis group had a significantly decreased mean telomere content compared to controls (respective means [SD] 93.8% [13.2] vs. 101.5% [16.2]; $P = .042$). Interpretation: Our results suggest that even prior to antipsychotic treatment, schizophrenia is associated with chromosome structure abnormalities that are linked to metabolic/cardiovascular disease and an increased mortality rate.

Table. Characteristics of the Nonaffective Psychosis and Control Subjects

	Psychosis ($N = 32$)	Control ($N = 32$)
Mean age [SD]	30.0 [10.2]	27.9 [7.2]
Male/female	21/11	21/11
Mean body mass index [SD]	23.1 [4.4]	24.0 [3.0]
Mean number cigarettes per day [SD]	7.9 [8.9]	6.2 [8.4]
Residing in the hospital's catchments area	21 [65.6%]	24 [75.0%]
Resting heart rate [SD]	77.4 [11.5]	74.9 [11.6]
Systolic blood pressure	120.0 [12.4]	120.5 [12.2]

For all variables, $P > .30$
ID: 551028

LYMPHOBLASTIC CELL LINE EXPRESSION, BLOOD AND BRAIN COMPARABILITY AND CIRCADIAN RHYTHM OF CANDIDATE GENES FOR SCHIZOPHRENIA

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The purpose of this study was to correlate three features of candidate genes for schizophrenia and their potential as biomarkers of schizophrenia. A total of 84 candidate genes were selected based upon recent meta-analysis (Allen et al. 2008) of candidate genes and genome-wide association and copy number variation studies implicating regions of interest in schizophrenia. We examined differential expression, blood and brain comparability, and circadian effects on expression of candidate genes. First, we examined differential expression of candidate genes in lymphoblastic cell lines in subjects with schizophrenia and their non-psychotic relatives by exon array and observed significant diagnosis effects ($P < .05$) on expression of APOE, PRKAB2, CLTCL1, PIAS3, TMEM108, and HTF9C. To assess blood and brain comparability of candidate genes, we then compared transcript level expression of cerebellum and lymphoblastic cell lines by exon array. From the list of 84 genes, there were 17 blood and brain correlations over 0.80, including APOE and HTF9C ($r = .98$ and $r = .82$, respectively). Because circadian rhythm effects on gene expression may confound biomarker research, we examined the circadian rhythm of peripheral blood gene ex-

pression of these candidates in a separate sample of 4 male and 4 female control subjects, with blood collected at 9 time points over 48 hours. There were 5 significant circadian rhythms detected using COSOPT ($P < .05$) and 27 trends toward significant circadian rhythm effects ($P < .10$), including trends toward circadian rhythm effects for the schizophrenia candidate genes APOE, CLTCL2, TMEM108 and HTF9C. These results underline the importance of controlling for circadian effects in biomarker research and provide further information of the possible utility of these candidate genes, particularly APOE and HTF9C, as potential biomarkers in schizophrenia research.
ID: 550929

LARGE-SCALE CANDIDATE GENE ANALYSIS OF ENDOPHENOTYPES FOR SCHIZOPHRENIA

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We developed a custom SNP chip consisting of 1536 SNPs within 94 candidate genes for schizophrenia and related endophenotypes based on knowledge of relevant neurobiological systems and an extensive review of published model organism, linkage, and association studies. We utilized this SNP chip to conduct association analyses of three neurophysiological and three neurocognitive endophenotypes for schizophrenia in a sample of 127 schizophrenia patients and 92 controls from the UCSD Schizophrenia Research Program. Endophenotypes for analysis included Prepulse Inhibition, P50 Suppression, the oculomotor Antisaccade Task, the Letter-Number Sequencing Test, the California Verbal Learning Test, and the Wisconsin Card Sort Test tapping critical schizophrenia-related domains. Schizophrenia diagnosis was also included as a phenotype for analysis. Of the 1536 SNPs, 1385 remained for analysis following elimination based on quality control thresholds for call rate, cluster separation, and marker informativity. A total of 30 genes were found to be associated with at least one endophenotype or schizophrenia (empirical $P < .01$). Many of these genes also interact on a molecular level, and seven genes displayed evidence for pleiotropy, revealing significant associations with two or more of the six endophenotypes. Among these genes were ERBB4 and NRG1, providing further support for a substantial role for these genes in mediating susceptibility to schizophrenia. The observation of extensive pleiotropy for some genes and singular associations for others in our data suggests alternative, independent pathways mediating schizophrenia pathogenesis. Supported by R01-MH042228 and MH79777.
ID: 550899

UNDERSTANDING PATHOGENIC MECHANISMS OF SCHIZOPHRENIA USING PLURIPOTENT HUMAN STEM CELLS

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Severe psychiatric illnesses, such as schizophrenia and bipolar affective disorder, are chronic and generally disabling brain diseases in need of effective treatments. Accumulative evidence supports the view that schizophrenia is a disease of neuronal development in nature, however, the underlying

cellular and molecular mechanisms remain large unknown. A number of susceptibility genes have recently been identified from human genetic association studies. Two genes, disrupted-in-schizophrenia 1 and 2 (DISC1 and DISC2), were identified at the breakpoint of a balanced translocation that co-segregates with schizophrenia and major affective disorders in a large Scottish family. Interestingly, DISC2 is only present in primates and humans, but not in lower species. Little is known about functions of DISC1 and DISC2 in human development due to a lack of experimental systems. We recently made some interesting discoveries on the role of DISC1 in regulating several essential steps of neurogenesis *in vivo*, including neuronal morphogenesis, migration and positioning, axon/dendritic development and synapse formation (Duan et al.,Cell 2007; Faulkner et al., PNAS 2008). We are extending these findings in animal models to human neurons. Specifically, we have developed methodologies to culture human embryonic stem cells (hESCs) and examine their neuronal development both *in vitro* and after in utero transplantation into E13.5 mice *in vivo* with immunocytochemistry, confocal and electron microscopy, FM imaging and electrophysiology (Song et al., Nat. Neurosci. 2002; Ge et al., Nature 2006; Ge et al., Neuron 2007). More recently, it has been possible to reprogram human skin fibroblasts into induced-pluripotent stem (iPS) cells that exhibit similar properties as hESCs. We were able to generate iPS cells from human patient fibroblasts. These cells exhibit all known hESC markers, normal karyotyping and retain the ability to differentiate into cell lineages in three germ layers. We have recently derived fibroblasts from several patients with schizophrenia and age-matched controls. Such an experimental platform using hESCs and iPS cells from schizophrenia patients may provide a novel means to understand the molecular and-cellular mechanisms underlying neuronal developmental defects in schizophrenia.
ID: 550890

GENETIC VARIATIONS IN THE 6P24–21 GENOMIC REGION THAT AFFECTS THE EYE TRACKING ABILITY IN SCHIZOPHRENIA PATIENTS.

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Smooth pursuit eye movement (SPEM) is one of the most established intermediate phenotypes linked to schizophrenia. Two linkage studies implicate chromosome 6p21–24 as a candidate locus for the oculomotor deficit; other linkage studies that used schizophrenia diagnosis as a phenotype have also implicated this region. This genomic region is of interest in developmental dyslexia, a disorder associated with motion processing and SPEM abnormality. In the current project we examined (i) phenotypic overlap between reading ability and the predictive pursuit gain (PPG) subcomponent of SPEM; and, (ii) effects of select candidate genes within 6p24–21 on PPG. We selected candidate genes based on findings of association with schizophrenia (DTNBP1), dyslexia (TTRAP, KIAA0319, DCDC2), or their role in GABA pathway (ALDH5A1). Schizophrenia (SZ) patients ($n = 175$) and matched healthy control (HC) subjects ($n = 171$) both between the ages of 15–58 years participated in the study. Eye tracking was performed using standard methods; PPG was measured when the moving target became briefly invisible. We selected 13 SNPs covering the 5 genes that were independent (not correlated) and resulting genotypes were frequent enough (ie, > 5%) in our sample. Analyses used ANOVAs to examine the effects of the genotypes on PPG; the p values were adjusted using the false discovery rate (FDR) adjustment. Examination of reading ability in a small sample of schizophrenia patients showed a significant correlation between Nelson reading speed and PPG ($r = 0.57$, $P < .05$, n–17). The genetic analyses showed that, there was a significant ALDH5A1 rs2328824 genotype by diagnosis interaction; GG (minor genotype) was associated with poor PPG compared with AG in SZ, while AA showed significantly better PPG than

AG in HC. Variation in a dyslexia related gene, TTRAP, significantly affected PPG such that the major homozygous was associated with worst PPG. Lastly, there was a trend for DCDC2 genotype by diagnosis interaction effect on PPG ($P = .06$ after adjusting for FDR). Our data suggest that two genes within 6p24–21, ALDH5A1 and TTRAP are associated with SPEM deficit. ALDH5A1 encodes an essential enzyme required for degradation of gamma-aminobutyric acid (GABA). Whereas, TTRAP is a dyslexia related candidate gene. In our sample, preliminary data from a small subgroup showed that patients with poor PPG perform poorly on a reading test.
ID: 550881

GENE PROFILING OF SINGLE-CELL POPULATIONS OF THE SUPERIOR TEMPORAL GYRUS IN SCHIZOPHRENIA

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Disturbances in postnatal developmental synaptic pruning may contribute to the onset of schizophrenia. In support of this hypothesis, recent postmortem studies have revealed that deficits of glutamatergic synapses may in fact be a prominent pathophysiologic feature of the illness. In addition, evidence suggests that the maturation of parvalbumin (PV) inhibitory neurons, that modulate pyramidal neuron output, may be important in regulating the critical period for synaptic plasticity and pruning. However, the possible molecular mechanisms that underlie the postulated disturbances of synaptic pruning have been largely unexplored. In a cohort of postmortem brains from 10 schizophrenia and 10 matched normal control subjects, we used laser capture microdissection to isolate subsets of pyramidal and inhibitory neurons in the superior temporal gyrus (BA 42), which exhibits pronounced gray matter reduction during the early course of schizophrenia. In pyramidal neurons, preliminary data revealed 58 genes that were differentially expressed ($2 – 4$ fold, $P < .05$) in schizophrenia. Biological networks were generated through the use of Ingenuity Pathway Analyses (Ingenuity® Systems, www.ingenuity.com). Three main biological networks were identified: Molecular transport, nervous system development/function, and cellular assembly/organization (significance scores: 21–26). Three down-regulated genes were pinpointed as central to the merged network ie, neuregulin-4 (nrg-4), early growth response-1 (egr-1) and a calcium channel subunit, cacna1a. This cell-type based profiling affords us the molecular resolution to generate hypotheses as to how neuronal connectivities and their molecular signaling control might be altered within and between cells and could lead to novel therapeutic strategies by directly correcting neural circuit disturbances.
ID: 551928

REFINEMENT OF GENETIC MARKERS ASSOCIATED WITH CLOZAPINE-INDUCED AGRANULOCYTOSIS USING WHOLE GENOME AND HLA TYPING APPROACHES

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Clozapine is a highly efficacious drug for the treatment of schizophrenia, but its use is limited in part due to the side effect of agranulocytosis. We have previously reported genetic variants in five genes associated with clozapine-induced agranulocytosis (CIA) from a candidate gene study, and replication of the association in one gene (HLA-DQB1) in an independent cohort. We have now conducted additional studies to confirm and refine these associations through whole genome and high resolution HLA typing approaches. Samples from our previously collected case/control cohort (CARING, N = 87) were genotyped on the Illumina HumanCNV370 panel to identify new genetic markers, as well as to refine the association in HLA-DQB1 previously reported. Multiple signals were detected in the major histocompatibility complex on chromosome 6 through the whole-genome analysis, including one highly significant HLA-region marker that warrants replication. High resolution HLA typing of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 was then conducted on subjects from the CARING cohort including clozapine-treated controls, CIA cases and granulocytopenia cases (N = 115). HLA typing was conducted to replicate and refine previously reported associations by our group and others. The SNP previously identified through our candidate gene studies as a marker of CIA (HLA-DQB1 + 6672G>C) was found to be highly correlated with an HLA type in HLA-DQB1. The details of all markers, as well as characteristics for a pharmacogenetic test for CIA will be provided.
ID: 556979

ASSOCIATION OF GAD67 EXPRESSION AND CELL CYCLE REGULATION IN HIPPOCAMPAL GABA CELLS IN SCHIZOPHRENICS (SZS) VS BIPOLARS (BDS)

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Decreased expression of GAD67 is present in the patients with both SZ and BD and a recent network association analysis has demonstrated that the regulation of this gene is linked to those involved in cell cycle progression via cyclin D2 (Benes et al., 2007). Laser microdissection (LMD) was used to dissect out GABA cells in the stratum oriens of sectors CA3/2, a key locus along the trisynaptic pathway where oscillatory rhythms are generated. In SZs, the most significant changes involved genes involved in the epigenetic regulation of the transcriptional complex that regulates progression from G1/S to G2/M. Upregulation of MBD4, HDAC1 and DAXX would put this complex in the "OFF" state. In BD, important changes in the expression of genes involved in G1 arrest and progression toward the G2 checkpoint and DNA repair were observed. BDs showed a significant down-regulation of TGFβ2, neuregulin I, four different nicotinic receptor subunits, cyclin D2, HDAC3, E2F, p53, CHK2, the RP-1 replication protein, two DNA polymerases (POLG2 and POLL) and two anaphase promoting complexes (APC1 and 5). Taken together, these findings suggest that there may be a failure of G1S arrest and DNA repair in GABA cells of the SO in CA3/2 in BDs. These changes may have a negative impact on genomic and functional integrity of this discrete subpopulation of GABAergic interneurons. Overall, decreased GAD67 expression in SZ and BD seems to involve fundamentally different mechanisms and these probably reflect unique molecular endophenotypes for these two psychotic disorders. Supported by MH42261, MH62822, MH068855 and MH60450.
ID: 556965

GENE VARIANTS ASSOCIATED WITH ANTIPSYCHOTIC INDUCED WEIGHT GAIN

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Introduction: Clozapine and olanzapine have been associated with substantial weight gain in many patients. However, an individual's propensity to develop weight gain largely depends on genetic factors that will be reviewed. A possible mechanism may involve the endocannabinoid system which has been implicated in the regulation of appetite signalling and food intake through the dorsal vagal complex (DVC) of the brainstem. Animal models have shown that olanzapine significantly decreased cannabinoid receptor binding in the DVC (Weston-Green et al. 2008). Furthermore, the cannabinoid-1 (CB-1) receptor antagonist rimonabant has been shown to induce weight loss. The purpose of this study has been to analyze whether variants (SNPs) of the CB-1 receptor gene potentially modulating the endocannabinoid system were associated with antipsychotic induced weight gain. Methods: We have been genotyping several SNPs in a larger sample of antipsychotic induced weight gain using three different samples from the US (A, B and C; total n = 139) and one sample from Germany (D; n = 70; total n = 209), mainly treated with clozapine and olanzapine on average for 11 weeks. Mean weight gain was compared across the genotypic categories using ANOVA as well as ANCOVA including baseline weight or sex as covariate. Results: Mean weight gain in the sample was + 4.0 kg (± 4.8 kg). In the sample of Europeans (n = 123), carriers of the C/C genotype of the promoter region SNP rs806378 gained only 2.3 kg as compared to C/T and T/T carriers who gained on average 4.2 kg. This association was significant when corrected for baseline weight (P = .049). We then excluded those patients who received medications other than clozapine or olanzapine and found a more significant association ($F_{2,72}$ = 4.48, P = .01 where homozygotes for T/T gained 6.25 kg as compared to 1.90 kg in homozygotes for C/C carriers. The most significant finding was then obtained when examining only patients treated with clozapine $F_{2,61}$ = 7.49, P = .001. Results remained unaltered when including covariates such as baseline weight or sex. Summary: Our studies suggest that a promoter variant of the CB-1 receptor gene is associated with clozapine and olanzapine induced weight gain. We are currently expanding our analyses with including a total of 10 tag SNPs spanning the entire CB-1 gene. These findings may have important implications for discovery of novel antipsychotic drug targets that do not result in weight gain side effects.
ID: 555296

NEUROCOGNITIVE MEASURES IN MULTIPLEX MULTIGENERATIONAL INVESTIGATION OF SCHIZOPHRENIA (MGI)

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Background: Cognitive deficits are evident in schizophrenia. We reported significant heritabilities for neurocognitive tests for multiplex, multigenerational families affected by schizophrenia, suggesting that some variation in traits is affected by genetic factors. How the traits vary together may

advance the understanding of cognitive processes in schizophrenia. Methods: The Consortium ascertained European-Americans from multiplex multigenerational families. The computerized neurocognitive battery (CNB) measures accuracy and speed on abstraction and mental flexibility, attention, verbal, face, and spatial memory, emotion processing, and sensorimotor processing. Heritability was estimated using SOLAR. Overall variance of the trait was divided into portions due to genetic factors determined by pedigree relationships, environmental factors, and specific covariates such as age and sex. Results: Heritability estimates ranged from 0.21 for spatial memory to 0.72 for language. Mean efficiency levels varied with age for all traits, and the square of age was significant for abstraction and mental flexibility, attention, face memory, and emotion processing, while sex was significant for abstraction and mental flexibility, spatial processing, face memory, verbal memory, and emotion processing. The interaction of sex and the square of age was significant for spatial memory and verbal memory. All genetic and environmental correlations were negative. The genetic correlations between affection status with abstraction and mental flexibility, attention, and emotion processing were significantly different from zero, and the genetic correlations between affectation status and all cognitive traits were significantly different from one. Environmental correlations were not statistically significantly different from zero. Conclusions: The genetic correlations of neurocognitive traits with schizophrenia suggest that they are valid endophenotypes for schizophrenia. Since these traits can also be measured in relatives, they may provide a powerful strategy for linkage and association studies, helping distinguish unaffected individuals who carry alleles predisposing to schizophrenia. The quantitative nature of these traits also provides increased power for genetic studies, potentially differentiating levels of risk in unaffected individuals and levels of severity in affected individuals.
ID: 554994

FAMILY-BASED ASSOCIATION STUDY OF NALCN GENE WITH SCHIZOPHRENIA

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Schizophrenia affects about 1.0% of the population worldwide, with devastating consequences for both patients and their families and is the seventh most costly medical illness. Linkage and association studies have now implicated several loci in the genome that likely harbor genes conferring risk for schizophrenia. NALCN (sodium leak channel, non-selective) is a gene located on chromosome 13q in a suggested linkage region for schizophrenia. Mouse NALCN mediates some background sodium leak in hippocampal neurons and plays a role in neuronal excitability. Abnormalities in hippocampal activity and neuronal excitability have been implicated in schizophrenia. In this study, we examined association with schizophrenia using family-based analysis. Twenty six NALCN polymorphisms were analyzed and allelic; genotypic and haplotypic frequencies were compared across 85 small nuclear families. We did not find any significantly altered transmission. Our results suggest that the NALCN may not affect susceptibility to schizophrenia.
ID: 554883

UPDATE ON THE PROJECT AMONG AFRICAN AMERICANS TO EXPLORE RISKS FOR SCHIZOPHRENIA (PAARTNERS)

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Background: A genetic etiology is now widely accepted for schizophrenia (SZ). Recent reviews have identified several suggestive linkages, eg, 1q22, 6q25, 8p21–22, and 11q21, primarily in Caucasian populations. The Project among African-Americans to Explore Risks for Schizophrenia (PAARTNERS) is a multi-site study that seeks to identify genes that confer susceptibility to schizophrenia and neurocogntive endophenotypes by linkage mapping and targeted association analyses. Methods: PAARTNERS utilizes for diagnostic assessment, the Diagnostic Interview for Genetic Studies (DIGS) and the Penn Computerized Neurocognitive Battery (CNB) to assess cognitive abilities. Medical chart information is incorporated into the DIGS. The Family Interview for Genetic Studies (FIGS), conducted with family member informants, provides additional diagnostic. A Best Estimate Final Diagnosis (BEFD) is reached by the clinicians on each participant based on this information. Genome wide linkage analyses using the Center for Inherited Disease Research (CIDR) Linkage IV SNP Panel genotypes, are performed using MERLIN and SIBPAL on clinical phenotypes, while MERLIN-regress and SOLAR are used for the normalized cognitive domains. Results: Preliminary linkage results on 217 families with the clinical phenotypes schizophrenia (S), or schizophrenia and schizoaffective disorder (SS), or any DSM IV diagnoses with psychoses (P) are presented. Conclusions: Our preliminary results indicate that several linkage peaks, especially on chromosome 11(30 cM, 68 cM), 8p, and chromosome 4 (20 cM) exhibit significant linkage. The overlapping loci identified by this study and two other previous studies of A-A families gives us great hope that loci affecting risk for schizophrenia in African Americans will soon be uncovered.
ID: 554780

UBIQUITIN PROTEASOME GENE EXPRESSION AS A BIOMARKER FOR SCHIZOPHRENIA AND BIPOLAR DISORDER: CONVERGENT FINDINGS FROM TWO INDEPENDENT COHORTS

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It is probable that schizophrenia (SCZ) and bipolar disorder (BPD) are etiologically diverse and may be represented by different sets of genes in each individual. Thus, we hypothesized that searching for dysregulated molecular and cellular pathways and functions would be more fruitful in that different genes could populate an identified biological pathway or function but the pathophysiological outcome for the cell or tissue would be the same. We conducted a blood-based transcriptomic study in two independent populations with SCZ and BPD in San Diego (SCZ = 13; BPD = 9, control = 8)

and Taiwan (SCZ = 11; BPD = 14, control = 16). Each diagnostic group was compared to controls as well as subjects with a history of psychosis [PSYCH(+):San Diego ($n = 6$), Taiwan ($n = 14$)] to subjects without such history [PSYCH(-): San Diego ($n = 11$), Taiwan ($n = 14$)]. For both cohorts analyses compared diagnostic groups on the mean expression level on a gene-by-gene basis through analyses of covariance (ANCOVAs) which included demographic (eg, age, sex, ancestry) and clinical (eg, current psychotropic medications) factors. Following ANCOVAs, the top 100 genes in both cohorts for each diagnostic group that were significantly dysregulated at $P < .05$ were imported into Ingenuity Pathway Analysis (IPA) software. Results showed the ubiquitin proteasome pathway (UPS) was listed in the top ten canonical pathways for all diagnostic groups among both cohorts with between two and five genes populating the pathway and a considerably low likelihood ($P = 6.21e–05$) of a chance occurrence. Between both cohorts across all diagnostic groups no overlap in biological functions or dysregulated genes populating these functions were observed. However, comparison of the SCZ groups from both cohorts revealed that the general biological pathway of 'cell death' was shared. Furthermore, comparing the PSYCH(+) groups for each cohort showed that three of the ten most dysregulated general biological pathways for both cohorts was 'cancer'; however, specific biological functions populating the 'cancer' pathway across cohorts did not concur. Our findings provide convergent evidence of ubiquitin proteasome pathway dysregulation and support for further investigation of ubiquitin proteasome gene expression as a potential biomarker for SCZ, BPD, and/or psychosis.
ID: 554733

UPDATE ON THE CONSORTIUM ON THE GENETICS OF SCHIZOPHRENIA (COGS)

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Background: Converging model organism, candidate gene and genome-wide association (GWA) studies offer much promise in explicating theneurobiological significance of genes implicated in schizophrenia. Methods: The COGS has constructed a 1536 COGS SNP Chip to interrogate 94 schizophrenia-related genes of interest in schizophrenia. CIDR linkage analyses are also forthcoming. COGS families include both parents, one proband and one or more unaffected siblings, and 12 heritable endophenotypes are assessed. In addition to the COGS primary endophenotypes, "secondary" endophenotypic data will be presented. For example, the oculormotor domain antisaccade is more robustly heritable than is smooth pursuit eye movement (SPEM). Results: 129 (of 350) families have been examined using the COGS SNP Chip. We will illustrate the distribution of SNPs that are interrogated. The Table shows a partial representation of the striking results. Genes such as NRG1 have significant "hits" on almost all of the 12 endophenotypes, suggesting pleiotropy, and possible common pathways that influence the expression of multiple endophenotypes. Other genes "light up" singular endophenotypes suggesting alternative, perhaps simpler pathways, leading to schizophrenia. Conclusions: The initial analysis of the COGS SNP Chip SNPs provide a wealth of data on (1) the heritabilities of neurophysiological and neurocognitive endophenotypes, (2) the strong inference based SNPs reveal many ($N = 194$) significant associations between heritable endophenotypes and the 94 genes in the SNP Chip.Novel permutation and simulations will be presented on these data analyses. These results will be discussed.
ID: 554724

NRXN3, A NOVEL RISK GENE FOR SCHIZOPHRENIA

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In spite of numerous exciting susceptibility genetic variants disclosed by recent studies, only few of these candidate loci have been found to be unequivocally associated with schizophrenia across different studies. Such inconsistent results may be attributable to genetic heterogeneity reflected by genetic heterogeneity. Therefore, we propose to take advantage of a clinical marker, smooth pursuit eye movement (SPEM), to help circumvent the problem of genetic heterogeneity. In the current study we have analyzed the genomic DNA of 100 subjects (ie, 51 schizophrenic patients and 49 healthy controls, who are mostly Caucasian) using the Affymetrix 6.0 SNP array. Four of these subjects were excluded due to missing diagnostic data and hence 47 cases were 49 controls were analyzed. Initially a total of 909,622 SNPs were analyzed, while approximately 30% of these SNPs were excluded due to the concerns about possible genotyping errors (corresponding P-values derived from Hardy-Weinberg Equilibrium tests were less than $1×10^{-7}$). SNPs with a minor allele frequency $< 1\%$ were also excluded due to sparse data in a particular genotype subgroup. Marker-by-marker association tests were performed across the whole genome using the allelic trend tests implemented in the software PLINK. Fifteen SNPs were hence found to be significantly associated with risk of schizophrenia (p-value $< 1×10^{-7}$). Eight of these 15 SNPs are located within 7 genes. All of these 7 genes contained other SNPs nominally significantly associated with schizophrenia ($P < .05$). Among these genes the NRXN3 gene may warrant further study since it contains two SNPs, at which associations reached the genome-wide significance. Neurexin 3 encoded by the NRXN3 gene plays a key role in brain neuronal connectivity. In addition, the NRXN3 gene has been found to be associated with alcohol dependence and autism spectrum disorder. Our unpublished gene expression data also indicated that NRXN3 gene was expressed differently between schizophrenic patients and healthy control subjects. Taken together, NRXN3 may serve as a novel candidate gene for schizophrenia.
ID: 552081

Table. Partial Representation of the most significant p value for each of the 12 COGS endophenotypes and 5 of the 94 candidate genes

Chr	Gene	PPI	P50	Antisaccade	DS-CPT	LNS	CVLT	ABF	FMEM	SMEM	SPA	S-M	EMO
1	NOS1AP	$P < 0.01$			$P < 0.01$		$P < 0.01$			$P < 0.01$		$P < 0.01$	$P < 0.001$
2	ERBB4		$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.001$	$P < 0.01$	$P < 0.01$	
4	GRID2	$P < 0.001$	$P < 0.01$		$P < 0.01$						$P < 0.01$	$P < 0.01$	$P < 0.01$
6	GRM1				$P < 0.01$		$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.001$	$P < 0.01$	$P < 0.01$	$P < 0.01$
8	NRG1	$P < 0.01$		$P < 0.01$	$P < 0.01$		$P < 0.001$	$P < 0.001$			$P < 0.0001$	$P < 0.01$	

ANALYSIS OF BDNF VAL66MET ALLELE-SPECIFIC MRNA LEVELS IN SUBJECTS WITH MAJOR PSYCHOSIS AND SUICIDE BEHAVIOUR

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We investigate here the hypothesis that the BDNF Val66Met polymorphism is associated with suicide attempt in major psychosis. However, the possibility that genomic imprinting in BDNF gene affects risk for suicide has not been investigated before. To examine the possibility of genomic imprinting in the BDNF gene in suicide attempt, we analyzed the parent-of-origin effect (POE) and differential expression of the BDNF Val66Met alleles in a sample of families with at least one subject affected by schizophrenia or bipolar disorder. We performed a family-based association study and ETDT analyses of the Val66Met polymorphism and the GT repeat polymorphism in 432 nuclear families, and compared allele-specific mRNA levels in both post-mortem brain samples of suicide victims and controls. The BDNF Val66 allele was not transmitted significantly more often to patients with suicide attempt. There was no significant difference between maternal and paternal transmission ratios. There was no significant difference in the ratio of Val/Met-specific mRNA expression between suicide victims and controls. These data do not support a role for genomic imprinting as a modifier of the contribution of BDNF gene to risk of susceptibility to suicide in major psychosis.
ID: 551987

9. 9. Health Economics and Services Research

REDUCING STIGMA: THE EFFECT OF AN EARLY PSYCHOSIS EDUCATIONAL PROGRAM

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Objective: The stigma associated with a mental illness can be an impediment to recovery. In addition, stigma related to psychosis is more pronounced than in other mental illnesses (Sartorius and Schulze, 2005; Jorm and Wright, 2008). A brief educational program has been shown to be effective in increasing knowledge and improving attitudes about mental illness (Watson, 2004). The purpose of this project was to determine whether an educational intervention that focuses on psychosis delivered to high school students increased their knowledge about signs and symptoms of early psychosis and whether the same intervention reduced negative attitudes toward people with schizophrenia. Methods: The study was a pre-post nonequivalent groups quasi-experiment. One week before the educational program, students were invited to complete a survey to assess their knowledge about psychosis and their attitudes towards people suffering from psychosis. The survey entailed review of a vignette about a fictitious character, "Harry", who is showing signs of early schizophrenia. The students then answered a series of questions to assess their attitudes towards "Harry" adapted from Corrigan et al. (2002), and a series of questions to assess their prior experience and knowledge relating to psychosis adapted from Stuart and Arboleda-Florez (2001). Upon completion of the educational program the students completed the survey a second time. Results: Paired sample t-tests were used to examine pre-and post-presentation differences of 24 completed surveys. Students' attitudes were generally more positive in the current sample relative to scores reported from similar previous investigations, but the scores were also stable over time and gave no indication of a change after the educational intervention. Conclusion: The educational intervention did not produce a significant change in students' attitudes towards people with psychosis. This may relate to low statistical power, and a larger sample size might detect subtle shifts related to the intervention. However, this sample also reported more prior knowledge and more positive attitudes towards people suffering from psychotic illnesses, perhaps resulting in a ceiling effect that is less sensitive to change. The consenting procedures in the present study were somewhat onerous, and this may have resulted in a sample selection bias towards participants with more knowledge and less negative attitudes towards people with psychotic disorders.
ID: 535672

THE 2009 SCHIZOPHRENIA PATIENT OUTCOMES RESEARCH TEAM (PORT) TREATMENT RECOMMENDATIONS: OVERVIEW AND UPDATE PROCESS

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Background: The past decade has seen the advent of multiple sets of guidelines for the treatment of schizophrenia, including those developed by the Schizophrenia Patient Outcomes Research Team (PORT). In contrast to other guidelines, the Schizophrenia PORT treatment recommendations are driven by the available evidence base. Expert opinion plays a limited role. The original Schizophrenia PORT treatment recommendations were published in 1998 and underwent revision in 2003. Over the last 5 years, there have been new developments in the pharmacological and psychosocial treatment of schizophrenia, which warrant another update of the PORT recommendations. Methods: Two Evidence Review Groups (ERGs) comprised of over 20 faculty and trainees in psychiatry from the University of Maryland, under the guidance of external Advisory Boards, have recently conducted systematic literature searches to identify all studies of psychopharmacologic and psychosocial treatments for schizophrenia published since 2002. All studies that met pre-specified design standards were reviewed, and pertinent data were abstracted in an online database to facilitate the development of drafts of the updated treatment recommendations along with accompanying evidence summaries. Treatments for which the evidence is unlikely to be sufficient to warrant a treatment recommendation have also been reviewed. Results: The draft proposals will be posted on a dedicated website and an Expert panel, comprised of the two ERG Advisory Boards, additional clinical scientists and relevant stakeholders, will provide feedback on the draft recommendations and evidence summaries and will rate the quality, quantity, and consistency of the evidence. In November 2008, we will hold a conference, at which the Expert Panel will discuss with PORT investigators their critiques and ratings of the evidence for each recommendation and will reach consensus on the content of the recommendations. The final updated recommendations will be published in manuscript form and also displayed on a website for dissemination to professionals and the public. Discussion: The proposed presentation will provide an overview of the process and the challenges of synthesizing evidence for the 2009 Schizophrenia PORT Recommendations.
ID: 550779

THE EFFECTS OF SUBSTANCE USE ON BREAST CANCER AND OSTEOPOROSIS SCREENING IN WOMEN WITH SCHIZOPHRENIA: A REVIEW OF CONTINUOUSLY COVERED MEDICAID BENEFICIARIES

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Breast cancer (BC) and osteoporosis are major public health concerns in women. These health risks may be significantly elevated in women with schizophrenia, however evidence remains conflicting. Environmental factors may play a role in BC and osteoporosis risk and recent evidence suggests BC mortality is increased in the general population with a substance use disorder (SUD). SUD may also contribute to bone mineral density loss in women with schizophrenia, however its contribution to risk has not been examined. This study examined differential rates of BC and osteoporosis screening in Maryland Medicaid beneficiaries. Subjects included only non-pregnant females aged 18 to 64 with continuous (12 month) Medicaid enrollment in FY2005. We examined administrative data from the following

four groups of women: 1) schizophrenia and no SUD ($N = 3,807$), 2) schizophrenia and SUD ($N = 593$), 3) no major psychiatric diagnosis or SUD (a control group, $N = 41,815$), and 4) SUD in the absence of schizophrenia ($N = 3,600$). The mean age and race overall was 42.2 years and 56.9% were African American. The unadjusted frequency of BC screening in women ages 40–64 years was 29.4% with schizophrenia, 23.3% of the control group, 19.1% of those with schizophrenia and SUD, and 15.3% with SUD only. Logistic regression models adjusting for race and Medicaid eligibility categories found significant group effects ($P < .0001$) that were consistent in magnitude and direction with these results. Screening for osteoporosis was lower across all groups ($<5\%$ for women age 50–64) than BC screening rates, and logistic regression modeling failed to identify significant group effects ($P > 0.25$). Related sample isolation analyses found that the prevalence of non-benign BC was 1.9% to 3.3% across the 4 groups, and osteoporosis was present in 5.0% to 7.5%. Preliminary analyses also suggest that women with schizophrenia and SUD may be at the highest risk for bone loss and fracture. Overall, this work indicates that Medicaid beneficiaries with schizophrenia and SUD (dually diagnosed), or SUD alone, have lower rates of BC screening than comparison subjects, and that the dually diagnosed group may be at slightly heightened risk for osteoporosis. These results suggest that increased preventative care efforts may be of special benefit to women with SUD and in women who are dually diagnosed.
ID: 550336

THE 2009 SCHIZOPHRENIA PORT PSYCHOSOCIAL TREATMENT RECOMMENDATIONS

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Background: The Patient Outcomes Research Team for Schizophrenia (Schizophrenia PORT) project has had a major impact on the development and dissemination of evidence-based practices for the treatment of people with schizophrenia. In comparison to other treatment guidelines or algorithms, the Schizophrenia PORT treatment recommendations are based solely on empirical data. The original Schizophrenia PORT treatment recommendations were published in 1998, and underwent their first revision in 2003. Over the last 5 years, there have been a number of new developments in the psychosocial treatment of schizophrenia, which warrant an update of these treatment recommendations. Methods: Schizophrenia PORT investigators conducted extensive electronic literature searches to identify all psychosocial treatment studies in schizophrenia published since the 2002 PORT literature review. We also reviewed studies preceding 2002 in areas not covered by previous PORT reviews including smoking cessation, substance abuse, weight loss, and peer-based interventions. The abstracts of all studies focusing on supported employment, family interventions, assertive community treatment, cognitive behavioral therapy, cognitive remediation, medication adherence, and interventions for individuals experiencing a first psychotic episode were reviewed and abstracted. Specific intervention outcomes were recorded including employment, hospitalization, symptoms, quality of life, functioning, and substance abuse. If the article met pre-specified design standards, then the article was selected for review and included in the PORT database. These articles were then used to update current PORT psychosocial treatment recommendations and to develop draft proposals for new treatment recommendations. Results: In November 2008, the new treatment recommendations will be presented to a group of experts in the treatment of schizophrenia, who will review the evidence for each treatment recommendation and recommend revisions. Discussion: The proposed presentation will discuss the final psychosocial treatment recommendations for the treatment of first-episode and multi-episode people with schizophrenia and will present areas of treatment that require further investigation.
ID: 550118

THE 2009 SCHIZOPHRENIA PORT PSYCHOPHARMACOLOGICAL TREATMENT RECOMMENDATIONS

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Background: The Patient Outcomes Research Team for Schizophrenia (Schizophrenia PORT) project has had a major impact on the development and dissemination of evidence-based practices for the treatment of people with schizophrenia. In comparison to other treatment guidelines or algorithms, the Schizophrenia PORT treatment recommendations are based solely on empirical data. The original Schizophrenia PORT treatment recommendations were published in 1998, and underwent their first revision in 2003. Over the last 5 years, there have been a number of new developments in the pharmacological treatment of schizophrenia, which warrant an update of these treatment recommendations. Methods: Schizophrenia PORT investigators conducted extensive electronic literature searches to identify all pharmacological treatment studies in schizophrenia published since the 2002 PORT literature review. The article abstracts of all studies conducted with first and second generation antipsychotics, antidepressants, antiepileptics, benzodiazepines, and lithium and abstracts of all studies examining specific outcomes, including agitation, cognition, first episode, metabolic abnormalities, negative symptoms, quality of life and functional outcomes, and substance abuse were reviewed. If the article met pre-specified design standards, then the article was selected for review and included in the PORT database. These articles were then used to update current PORT psychopharmacological treatment recommendations and to develop draft proposals for new treatment recommendations. Results: In November 2008, the new treatment recommendations will be presented to a group of experts in the treatment of schizophrenia, who will review the evidence for each treatment recommendation and recommend revisions. Discussion: The proposed presentation will discuss the final psychopharmacological treatment recommendations for the treatment of first-episode and multi-episode people with schizophrenia; the use of adjunctive medications for indications other than positive symptoms; and the treatment of co-occurring conditions, and will present areas of treatment that require further investigation.
ID: 550008

STEP: PRAGMATIC RANDOMIZED PILOT TRIAL OF INTEGRATED TREATMENT FOR FIRST EPISODE PSYCHOSIS VS USUAL CARE IN THE UNITED STATES

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Prospective studies of early psychosis suggest that most functional deterioration occurs within the first few years after onset. The critical period hypothesis holds that intensive intervention during these first few years could lead to better functioning sustained over the long run. Randomized studies in Europe suggest that intensive intervention for first episode patients produces better outcomes and economic benefits that outweigh the

increased treatment costs. These findings may not generalize automatically to the United States (US), however, where medical care delivery is organized very differently, where the outcomes of usual care may differ, and where the opportunity for economic benefit may also differ. The overall objective of Systematic Treatment for Early Psychosis (STEP) is to provide preliminary evidence bearing on the early intervention hypothesis in the US, within a cost-effectiveness paradigm, by conducting a randomized clinical trial of integrated specialized services vs usual care. Insured first episode patients are randomly assigned to receive access to STEP care in the public sector at the Connecticut Mental Health Center, for which they would ordinarily not be eligible because of having insurance, vs using their insurance in the private sector as usual (usual care). Preliminary treatment utilization data from the ongoing trial at six month follow-up show that nearly all patients in both groups received medication but that far more patients randomized to STEP received psychosocial treatment than those randomized to usual care (any psychotherapy or case management, 85% vs 33%; any cognitive behavior therapy, 77% vs 0%; any family therapy, 60% vs 0%). Preliminary outcomes data show that 8/13 patients randomized to STEP treatment were working or going to school at least half-time (62%), compared to 3/9 patients randomized to usual care (33%). These interim findings suggest that a pragmatic trial of intensive treatment for first episode psychosis is feasible in the US and underscore the question whether both treatment effect sizes and economic benefits of specialty first episode care may be more substantial in the US than reported by previous European studies.
ID: 549955

A COST-BENEFIT ANALYSIS OF HIGHER MEDICATION COPAYMENTS IN VETERANS WITH SCHIZOPHRENIA

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Medication non-adherence represents a significant problem for patients with schizophrenia, substantially increasing psychiatric admission risks. The 2002 Veterans Health Care Act raised medication copayments from $2 to $7. From the VA's perspective, such health policy decisions affect both financial benefits and the potential costs associated with unintended clinical consequences. This observational study documents the cost-offset of copayment revenue versus subsequently higher inpatient and emergency department (ER) costs. Pharmacy prescriptions, health services utilization, and costs for all veterans ($N = 69,986$) diagnosed with schizophrenia were analyzed 33 months Pre and Post policy change. We calculated additional copayment revenue versus utilization costs (1999 adjusted dollars), contrasting veterans subject to copayment increases with a natural control group of exempt patients. In comparison to the pre-policy period and Exempt patients, total prescriptions for Copayment veterans ($N = 33,431$) increased slightly, but psychotropic fills dropped 21%. During the same period, psychiatric admissions and hospital days rose 4%, reversing downward trends seen over the past decade. Overall, total prescriptions yielded $17.3 million in new copayment revenue, but higher pharmacy costs of $5.5 million. Furthermore, inpatient and ER costs increased $13.3 million and $0.6 million, respectively. Therefore, the net cost-benefit revenue change was a negative $2.1 million, or $745 000 annualized losses. Sensitivity analyses altered utilization costs and the proportion of post-policy changes due

to higher copayments, with annualized cost-benefits ranging from -$1.4 million to -$0.1 million. This descriptive study implies that the policy change indeed translated into greater copayment revenue. However, unanticipated consequences included sharply reduced psychotropic fills leading to poorer adherence and higher utilization. Recognizing complex causality assumptions, the VA nevertheless appeared to experience financial losses while simultaneously reducing veterans' quality of life. Policy changes targeting essential pharmacy benefits for vulnerable patients with schizophrenia should be implemented carefully, evaluating trade-offs between immediate financial gains and potential costs associated with clinical deterioration. Longer term studies are needed to gauge the sustained effect over time as veterans reconcile treatment decisions with their higher medication expenses.
ID: 549869

THE EFFECTS OF A DOCUMENTARY FILM ON REDUCING STIGMATISATION ABOUT SCHIZOPHRENIA IN A SAMPLE OF UNDER-GRADUATE PSYCHOLOGY STUDENTS

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Negative public reactions concerning mental illness, and in particular schizophrenia, may result in a number of negative consequences, including aggravating their clinical condition and making it even more difficult for patients to assimilate into society. The present study examined young people's attitudes about schizophrenia and furthermore evaluated the effect of a documentary film (that depicts the lives of schizophrenia patients) on reducing stigmatization about schizophrenia. One hundred and fifteen undergraduate psychology students first provided information concerning their attitudes and knowledge about schizophrenia, in addition to filling out a questionnaire assessing their degree of acceptance of stereotypes and degree of social distance towards schizophrenia patients. One week later, participants viewed the documentary film and completed the same questionnaire. The film significantly and positively influenced participants' attitudes concerning schizophrenia. In particular, after having watched the film, participants revealed less stereotypical attitudes about schizophrenia and desired less social distance with schizophrenia patients. This change was not related to social desirability or to age, sex or years of education.
ID: 549627

THE ROLE OF PATIENT RATED ASSESSMENTS IN INTEGRATED CARE PATHWAYS FOR SCHIZOPHRENIA

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Introduction: The Scottish Schizophrenia Outcomes Study(SSOS) demonstrated that patient rated assessments of mental health are an important source of complimentary data for care planning(1). Following SSOS,

Quality Improvement Scotland, the agency in Scotland for assuring standards of healthcare, developed a new strategy for mental health in Scotland(2). This recommended the introduction of routine outcome data collection in mental health, including assessments made by patients (PROs). This paper describes how this approach was researched and developed including: 1.the use of qualitative methods of consultation to assess the views of patients who participated in SSOS over 3 years; 2.the work of the Avon Development Group in Scotland (ADGS) to update the Avon measure; 3.the use of patient rated outcomes (PROs) / needs assessment in an Integrated Care Pathway(ICP) model of quality assurance. Methods: A random 10% sample of the original cohort participated in 5 focus groups consisting of patients with ICD10 F20–25 schizophrenia who had participated in SSOS(1). Standard qualitative methods and analysis of responses were employed. The work of ADGS will also be described. The use of ICPs in schizophrenia will be described and an analysis of variance approach to illustrate the quality improvement cycle for patients that utilizes outcomes data, including self report PRO information such as Avon. Results and Commentary: The routine collection and use of outcomes data in psychiatry is underdeveloped in most if not all psychiatric services. This is surprising given the challenges of patient management in schizophrenia and the paucity of reliable outcomes and biomarkers, and the need to assess new interventions or improve care delivered. SSOS has demonstrated that routine data collection is possible and furthermore that patients can contribute meaningfully to this process (using PROs) as recommended for future trials by the FDA(3). The use of patient reported assessments and ICPs to help improve the quality of care delivered appears a promising approach for the future.

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ID: 549532

ATTITUDES OF PATIENTS WITH SCHIZOPHRENIA AND DEPRESSION TOWARDS PSYCHIATRIC RESEARCH

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Objective: Despite considerable attention to general problems around the availability of patients suffering from psychiatric disorders for research, relatively little empirical work focusing on patients' attitudes has been done. In an attempt to replicate previous findings and extend results beyond the group of schizophrenia patients we interviewed patients suffering from schizophrenia and depression in a large academic centre regarding their attitudes towards psychiatric research in a large academic centre and a non-university psychiatric state hospital. Methods: Patients completed the "Hamburg General Attitudes to Psychiatric Research Questionnaire" a newly created self-report questionnaire. Furthermore, demographic and clinical data were collected. Illness severity was evaluated using CGI- and GAF- Scores. Results: In general, patients in the university hospital approved of psychiatric research. Patients' attitudes towards specific areas of research and research methods were rather positive. There were no significant differences between the two diagnostic groups regarding reasons for participation or non-participation in a clinical trial. In both groups the theoretical willingness to participate in studies was highest for studies using a questionnaire. It was deemed highly important by all patients to receive sufficient information about the study before taking part. Additional findings in patients treated in a non academic hospital will be available in time for the meeting. Conclusion: As our positive findings confirm and extend those of other groups, psychiatrists should be encouraged to approach patients to take part in clinical research.
ID: 549420

A LAYERED SERVICE AUDIT OF CLIENTS PRESENTING TO A COMMUNITY-BASED SERVICE FOR YOUNG PEOPLE AT INCREASED RISK FOR PSYCHOSIS

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The early detection and treatment of psychosis has been associated with a shorter duration of untreated psychosis and better clinical outcomes. The Psychological Assistance Service (PAS) is a community-based service for young people at increased risk of developing a psychotic disorder, which specialises in assessments and interventions similar to those of the Melbourne PACE clinic. Recently, we commenced a layered service audit of all presentations to PAS during the past ten-years. This project will: document the socio-demographic and clinical characteristics of the PAS clients, together with their estimated risk status; document patterns of service use in the years subsequent to PAS presentation, together with any evidence of psychosis 'transition'; and examine relationships between baseline risk status and service level outcomes. Preliminary findings from our service audit will be reported, based initially on paper-based records that we have collated in a database, which will be linked to regional electronic clinical and service utilisation records. There were 2073 clients from Jan. 1997 to Dec. 2007, 22.5% were self or family referrals and 42.1% were referred by mental health services. One-quarter (25.4%) completed a full review (ie, using the comprehensive assessment of at risk mental states, CAARMS, or equivalent). Socio-demographic, risk, referral and clinical profiles will be reported, together with service utilisation patterns over subsequent years. Among the first 500 clients with full reviews, 23.7% met criteria for 'high risk', 16.7% were experiencing their first psychotic episode, 16.3% had an 'existing psychosis', and 38.9% had another disorder (typically depression). This project provides a unique opportunity to examine service level outcomes among clients with different patterns of risk for psychosis, and to help to optimise future assessment and intervention strategies. We thank the Australian Rotary Health Research Fund for their support.
ID: 549030

CONTINUITY OF CARE AFTER PSYCHIATRIC HOSPITALIZATION

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Together with our local community mental health center, we conducted a demonstration project in which Medication Management Coordinators (MMCs) contacted psychiatrically hospitalized patients assigned to one of its clinics and followed them for six months after discharge. The program focus was on patients with schizophrenia spectrum disorders. A comparison group consisted of similarly diagnosed hospitalized patients assigned to another clinic post discharge. The roles of the MMCs were to make initial contact during the index hospitalization, to summarize the medication history for the treating inpatient and outpatient prescribers, to assess symptoms and record recent medication use at each clinic medication visit, and to provide medication education and support. Service utilization in both groups of patients was evaluated from records of the area's state and county psychiatric units, from the Medicaid database, and from clinical and administrative records of the community mental health center. Three periods were examined: 12 months prior to index hospitalization discharge date, and the subsequent two six month periods. There were 326 subjects in the MMC group and 339 in the comparison group. Of the MMC group, 208 had their initial contact with an MMC while hospitalized and 118 were first seen at a post-discharge clinic visit. The latter group was removed from the analyses reported here. A striking finding was the frequency of patients having no medication visits to the clinics in each time period. During the baseline period 57% of the entire group had no recorded medication visits. During the period after the index hospitalization this number decreased to 38%, but is unacceptably high for a group with recently exacerbated psychoses. There was evidence that being seen by an MMC prior to hospital discharge promoted coming in for a medication visit within 30 days. Of the patients not coming to clinic within 30 days, 71% were in the comparison group and 29% in the MMC group. The MMC group had significantly more clinic visits, but the groups did not differ in hospitalizations or days in the hospital during the intervention or follow-up periods. These data illustrate lack of engagement of many patients in post-hospital care. The MMC intervention improved clinic show rates within 30 days, but it is clear that other approaches must also be used in dealing with the lack of engagement problem.
ID: 548021

THE COST OF RELAPSE FOR SCHIZOPHRENIA: A COMPARISON OF A STATE HOSPITAL, A PRIVATE CONTRACTED SERVICE AND A STATED COMMUNITY ATTENDANCE

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Objective: Relapse is an important component of the high overall cost for Schizophrenia. The main objective of this survey is to compare the cost of relapse in the three main settings where acute patients are admitted in the city of Sao Paulo: a Public Hospital (PH); b) a Private Hospital partner of the Public Health System (PHP; and c) a Psychosocial Center for Community Care (CAPS). Methods: 30 randomly selected records of acute admissions in each setting ($n = 90$) were selected for the year 2006. Costing of the admissions included resources like medication, tests and consultations (medical and other professionals), food, hosting, and service administration. Results: The total Medical-Hospital Direct Cost for relapse in schizophrenia, per patient, was 8.167,58 reais ($4950) in PH; 4.605,46 reais ($2791) in CAPS and 2.397,74 reais ($1453) in PHP. The main component of cost was related to human resources (42 a 75%) The cost of medicines varied according to the extent of using typical or atypical antipsychotics: typical antipsychotics were more used in the PHP and atypical in the community centers (CAPS). Conclusion: The highest cost of relapse was found to be in the public hospital and the lower cost in the private hospital partner. The management of the crisis in the community centers presented a intermediary cost, but patients were more likely to be under treatment of atypical anti-psychotics. Therefore, treating patients in the community had an intermediary cost between Public Hospitals and Contracted Private partners, with the benefit of treating the patient closer to his/her family, with fewer adverse events and quality of life.
ID: 543752

THE FIRST THREE YEARS OF PHARMACOTHERAPY IN PATIENTS WITH PSYCHOTIC DISORDERS: A COMPARISON BETWEEN THE EARLY INTERVENTION PROGRAMME AND STANDARD CARE SERVICE IN HONG KONG

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This naturalistic study reviews the use of antipsychotics in patients with psychotic disorders in the first three years of psychiatric treatment. This historical-controlled study included 700 patients first presented to the local early intervention programme (EI) from 2001 to 2003, and 700 patients first presented to standard care service (SC) from 1998 to 2001. The data were systematically extracted from medical records according to operationalized definitions. In the EI group, 22.2% of cases were prescribed atypical antipsychotics as the initial pharmacotherapy, which increased to 59.4% and 58.7% in the first and second switches of antipsychotics respectively. Respective statistics in the SC group (6.3%, 19.5% and 23.4%, all p-value <.001) were significantly lower than the EI group. In EI, the three most frequently prescribed antipsychotics in initial treatment were conventionals: haloperidol (28.6%), trifluoperazine (23.7%) and sulpiride (14.5%). First switch of antipsychotics was mainly risperidone (22.0%), olanzapine (19.3%) and sulpiride (11.1%). Second switch of antipsychotics was mainly to olanzapine (19.9%), risperidone (13.6%) and sulpiride (10.7%). In SC, the three most frequently prescribed antipsychotics in the initial treatment were haloperidol (32.1%), trifluoperazine (26.6%) and chlorpromazine (12.7%). First switch of antipsychotics were mainly conventional antipsychotics, which were trifluoperazine (15.3%), sulpiride (15.0%) and chlorpromazine (11.1%). The second switch of antipsychotics was similar to the first switch: sulpiride (16.9%), chlorpromazine (14.9%) and trifluoperazine (12.9%). In the first three years of psychiatric treatment, the findings revealed that early intervention programme in Hong Kong had a different practice in prescribing antipsychotics. Atypical antipsychotics were more widespread in use in the EI group while conventional antipsychotics remained to be the major pharmacotherapy in the SC group. This study was fully funded by Health and Health Services Research Fund, by Food and Health Bureau, The Government of the Hong Kong Special Administrative Region. The reference number is 03040141.
ID: 550953

MANAGEMENT OF ANTIPSYCHOTIC MEDICATION ASSOCIATED OBESITY

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The primary objective of this research proposal is to elaborate and test the effectiveness of a program to combat the most serious side effect of antipsychotic medication treatment, obesity, in severely mentally ill patients. Specifically, we wish to test the effect of the Lifestyle Balance (LB) program, a year-long psychoeducational intervention, on knowledge about healthy lifestyles and determine if the classes along with a prescribed diet and exercise regimen improve patients' metabolic profiles, cardiovascular risk factor status, and mental health compared to usual psychiatric treatment. A secondary objective of the LB program is to learn what the barriers are to achieving weight loss in this population, and to try to create a program that psychotic individuals will master that are easily implemented in any psychiatric setting and can be taught by almost any mental health staff. 120 patients with severe mental illness, identified as having gained weight resulting in obesity (an increase in body weight of 7% or more, or a BMI greater than 25) while taking an antipsychotic medication, were referred for this one year randomized research program. Each patient's medications, mental status, cardiovascular risk factors and metabolic status are carefully evaluated at baseline and then quarterly. Patients are interviewed to assess their mental status, insight into their mental illness, and knowledge of healthy lifestyles, diet, exercise, and nutrition. Patients were randomized to either usual care (UC) or to the LB program. The LB program includes standardized classes, meetings with a dietician, exercise sessions, field trips, and rewards to promote healthy eating and an active lifestyle. We have enrolled 109 patients after 30 months of recruitment, 53 to LB and 56 to UC. So far, 59 of these patients have completed at least the first 6 months of the study, 45% from LB and 54% from UC. Among LB participants, 37% lost weight by month 6, 52% maintained their weight, and 11% continued to gain weight. Among those in UC, 16% lost weight by month 6, 46% maintained their weight, and 38% gained weight. Weight change was defined as being five or more pounds above or below baseline weight. To date the average LB participant lost .13 lbs per week over the 52 weeks, while the average UC participant gained .1 lbs/week. There was a statistically significant difference in weight between the two groups ($F = -25$; df 1,935; $P = .01$) utilizing a random intercept model.
ID: 551919

HIGH UTILIZERS OF INPATIENT STATE HOSPITAL SERVICES

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High utilization of the local state hospital services by a small proportion of the population accounts for a large proportion of inpatient services for clients of the area community mental health center (CMHC). Reduction of inpatient hospital services requires detailed characterization of the high utilizer population to design and implement interventions. The primary objective is to describe high utilizers of inpatient state hospital services in Bexar County, Texas. State hospitalization use data was obtained for patients assigned to the area CMHC from September 1, 2006 to January 31, 2008. "High utilizers" were patients with ≥3 hospitalizations having an admission and/or discharge date within the study period. The number of high utilizers; number of hospitalizations/patient; average length of stay/hospitalization; total bed days/patient; diagnosis; outpatient activity and service level status; most recent outpatient clinical contact; and outpatient chart availability were examined. 80/1150 hospitalized patients (7%) met the definition of "high utilizer". 85% of the high utilizer population had 3–4 hospitalizations. The average length of stay/hospitalization was 37.8 days. The average total number of bed days/patient was 124. High utilizers accounted for 19.2% of the total hospital days for the entire hospitalized population. 74% of the population had a schizophrenia spectrum disorder. Outpatient psychiatric clinic status was "closed" for 38/80 (48%) patients,

meaning they were not currently receiving any mental health services from the CMHC. 18/42 (43%) patients with "open" charts were receiving ACT services. Fifty-four high utilizers (68%) had CMHC charts available for review. Of these, 18 only had a CMHC intake interview, 7 patients had only one outpatient follow up visit, and 29 patients had multiple outpatient follow up visits. Many high utilizers of inpatient state hospitalization services in Bexar County do not engage in outpatient treatment despite being assigned to the CMHC. Further analyses of clinical and demographic characteristics that differentiate engaged versus non-engaged high utilizers are planned.
ID: 551764

RISK ADJUSTMENT MODEL FOR HOSPITAL ADMISSION IN AN EARLY PSYCHOSIS TREATMENT SERVICE

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Background: Risk adjustment models are required in order to compare outcomes between early psychosis treatment services (EPTS) while taking into account case mix differences. Objectives: To develop a risk adjustment model for comparison of EPTS programs with respect to a key outcome measure: admission to hospital within one, two and three years of admission to the EPTS. Methods: A literature review was performed to identify potential risk adjustment variables for hospital admission. A panel of experts identified a set of candidate risk adjustment factors for hospital admission. Risk adjustment models were then developed and tested using data from one cohort of early psychosis patients ($n = 279$) and validated using data from a second cohort of early psychosis patients ($N = 300$). Eleven potential risk adjustment variables were age, gender, ethnicity, marital status, hospitalization prior to enrollment in EPTS, initial Global Assessment of Functioning (GAF) and Positive and Negative Symptom severity (PANSS) scores, co-morbid major depression, co-morbid substance abuse, and duration of untreated psychosis (DUP). Multivariable logistic regression modeling was employed. C-statistics (a measure of model discrimination) were calculated to assess model performance. Results: In the development data, preliminary results indicate that prior hospitalization was the only significant predictor for hospital admissions within one year of enrollment to the EPTS (OR = 1.88, 95%CI 1.01–3.52). Hospital admissions after two and three years were significantly associated with higher levels of initial positive symptoms (OR = 1.07, CI 1.02 – 1.13; OR = 1.07, CI 1.01–1.12) respectively and prior hospitalizations (OR = 2.73, CI 1.52–4.88; OR = 3.35, CI 1.88–5.98) respectively. The performance of the logistic modeling was good, with C-statistics ranging from 0.72 to 0.74 for the three outcomes. In the validation data, the C-statistics were slightly lower, ranging from 0.62–0.72. Conclusions: The C-statistic values indicate that this will be a useful method, and we are continuing our analyses to assess which variables to include in the final model.
ID: 551514

RECOVERY AND SCHIZOPHRENIA: EVALUATION OF A RECOVERY-BASED EDUCATIONAL PROGRAM

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Project GREAT (Georgia Recovery-Based Educational Approach to Treatment) developed an educational curriculum based on the SAMHSA-defined (2006) ten "Fundamental Components of Recovery". As an initial evaluation, we examined effects of the training program on recovery-based knowledge and recovery-consistent attitudes by comparing our clinicians (n = 43) knowledge and attitudes to those of a similar group of clinicians (n = 34) at a neighboring medical institution who did not receive the intervention and training. Clinicians knowledge and attitudes were assessed using a 26-item Recovery Knowledge Questionnaire developed for this project, by the Recovery Knowledge Inventory (Bedregal, O'Connell, and Davidson 2006), by the Recovery Attitudinal Pre-Post Survey (Cook, Jonikas, and Razzano 1995) and by the Attribution Questionnaire–27 (AQ-27; Corrigan, Watson, Warpinsky, and Gracia 2004). Clinicians showed significant change in three of the four measures (both knowledge and one attitude measure) but still demonstrated no significant change in their adoption of stigmatizing attitudes toward consumers as measured by the AQ-27. The clinicians receiving the educational intervention had significantly higher scores than the comparison group for both recovery knowledge measures and more recovery-promoting attitudes, although as important limitations these comparisons were constrained by differences in baseline pre-test scores between both groups, by sample size and by the use of self-report attitudinal scales. While these results at least suggest the potential benefit of a Recovery-based Educational Program, whether knowledge and attitude change then produces meaningful behavioral change is of course another, more fundamental question.
ID: 551383

A CASE-CONTROLLED STUDY ON THE OUTCOME OF AN EARLY INTERVENTION PROGRAMME FOR PSYCHOSIS (EASY)

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In an attempt to improve the outcome for psychotic disorders, the EASY (Early Assessment Service for Young People with Psychosis) programme was launched in Hong Kong in 2001. Being one of the first in Asia, it comprised of two major components, namely early detection and critical period intervention. Comparison was made with a matched historical control group under standard care where the first psychotic episode was usually managed under in-patient care, followed by relatively sparse outpatient visits with little psychosocial support. The EASY service provides specialised multidisciplinary team to offer a comprehensive package of intervention targeting the specific needs of patients and their carers at this stage of the disorder. It adopts a case-management approach and assertively follows first-episode patients for 2 years after the initial episode. Results at three years showed that EI patients had fewer days in hospital, better functional outcome, lower likelihood of disengagement from service, and less aggressive behaviour, completed suicides or suicide attempts. No significant difference was found for relapses and the duration of untreated psychosis

(DUP) suggesting that in Hong Kong, the improved outcome was not mediated by these two variables. The present study suggests that early psychosis programme in Hong Kong is successful in improving the 3-year outcome of psychotic disorders. The effect appears to be attributable to improved intervention rather than to a reduction of DUP, relapses or atypical medication.
ID: 551148

THE UK MENTAL HEALTH RESEARCH NETWORK: LARGE SCALE TRIALS FOR NON-DRUG INTERVENTIONS IN SCHIZOPHRENIA

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The UK Mental Health Research Network has been funded by the UK Department of Health since 2005 to provide the clinical and scientific infrastructure to run large scale externally-funded trials and cohort studies. It comprises a coordinating centre run jointly from the Institute of Psychiatry, London, and the University of Manchester and a network of 8 research hubs. Each research hub contains a University department and a series of linked clinical sites and total population covered is about 50% of England or 20 million people. Input from patient and carer groups is standard. Links to industry, primary care and social care are important and links to other European mental health research networks are developing. The main aims of the network are quality assurance of study design, to accelerate start-up of multi-centre research projects, ensure timely recruitment to target and provide secure web-based data entry. The network hosts 130 studies in its current portfolio totalling research costs in excess of $100 million, across all disease areas in mental health. Three examples of large scale studies in schizophrenia will be discussed: two multisite randomised controlled trial of psychological interventions for psychosis, one in dual diagnosis (sample recruited 230) and one for at risk prodromal mental states, and one cohort study in first episode psychosis (sample recruited 680).
ID: 551094

INTEGRATING UHR RESEARCH AND PRACTICE INTO THE PUBLIC HEALTH AGENDA: THE BIRMINGHAM ED:IT PROGRAMME

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The ED:IT programme has been in operation since 2000 and is a core service of the Birmingham Early Intervention in Psychosis service; both are embedded within a youth mental health services structure. The function of ED:IT is to reduce DUP across the city by one of two strategies: engaging and intervening with youth at high risk of psychosis and by a unique public health programme across the city targeting 'at risk' populations, communities and key care pathways. This includes a focus on the minority ethnic communities and their care pathways, neighbourhoods with high incidence of psychosis and primary care. UHR youth are accessed via help seeking pathways, including schools and colleges, counselling, drug agencies and primary care. We illustrate the pathways approach using data from the

UK National Evaluaton of Early Intervention Services that we lead (National EDEN) and the EU Prediction of Psychosis (EPOS) project in which we are co-grantholders and a collaborating site. Funding for a 5-year public health programme to reduce DUP and UHR transitions has recently been won from the UK Department of Health, to begin in April 2009. This brings together the unique public health strands of ED:IT to reduce DUP across Birmingham (pop 1.2m) from 12 to 3 months. This research programme will be described and how it fits in with previous population based studies.
ID: 552120

TYPICAL V ATYPICAL ANTIPSYCHOTICS: WHAT ARE PATIENTS' VIEWS AND EXPERIENCE?

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Introduction: RCTs have limitations as a means of assessing effectiveness and adverse impact on patients. Many therapeutic advantages and adverse consequences are only identified post launch from observational studies and patient feedback. While RCTs have an important role in assessing efficacy, there is a need for complimentary studies which report patients' experience of treatments. This approach has been utilized in other healthcare areas, and in psychiatry in the Scottish Schizophrenia Outcomes Study, SSOS (Hunter etal 2008). Importantly the FDA has also recommended that Patient Reported Outcome Measures should be part of the portfolio of assessments employed in clinical trials. In this paper we report the results of a large survey of psychiatric patients in Scotland to elicit a wide cross-section of views from people currently treated with antipsychotic and other medication. Method: A standard survey form was developed and distributed thru a major mental health charity, (Scottish Association for Mental Health), including the SAMH website. The survey form was completed by service users and returned to the research team; a number of focus groups were also held across Scotland. Data analysis was undertaken independently at the University of Strathclyde. The results were interpreted in the light of clinical experience and evidence from trials such as CATIE. Results: A total of 1012 participants completed and returned survey forms. Of these, 76% were analyzable, with equal numbers of M and F participants; 61% aged 30–49; diagnoses: 47% depression, 22% schizophrenia, 21% anxiety disorder and 20% bipolar disorder. Only 50% of respondents reported satisfaction with treatment experience and doctor. This report describes respondents' views on the usefulness and adverse effects of antipsychotics, comparing first and second generation; in addition participant views on antidepressants, mood stabilizers and anxiolytics will be presented. Comment: Successful healthcare requires partnership with service users: this is particularly important in psychiatry. This survey provides useful information on the experience of medication of a large and representative sample of people with severe and enduring mental disorders in the UK. Despite concerns about insight and subjectivity, the views of participants using inexpensive methods are consistent with results from CATIE.

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ID: 553679

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ROLE OF MYELINATION GENES IN VIRALLY-INDUCED BRAIN DISORDER IN MOUSE: A DNA MICROARRAY AND MRI STUDY

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Maternal viral infection is known to increase the risk for schizophrenia in the offspring (Fatemi et al. 2008). We sought to pursue the effects of E16 (middle 2nd trimester) infection on brain morphology and gene expression, at postnatal days 0, 14, 35 or 56, in virally-exposed ($N = 4$) or sham-infected controls ($N = 4$) offspring. Brains were fixed for MRI or homogenized and subjected to DNA microarray. Morphometric analysis of brain following infection of C57BL/6 mice at E16 revealed numerous defects. The area for hippocampus at P35 and cerebellum at P14 were both reduced ($P < .014$ and $P < .029$, respectively). Overall brain volume was reduced at P14 ($P < .018$) and ventricle volume was reduced at P0 ($P < .025$). Moreover, fractional anisotropy (FA) revealed the following changes: decrease in white matter thickness in the internal capsule (IC; right) at P0 ($P < .033$); and increases in white matter thickness in the corpus callosum at P14 ($P < 0.024$) and the middle cerebellar peduncle (MCP; right) at P56 ($P < 0.006$) Microarray analysis of brains from exposed C57BL/6 mice following infection at E16 showed a significant ($P < .05$) at least 1.5 fold up- or downregulation of genes in frontal (151 upregulated and 35 downregulated at P0; 106 upregulated and 86 downregulated at P14; and 107 upregulated and 118 downregulated at P56), hippocampal (300 upregulated; 190 downregulated at P0; 33 upregulated and 45 downregulated at P14; and 86 upregulated and 17 downregulated at P56), and cerebellar (26 upregulated and 72 downregulated at P0; 204 upregulated and 15 downregulated at P14; and 449 upregulated and 204 downregulated at P56) areas of virally-exposed mouse offspring ice. Quite interestingly, myelin related genes (MAG, MBP, MOBP, MOG) were significantly upregulated in cerebella of P14 offspring of virally-exposed mice, explaining the increased FA (increased white matter) in the right middle cerebellar peduncle. These results implicate long-term effects of viral infection in utero on brain development in the mouse progeny. The generous support by the National Institute for Child Health and Human Development (5R01-HD046589-04) to S.H.F. is greatly appreciated.

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ID: 549084

THE IMPACT OF ADVANCED PATERNAL AGE ON INTERMEDIATE PHENOTYPES RELATED TO NEURODEVELOPMENTAL DISORDERS

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Epidemiological evidence suggests that advancing paternal age leads to an increased risk of various adverse health outcomes in offspring, including schizophrenia and autism. The biological mechanisms underlying these associations are not known. However, because there are many more germ-line cell divisions in the life history of a sperm relative to that of an oocyte there may be more opportunities for copy errors in germ cells from older fathers. Here we report data on various behavioural and neuroanatomical parameters related to schizophrenia and autism from a mouse model of Advanced Paternal Age (APA). Young and aged C57Bl/6J males (4 versus 18 months) were mated with 4 month old females. Adult (4 month old) offspring were examined using a comprehensive behavioural test battery to establish that APA induced no gross morphological or neurological abnormalities. Next tests incorporating animal models of anxiety (elevated plus-maze), exploration (holeboard test), sensorimotor gating (PPI), locomotion (open field test), working memory (8-arm radial maze) and spatial memory (Morris water maze) were examined. Brain anatomy in these same animals was assessed using the 16.4 Tesla microimaging facility (Bruker BioSpin; Centre for Magnetic Resonance, Univ. of Qld). The adult offspring of older sires (APA group) differed significantly from the offspring of younger sires on a range of behaviours related to exploratory and 'anxious' phenotypes. The APA group spent significantly less time on the open arms of the elevated plus maze than the control group. The APA group also performed significantly fewer head dips and bouts of rearing on the elevated plus maze, had significantly more head dips in the hole board test and showed reduced rearing behaviour in the open field. There were no significant group differences for the other behavioural measures. Analysis of brain structure using MRI indicated that the male APA adult offspring had a significantly enlarged cerebral cortex compared to control male mice. Taken together these data reveal subtle changes in behaviour and altered brain morphology as a consequence of APA. These findings do not map neatly onto animal models of schizophrenia, but are more reminiscent of animal models related to autism (anxiety, cortical overgrowth). Future animal studies will allow us to refine the behavioural and structural phenotype and explore genetic and epigenetic mechanisms that may underpin these changes.
ID: 550168

EARLY GLUTATHIONE DEFICIT IMPAIRS PARVALBUMIN EXPRESSION IN GABA INTERNEURONS AND KAINATE-INDUCED GAMMA OSCILLATIONS

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An increased oxidative stress and alteration of the antioxidant systems have been observed in schizophrenia. Glutathione (GSH), a major redox regulator, is decreased in patients' cerebrospinal fluid, prefrontal cortex in vivo and striatum post-mortem tissue. Most importantly, there is genetic and functional evidence for the implication of the gene of the glutamate cysteine ligase (GCL) catalytic subunit, the key GSH-synthesizing enzyme. We have developed animal models for a GSH deficit to study the consequences of such deficit on the brain development. A GSH deficit combined with elevated dopamine (DA) during development leads to reduced parvalbumin (PV) expression in a subclass of GABA interneurons in rat anterior cingulate cortex (ACC). Similar changes are observed in post-mortem brain tissue of schizophrenic patients. GSH dysregulation increases vulnerability to oxidative stress, that in turn could lead to cortical circuit anomalies in the schizophrenic brain. In the present study, we use a GCL modulatory subunit (GCLM) knock-out (KO) mouse model that presents up to 80% decreased brain GSH levels. During postnatal development, a subgroup of animals from each genotype is exposed to elevated oxidative stress induced by treatment with the DA reuptake inhibitor GBR12909. Results reveal a significant genotype-specific delay

in cortical PV expression at postnatal day P10 in GCLM-KO mice, as compared to wild-type. This effect seems to be further exaggerated in animals treated with GBR12909 from P5 to P10. At P20, PV expression is no longer significantly reduced in GCLM-KO ACC without GBR but is reduced if GBR is applied from P10 to P20. However, our result show that GCLM-KO mice exhibit increased oxidative stress, cortical altered myelin development as shown by MBP marker, and more specifically impairment of the peri-neuronal net known to modulate PV connectivity. In addition, we also observe a reduced PV expression in the ventro-temporal hippocampus of adult GCLM-KO mice, suggesting that anomalies of the PV interneurons prevail at least in some brain regions throughout the adulthood. Interestingly, the power of kainate-induced gamma oscillations, known to be dependent on proper activation of PV interneuron's, is also lower in hippocampal slices of adult GCLM KO mice. These results suggest that the PV positive GABA interneurons is particularly vulnerable to increased oxidative stress.
ID: 550998

PREFRONTAL NEURONAL ARCHITECTURE IS DISRUPTED IN THE RAT PRENATAL STRESS MODEL OF SCHIZOPHRENIA

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Although the etiology of schizophrenia remains a mystery, it is clear that both genetic and environmental factors can confer risk for the illness. Maternal stress, malnutrition, and viral infection during pregnancy—events which activate the hypothalamic-pituitary-adrenal axis—increase the risk that the offspring will later develop schizophrenia. Our laboratory has developed a paradigm in which maternal stress during the final week of rat gestation alters the offspring's HPA axis, neurodevelopment, and behavior in ways that are consistent with the pathology observed in schizophrenia (Koenig et al., 2005; Lee et al., 2007). In the present experiment, we hypothesized that exposure to gestational stress would result in reduced dendritic spine density and dendritic tree complexity of pyramidal neurons in layer III of the prefrontal cortex, as is observed in post-mortem tissue from individuals who suffered from schizophrenia (eg, Glanz and Lewis '00). Sprague-Dawley dams were exposed to repeated variable stress during days 14–21 of gestation. Male and female offspring of stressed and control dams were examined at multiple postnatal timepoints, and brains were processed using a Golgi Cox tissue preparation. Results support the hypothesis that prenatal stress reduces dendritic complexity of layer III pyramidal neurons in the prefrontal cortex. Interestingly, the treatment effect interacts with sex such that males, but not females, show reduced dendritic complexity as a consequence of prenatal stress. Thus the normal sex difference (male>female) in dendritic complexity is eliminated by exposure to prenatal stress. This pattern of results was observed both prior to (day 20) and following (day 56) puberty. Reductions in dendritic complexity among males exposed to prenatal stress were more striking in the basilar dendritic tree compared to the apical. The greater vulnerability of the male prefrontal cortex to gestational stress may be relevant to the finding that schizophrenia is approximately 40% more prevalent among men compared to women (Aleman et al. '03; McGrath et al. '04). Future experiments will test the hypothesis that gene expression in the prefrontal cortex and cognitive behavior supported by this region are also disrupted following prenatal stress as they are in schizophrenia. This work was supported by NIH grants MH067533 (J.A.M.) and RO1 MH073826 (J.I.K.).
ID: 551760

A LONGITUDINAL STUDY OF THE EMERGENCE OF POSTNATAL NEUROANATOMICAL ABNORMALITIES IN NON-HUMAN PRIMATES EXPOSED TO IRRADIATION IN UTERO: A NEURODEVELOPMENTAL MODEL OF SCHIZOPHRENIA

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Prenatal perturbation of brain development is associated with an increased incidence of schizophrenia. Yet symptoms of schizophrenia most often are not expressed until adolescence or even adulthood. In this study prenatal exposure to x-irradiation was used to disrupt neurogenesis in non-human primates in order to model the neurodevelopmental origin of schizophrenia. Here we examine the temporal emergence of neuroanatomical changes in macaques exposed prenatally to irradiation. Magnetic resonance scans were collected at 6 months, 12 months, 3 years, and 5 years of age in macaques exposed to x-irradiation ($N = 5$) or sham-irradiation ($N = 5$) during early gestation (E30–41). Volumes of the whole brain, cortical gray matter, striatum (caudate, putamen, nucleus accumbens), and the thalamus were compared between cohorts at each of the four ages. Irradiated monkeys showed reduced volume in all structures examined at all four ages. The magnitude of reduction of whole brain volume remained relatively constant (10–15%) with increasing age. In contrast, volumetric deficits of cortical gray matter, thalamus, and striatal structures became disproportionately larger with age in irradiated individuals, with thalamus (10–20%) and putamen (12–25%) showing the most pronounced reductions at older ages. These results indicate that disruption of neurogenesis during early gestation results in progressive volume loss in multiple brain structures during postnatal ontogeny and ultimately produces a global pathology resembling that of schizophrenia. These findings also provide biologic support for the concept that small prenatal changes may produce larger effects in adulthood. Work supported in part by MH071616, T32MH17104, and University of Missouri Department of Pathology and Anatomical Sciences.
ID: 551677

DEVELOPMENTAL REFINEMENTS IN PRIMATE PREFRONTAL CORTICAL CIRCUITRY

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In schizophrenia, working memory dysfunction is associated with altered GABA transmission in the prefrontal cortex (PFC). In primate PFC, the functional maturation of the synaptic connections of certain classes of GABA neurons is complex. For example, the levels of pre- and post-synaptic proteins that regulate GABA neurotransmission from chandelier GABA neurons to the axon initial segment (AIS) of pyramidal neurons undergo marked changes perinatally and during adolescence. To understand the molecular mechanisms driving these developmental refinements, we quantified the densities and lengths of pyramidal neuron AIS immunoreactive for ankyrin-G, BIV spectrin, or gephyrin, three proteins involved in regulating synapse structure and receptor localization, in the PFC of rhesus monkeys. Ankyrin-G- and BIV spectrin-labeled AIS declined in density and length during the first 6 months postnatal, but then remained stable through adolescence and into adulthood. In contrast, the density of gephyrin-labeled AIS was stable until approximately 15 months of age and then markedly declined during adolescence. Thus, molecular determinants of the

structural features defining GABA inputs to pyramidal neuron AIS undergo distinct developmental trajectories with different types of changes occurring perinatally and during adolescence. In concert with previous data, our findings reveal a two-phase developmental process of GABA synaptic stability and neurotransmission at chandelier cell inputs to pyramidal neurons that might contribute to the protracted maturation of working memory. We also evaluated developmental shifts in the expression of GABAA receptor α1 and α2 subunits because these subunits confer different functional properties to GABAA receptors. Expression of α1 and α2 subunits, at both mRNA and protein levels, progressively increased and decreased, respectively, throughout postnatal development including adolescence. Furthermore, as predicted by the different functional properties of α1-containing versus α2-containing GABAA receptors, mIPSP duration was significantly shorter in post-pubertal than in pre-pubertal animals. Thus, the developmental shift in GABAA receptor α subunit expression continues through adolescence, inducing a marked change in the kinetics of GABA neurotransmission. Since levels of GABAA receptor α1 and α2 subunits and ankyrin-G are altered in schizophrenia, disturbances in these developmental shifts might give rise to PFC dysfunction in the illness.
ID: 551591

DIFFERENTIAL TERMINAL EXPRESSION OF GAD67/GAD65-RELEVANCE TO SCHIZOPHRENIA

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The presynaptic strength of GABA neurotransmission is partially determined by the amount of terminal GABA available for release. Terminal GABA is synthesized locally by GAD67 and GAD65 proteins whose activities are differentially regulated. By expressing both GAD isoforms an interneuron has more flexibility in the regulation of GABA synthesis. Reduced expression of GAD67 mRNA is perhaps the most replicated pathological disturbance in schizophrenia. Although reductions in GAD67 expression may lead to reduced GABA synthesis, resulting in weaker GABA neurotransmission, the degree to which different classes of interneurons depend on GAD67 versus GAD65 for terminal GABA synthesis is unknown. Using an imaging methodology that allows for the quantification of fluorescently-labeled puncta (putative axon terminals), the colocalization of different labels in the same terminal, and the quantification of fluorescence intensity in these same structures, we examined, in the monkey prefrontal cortex, the level of GAD67 and GAD65 protein in the terminals of three types of GABA neurons, each of which is thought to underexpress GAD67 mRNA in schizophrenia: parvalbumin expressing chandelier (PVch) and basket (PVb) neurons, and cannabinoid receptor expressing basket (CB1rb) neurons. PVch interneurons were found to almost exclusively contain GAD67 in their terminals. In contrast, both GAD65 and GAD67 were easily detected in PV-immunoreactive terminals that presumably belong to PVb interneurons. Interestingly, there appeared to be at least two subpopulations of CB1rb interneurons: those that had high levels of terminal GAD65 and almost undetectable levels of GAD67; and those that had GAD67/GAD65 terminal ratios similar to PVb interneurons. Thus, of the interneuron subpopulations studied, the GAD67/GAD65 terminal ratio is highest in PVch, and lowest in a subpopulation of CB1rb interneurons. The finding that the terminals of PVch, PVb, and CB1rb

interneurons contain different levels of GAD65 and GAD67 protein suggests that these cells might be differentially affected by reductions in GAD67 mRNA expression. For example, a reduction in GAD67 expression would be more likely to negatively affect the activity of PVch interneurons (high GAD67/GAD65 terminal ratio) than those neurons with an inverse ratio (eg, certain CB1rb). These findings provide crucial information needed to formulate hypotheses about the cell type-specific consequences of the GAD67 mRNA reduction in schizophrenia.
ID: 551386

MODULATION OF PCP-ASSOCIATED METABOLIC NETWORKS IN THE RAT BRAIN BY ATOMOXETINE

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Cognitive and negative deficits in schizophrenia are likely to be reflected in abnormal metabolic patterns in neural networks. Approaches such as Principal Component Analysis can be used to identify metabolic patterns. We used a low dose PCP treatment regime in rats to mirror the pathophysiology of schizophrenia and tested whether atomoxetine, a putative procognitive drug, modulated PCP-associated alterations in metabolic networks. Rats were treated with vehicle or PCP for 5 days (2.5 mg/kg, i.p.). Three days later animals received vehicle or atomoxetine (0.5 mg/kg i.p.) followed by an iv bolus of 14C-2-deoxyuglucose. Autoradiographic measurements of 2-deoxyglucose uptake were taken in 40 regions of interest. Principal component analysis (PC) was used to identify spatial covariance patterns in the four treatment groups. In the vehicle group PC1 (51.9% of total variance) high loadings were found for the retrosplenial cortex and orbital cortex. PC2 (21.9% total variance) showed high loadings for the nucleus accumbens and prefrontal cortex. In the PCP group PC1 (67.1% of total variance) was a large scale network with high loadings for the prefrontal cortex, cingulate cortex, sensory and psychomotor-related areas. PC2 (16.4% total variance) included the lateral lemniscus and PC3 (6.5% total variance) consisted predominantly of hippocampal subregions. In the atomoxetine-PCP group, PC1 (69.6% of total variance) comprised of a smaller scale network of 9 regions with high loadings for the prefrontal cortex and cingulate cortex. Compared to the PCP group, low loadings were found in the frontal association cortex, ventral and lateral orbital cortex, septum and subiculum. This suggests that atomoxetine modulates PCP-associated metabolic networks. In conclusion, multivariate analysis at the group level can be used to study the effects of cognitive modulators on metabolic networks in an animal model of schizophrenia.

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SCHIZOPHRENIA-LIKE BEHAVIORAL ABNORMALITIES FOLLOWING PRENATAL MATERNAL IMMUNE SYSTEM ACTIVATION ARE PREVENTED BY PRE-TREATMENT WITH RISPERIDONE

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There is an increased interest in the prodromal stage of schizophrenia as an optimal stage to begin intervention with anti-psychotics. Neurodevelopmental models of schizophrenia, which mimic the characteristic maturational delay of the disorder, offer a valuable tool for the investigation of preventive interventions. Here we show that adult offspring of dams exposed to the viral mimic polyinosinic-polycytidilic acid (poly I:C, 4mg/kg) on gestation day 15, display selective attention deficit as manifested in the loss of latent inhibition (LI) and abnormally rapid reversal learning. However, treatment of the offspring with the atypical antipsychotic drug risperidone (0.045 mg/kg) on postnatal days 34–47 prevented the development of both behavioral deficits, assessed 50 and 80 days after cessation of pre-treatment. A higher dose of risperidone (1.2 mg/kg) prevented only rapid reversal learning. Given that maternal infection is a known risk factor for schizophrenia, our results support the clinical findings that treatment with drugs such as risperidone, during the prodromal stage may have some protective effect at least in the short term, reducing risk of progression to first-episode psychosis, or delaying the onset of psychosis.
ID: 546874

RECEPTOR BINDING PROFILE OF LURASIDONE: A NOVEL PSYCHOTROPIC AGENT UNDER DEVELOPMENT FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Lurasidone is a novel psychotropic agent under development for the treatment of schizophrenia and bipolar disorder. Lurasidone has been reported to reverse MK-801-induced impairment in learning and memory in the passive-avoidance test (Ishiyama et al. Eur J Pharmacol 2007;572:160–170), and Morris water maze and radial maze (Enomoto et al. Behav Brain Res 2008;186:197–207). The reversal of MK-801-induced cognitive impairment in these tests has been found to be more potent than the effects of other atypical antipsychotics. We summarize here *in vitro* studies designed to characterize the receptor binding profile of lurasidone. Methods: We evaluated the receptor binding affinities of lurasidone and several antipsychotic drugs with radioligand binding assay. Compounds were tested under comparable assay conditions using various receptor preparation. Results: Lurasidone was found to have high affinity for dopamine D2 and serotonin 5-HT2A receptors. Compared with other atypical antipsychotics, lurasidone had notably greater antagonist activity at serotonin $5-HT_7$, $5-HT_{1A}$, and noradrenaline α_{2c} receptors. Lurasidone had minimal affinity for α_1 adrenoceptors, dopamine D_1 and D_3 receptors, serotonin $5-HT_{2C}$ receptors, and α_{2A} adrenoceptors; and no affinity for histamine H_1 and cholinergic M_1 receptors. Conclusion: The current results indicate that lurasidone has a binding profile that differs in several potentially relevant respects from available antipsychotics. Consistent with favorable effects on learning and memory in animal models, lurasidone had no affinity for muscarinic acetylcholine and histamine H_1 receptors, but a high affinity for receptors implicated in enhancement of cognitive function (eg, $5-HT_7$, $5-HT_{1A}$, α_{2c}). Because of its serotonin $5-HT_2$ antagonist and other actions including $5-HT_{1A}$ partial agonist activity, treatment with lurasidone would be expected to be associated with fewer extrapyramidal side effects than conventional antipsychotic agents. Furthermore, lack of affinity for histamine H_1 or $5-HT_{2C}$ receptors suggests that lurasidone may have a reduced potential for weight gain (and related metabolic consequences) mediated by activity at these receptors. Finally, the risk of α_1 adrenergic-mediated orthostatic hypotension would appear to be low. Confirmation of the clinical implications of the receptor binding profile of lurasidone awaits the results of recently completed, and ongoing, clinical trials.
ID: 550786

ALPHA-7 NICOTINIC RECEPTOR ACTIVATION INCREASES GLUTAMATE RELEASE IN RAT MEDIAL PREFRONTAL CORTEX *IN VIVO*

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Alpha-7 nicotinic acetylcholine receptor (nAChR) agonists are promising therapeutic candidates for the treatment of cognitive dysfunction associated with a variety of disorders including schizophrenia and Alzheimer's disease. The diverse activity of alpha7 nAChR agonists can be attributed, at least in part, to their modulation of the release of a number of neurotransmitters. Among these, alpha7 nAChR agonists have been shown to regulate release of glutamate from prefrontal cortex synaptosomes *in vitro*. Since similar effects have not been studied extensively *in vivo*, we have examined the effect of selective alpha-7 nicotinic receptor agonists on glutamate levels in the rat medial prefrontal cortex (mPFC) *in vivo* using microdialysis. An acute administration of SEN12333 (10 mg/kg i.p.) significantly ($P = .035$) increased glutamate levels in mPFC to a maximum of 224% above basal levels. Interestingly, peak elevated glutamate levels were measured > 2–3 hr after drug administration, despite the fact that maximum drug levels in the brain were detected 30 min following administration of SEN12333 (10 mg/kg i.p.). A delayed temporal profile for alpha-7 nAChR agonist stimulation of glutamate release was also observed with the selective alpha-7 nAChR agonists SSR-180711A and PNU-282987. An acute administration of either SSR-180771A or PNU-282987 (3 mg/kg i.p.) significantly increased glutamate levels in mPFC to a maximum of 128% ($P = .022$) and 230% ($P = .018$), respectively, above basal levels. Similar to our observations with SEN-12333, peak glutamate levels were observed 2.5–3 hr following administration of either SSR-180711-A or PNU-282987, while peak drug levels in brain were detected 30 min after treatment. Administration of the selective alpha7 nAChR antagonist MLA, either systemically or by local infusion directly to the mPFC via the microdialysis probe, completely blocked the SEN12333-mediated increase in mPFC glutamate. The latter observation implicates local alpha7 nAChRs in the mPFC in the regulation of glutamate release. These results provide the first detailed characterization of alpha7 nAChR regulaton of mPFC glutamate release *in vivo*. Modulation of glutamate release in the mPFC may be an important property in the potential therapeutic use of alpha-7 nAChR agonists, in particular in the context of the glutamate hypofunction hypothesis in schizophrenia.
ID: 550748

PREVENTION OF POST-PUBERTAL SCHIZOPHRENIA-LIKE BEHAVIOR AND NEUROPATHOLOGY IN THE MATERNAL IMMUNE ACTIVATION MODEL

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Schizophrenia is believed to originate in early development but is manifested symptomatically after puberty. This maturational gap raises the question of whether schizophrenia can be prevented. Studies in individuals have suggested that preventive treatment with atypical antipsychotic drugs (APDs) may reduce the risk of progression to psychosis, but identifying and treating patients in the earliest disease states presents diagnostic, ethical and methodological limitations. Neurodevelopmental animal models could considerably aid in evaluating the plausibility of prevention. We used the prenatal immune challenge model of schizophrenia which is based on the association between maternal exposure to infection during pregnancy and increased liability to schizophrenia in the offspring. In the model, the viral mimic polyinosinic-polycytidilic acid (PolyI:C) is used to activate the maternal immune system. We report that: 1. Adult offspring of dams injected with Poly I:C (4mg/kg) on gestation day 15, exhibit the hallmark structural abnormalities associated with schizophrenia, namely, ventricular enlargement and smaller hippocampal volume, as well as the hallmark cognitive deficit of schizophrenia, namely, loss of attentional selectivity; [2]Both abnormalities are not seen at prepubertal age (35 days) thus exhibiting a maturational progression characteristic of the clinical condition; [3]Pretreatment with the atypical antipsychotic clozapine during prepubertal days 34–47, prevents the emergence of both cognitive and structural abnormalities in the adult offspring. These findings show that at least some of the neuropathological processes set in motion by early insults can be halted if targeted prior to overt manifestation of behavioral abnormalities, and support the notion that treatment with atypical APDs may prevent the appearance of first-episode psychosis.
ID: 550712

NEUROPLASTICITY CHANGES IN ANIMAL MODELS OF SCHIZOPHRENIA AS TARGETS FOR INNOVATIVE TREATMENTS

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According to Carlsson's accelerator/brake hypothesis(Biological Psychiatry, 1388, 1999) schizophrenia reflects a loss of a frontal cortical brake on VTA dopamine. Evidence also suggests that both genetic and environmental factors together combine in this imbalance. This hypothesis was tested in the socially isolated and maternally deprived rat models of schizophrenia by investigating the role of mPfc dopamine receptor activation on VTA glutamate and GABA transmission. Thus dual probe microdialysis was employed in the mPfc and VTA to investigate the effects of intra-mPfc perfusion with the selective dopamine D2 receptor agonist pergolide on dialysate VTA glutamate and GABA levels. The effect of chronic clozapine (5 mg/kg i.p. daily for 10 days) on the pergolide response was also investigated. Basal dialysate glutamate levels (μM) were similar in the vehicle-treated control and isolated rat (0.435 ± 0.268 ($n = 7$) and 0.936 ± 0.720, ($n = 8$) respectively) while GABA levels (nM) were 14.41 ± 4.47 ($n = 7$) in the vehicle-treated control but were reduced by 55% to 6.53 ± 1.55 in the isolated rat ($n = 8$), $P = .0066$ v's social control. Chronic clozapine had no effect on basal dialysate glutamate or GABA levels in both

groups. Intra-mPfc pergolide (1 μM, 60 mins) rapidly reduced VTA glutamate levels by -96% ($P < .001$ v's non-pergolide-treated control, ANOVA) and VTA GABA by -24% ($P = .023$) in the social control rat and increased VTA GABA by $+90\%$ in the isolated rat ($P = .016$ v's control). Clozapine counteracted the intra-mPfc pergolide-induced reduction in VTA glutamate from -32% to $+9\%$ (v's basal) in the social control rat ($P = .0103$ v's vehicle-treated group, ANOVA) while it reversed the intra-mPfc pergolide-induced increase in VTA glutamate release to a decrease (ie, from $+23\%$ to -21%, (v's basal) $P = .0085$, ANOVA) in the isolated rat. Clozapine also reversed the intra-mPfc pergolide-induced increase in VTA GABA in the isolated rat from $+99\%$ to -9% (v's basal) ($P = .0324$ v's vehicle-treated group, ANOVA). The findings confirm a frontal cortical brake on the VTA in the social control rat operating via a frontal cortical dopamine D2 receptor regulation of both corticofugal glutamate and local interneuronal GABA release in the VTA and which is abnormal or absent in the two animal models. Furthermore, the ability of clozapine to reverse the pergolide effect in the social controls and normalize it in the isolated rat suggests a role for clozapine in maintaining this brake on the VTA.
ID: 550669

CHRONIC ANTIPSYCHOTIC TREATMENT DECREASES PHOSPHO-TRKA NERVE GROWTH FACTOR RECEPTOR LEVELS IN THE RAT HIPPOCAMPUS

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Neurotrophins including the prototype nerve growth factor (NGF) are well documented to serve important roles in mammalian neurodevelopment as well as the support and maintenance of several neuronal phenotypes in the adult. The neurobiological effects NGF are mediated by two classes of cell surface receptors, high affinity tyrosine kinase (TrkA) receptors and the low affinity p75NTR receptor. Under normal conditions, NGF binding (ie, in its processed, mature form) to TrkA promotes TrkA autophosphorylation which activates pathways that enhance neuron survival and plasticity. Interestingly, there is growing evidence that neurotrophin signaling is negatively altered in neuropsychiatric illnesses such as schizophrenia and further, that neurotransmitters known to be adversely affected in schizophrenia (eg, dopamine) can activate neurotrophin signaling pathways via G protein-coupled receptors. It is unclear; however, how the primary therapeutic agents used in schizophrenia affect neurotrophin signaling. This is important given that all currently prescribed antipsychotics serve as ligands (in most cases antagonists) at dopamine receptors. The objective of the experiments described here was to evaluate the effects of chronic treatment with commonly prescribed first and second generation antipsychotics on NGF receptor levels in the rat brain, specifically the levels of TrkA and phospho-TrkA (ie, the activated form of the receptor). Male Wistar Rats 3–4 months old were treated in their drinking water with vehicle or one of the following antipsychotics for 90 days: haloperidol 2.0, chlorpromazine 10.0, risperidone 2.5, olanzapine 10.0, or ziprasidone 12.0 mg/kg/day. Subjects were given a 14 day drug-free washout period and then sacrificed. TrkA and phospho-TrkA levels were subsequently measured in the prefrontal cortex and hippocampus by ELISA. The results indicated that the antipsychotics had little effect on TrkA levels in the prefrontal cortex or hippocampus. In contrast, while only minor effects on phospho-TrkA levels were observed in the prefrontal cortex, all five antipsychotics were associated with significant decreases (ie, by up to a 50%) in phospho-TrkA levels in the hippocampus. These data indicate that chronic exposure to both first and second generation antipsychotics may result in deleterious effects on neurotrophin signaling in a brain region known to be important for information processing and cognition.
ID: 550655

GENETIC ANIMAL MODELS TARGETING THE MOLECULAR MACHINERY OF GLUTAMATE SYNAPTIC TRANSMISSION

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Roles for glutamate neurotransmission in the pathophysiology of schizophrenia have been suggested in many lines of evidence. Possible role for D-serine, an endogenous agonist to the NMDA-type glutamate receptor has been supported by genetic and pharmacological studies. Here I overview genetic animal models targeting the molecular machinery of glutamate synaptic transmission in schizophrenia research, and present data with mice that disturb D-serine metabolism in particular. PICK1 is a multifunctional protein, and modulates serine racemase (synthesizing enzyme of D-serine), AMPA-type glutamate receptor, and dopamine transporter DAT. In PICK1 knockout mice, levels of D-serine are specifically impaired in the forebrain of neonatal stages. Behavioral changes in PICK1 mice in comparison with other types of mice with disturbance of D-serine-mediated neurotransmission will be presented. Potentials of D-serine and enzymes/regulators for D-serine metabolism for therapeutic strategies to schizophrenia will also be discussed.
ID: 550413

TYROSINE INFLUENCES ON MESOCORTICAL DOPAMINE IN THE RAT

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Dysregulation of tyrosine transport in schizophrenia has been linked to mesocortical dopamine (DA)-mediated cognitive impairment. We previously showed that tyrosine availability affected stimulated but not baseline DA levels in the medial prefrontal cortex of the rat. We now examined the ventral hippocampus (VHIPP), another mesocortical DA region implicated in schizophrenia. Male (Harlan) rats had a cannula stereotaxically implanted over the VHIPP. Two to three days later a microdialysis probe was inserted. Data collection began on the following morning. After a stable DA baseline was reached, a tyrosine- and phenylalanine-free neutral amino acid mixture (NAA(-)) was administered in two equal doses one hour apart. NAA(-) lowered tyrosine levels by approximately 50% but did not affect tryptophan levels. Baseline levels of DA, norepinephrine or serotonin did not change. The data indicate that just as in medial prefrontal cortex, baseline catecholamine levels in VHIPP are not affected by a significant lowering of tyrosine availability. Additional studies will examine stimulated catecholamine levels.
ID: 550380

DEVELOPMENTAL VITAMIN D DEFICIENCY (DVD) AND BRAIN DOPAMINE ONTOGENY

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Developmental vitamin D (DVD) deficiency is a candidate risk factor for schizophrenia. Our group has developed a rodent model of DVD deficiency. In the adult offspring from this model we have previously described alterations in both spontaneous and psychomimetic induced locomotion.

The aim of this series of studies was to explore the role of vitamin D in the development of dopaminergic systems in this model. Vitamin D deficiency is induced in female Sprague-Dawley rats by dietary restriction. Females are then mated with vitamin D normal males and the pregnant females are maintained on their respective diets during this period. At birth all maternal animals are placed on a vitamin D normal diet. The period of DVD-deficiency is therefore restricted to the gestational period only. Resultant DVD-deficient progeny were examined either as embryos, as neonates or as adults. Our findings indicate dopamine signaling is disturbed in this model. a) the superior colliculus (the proto-basal ganglia) is the site where the receptor for vitamin D is first expressed in foetal rat brain (Embryonic day E12); b) mRNA for both Nurr-1 (a nuclear transcription regulator important in dopamine neuron development) and tyrosine hydroxylase (a marker of dopamine cell maturity) are both reduced in the embryonic DVD-deficient mesencephalon by E15; c) Catechol-O-methyl transferase (a major metabolic enzyme for dopamine) was reduced in the DVD deficient neonatal rat brain; d) the dopamine metabolic profile in these brains reflected this enzymatic change. e) As adults, dopamine transporter density and/or affinity were altered in DVD deficient adult female offspring whilst DA 1 receptor density, Catechol-O-methyl transferase and dopamine cell number were reduced in DVD deficient male offspring (all $P < .05$ n $\geq$ 8). The developmental absence of vitamin D affects dopamine neuron ontogeny. We believe that alterations in dopamine metabolism and/or release mediate the behavioural sensitivity to psychomimetics displayed in this model.
ID: 550230

STRESS-INDUCED ACTIVATION OF THE VENTRAL SUBICULUM-NUCLEUS ACCUMBENS PATHWAY AND THE MODULATION OF DOPAMINE NEURON ACTIVITY

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Stress has been associated with the onset and exacerbation of several psychiatric disorders, including schizophrenia. Indeed, recent evidence suggests that stress may play a major predisposing role in the premorbid state of schizophrenia, potentially facilitating the conversion to psychosis. It has been known for some time that stressors can affect the dopamine system; specifically, exposure to acute or repeated stress will cause a sensitized behavioral response to amphetamine administration, similar to that observed in schizophrenia patients. We investigated the manner by which stress can alter dopamine system function using single-unit recordings in anesthetized rats. We found that, although single electrical shocks delivered to the foot transiently inhibited dopamine neuron firing, if the shocks were maintained there was a pronounced and sustained activation of tonic dopamine neuron population activity (ie, the proportion of dopamine neurons firing spontaneously). A similar activation of tonic dopamine neuron firing was observed following 2 hours of restraint stress. Our previous studies showed in a developmental model of schizophrenia that increases in tonic DA activity corresponded with activation of the ventral subiculum of the hippocampus and contributed to the heightened behavioral response to amphetamine. We now report that restraint stress causes an activation of ventral subicular neuron firing, as does stimulation of two stress-related systems, the basolateral amygdala and the locus coeruleus. Moreover, inactivation of the ventral subiculum reversed both footshock- and restraint-induced increases in tonic DA neuron firing. Therefore, both in an animal developmental model of schizophrenia and with stress, the dopamine system is rendered in a hyper-responsive state secondary to activation of the ventral subiculum. Such a condition may underlie the ability of stressors to exacerbate or lead to relapse in schizophrenia. Moreover, a heightened response to stress during the premorbid state may contribute to the

hippocampal damage and interneuron loss proposed to trigger the conversion to schizophrenia in late adolescence/early adulthood.
ID: 550195

CANNABINOID EFFECTS ON CANNABINOID AND SEROTONIN RECEPTOR DENSITY AND DOPAMINE RECEPTOR FUNCTIONALITY IN THE RAT BRAIN

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Cannabinoids have been shown to interact with neurotransmitter systems implicated in psychosis such as serotonin and dopamine. However, the exact mechanisms of such interactions are not fully understood especially during adolescence a critical period for both the development of psychosis and for initiation to substance abuse. In the present study, we measured cannabinoid CB1, serotonin 5HT1A and 5HT2A receptor density and dopamine D2 receptor functionality in the brain of male rats treated with the synthetic cannabinoid HU210 (25,50 or 100ug/kg, ip) for 14 days or received a vehicle for 13 days and an acute dose of HU210 on day 14. CB1, 5HT1A and 5HT2A receptor density was measured on brain sections using [3H] CP55,940 [3H]8-OH-DPAT and [3H] ketanserin respectively, whereas D2 receptor functionality was examined by measuring activation of GTP-binding proteins by the D2 agonist (R(-)-Propylnorapomorphine,(NPA). A significant dose dependent reduction in CB1 receptor density was seen in cortical, basal ganglia and limbic brain regions examined after chronic administration of HU210 with overall decreases in binding of 70.3–89.2%, 56.3–85.2% and 41.6–68.6% (p,0.01) in 100, 50, 25 μg/kg treatment groups respectively when compared with controls. 5HT1A receptor density was significantly increased in hippocampal regions CA1 (28%, $P = .028$), CA2 (31%, $P = .024$) and dentate gyrus (20%, $P = .001$) of rats treated with the 100ug/kg of HU210 for 14 days compared to vehicle treated controls. In addition, 5HT2A receptor density was significantly decreased in the caudate nucleus of rats treated with the 100ug/kg of HU210 for 14 days compared to vehicle treated controls (34%, $P = .023$). Stimulation of GTP binding proteins by NPA was significantly increased in the caudate nucleus (12.3%, $P = .01$) and cortical layers I–III (19.6%, $P < .001$) and V–VI (24.3%, $P < .001$) of rats in the same treatment group compared to controls. Interestingly, the acute dose of HU210 resulted in a significant increase in NPA stimulation of GTP binding in the caudate nucleus only (17.4%, $P < .001$).The present results may have implications for understanding the mechanisms by which cannabis may trigger psychosis in vulnerable individuals and for treating cannabis dependent individuals.
ID: 550133

HIPPOCAMPAL HYPERACTIVITY DUE TO INTERNEURON LOSS ACCOUNTS FOR DOPAMINE HYPER-RESPONSIVITY AND DIMINISHED OSCILLATORY ACTIVITY IN MAM MODEL OF SCHIZOPHRENIA

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Recent imaging data suggest that the psychosis in schizophrenia is correlated with an increase in baseline activity within the hippocampal complex.

We have recently shown that in a rat developmental disruption model of schizophrenia, there is hyperactivity within the ventral subiculum of the hippocampus. Moreover, this hyperactivity causes an increase in the number of dopamine neurons firing spontaneously, thereby increasing the amplitude of a phasic burst response to stimuli. As a result, stimuli would produce an overactivation of dopamine neuron activity and pathologically high levels of dopamine release within the limbic striatum. In-activation of the ventral subiculum in these animals both restores the dopamine neuron population activity to normal, and eliminates the behavioral hyper-responsivity to amphetamine administration. We now find that there is a selective loss of parvalbumin interneuron staining within the ventral subiculum, and moreover this correlates with a loss of evoked rhythmic activity. Rats administered the mitotoxin methylazoxymethanol acetate (MAM) during gestational day 17 exhibit anatomical, behavioral, and pharmacological responses consistent with an animal model of schizophrenia. When examined as adults, these rats demonstrated a significant loss of parvalbumin-containing interneurons within the ventral (but not dorsal) subiculum of the hippocampus and the medial prefrontal cortex. This reduction occurs in parallel with a significant reduction in theta and beta/gamma band responses evoked by a conditioned tone. Moreover, in a latent inhibition paradigm, the deficit in evoked oscillatory activity in the ventral hippocampus and prefrontal cortex is associated with behavioral impairment in the MAM-treated rats compared to controls. These data suggest that a deficit in GABAergic signaling within the hippocampal-prefrontal cortical system leads to hippocampal hyperactivity and overdrive of the dopamine system, as well as an impairment in cognitive task performance due to loss of oscillatory activity. Moreover, it suggests that a more effective therapeutic approach to the treatment of schizophrenia may reside in restoring normal activity states within the hippocampus.
ID: 549996

INDUCIBLE EXPRESSION OF HUMAN MUTANT DISC1 IN THE MOUSE IS ASSOCIATED WITH A NEUROCHEMICAL SHIFT RELEVANT TO THE KYNURENINE PATHWAY

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Kynurenine pathway dysfunction has been implicated in the pathogenesis of schizophrenia by several research laboratories around the world. Here we present data for extracts of mutant human DISC1 (mhDISC1) transgenic mouse brains, analyzed by reverse-phase HPLC coupled to UV detection. All analyses were conducted while blinded to mouse category. Consistent with a report of tryptophan increases in postmortem brain samples of schizophrenic humans, tryptophan concentrations were found to be significantly elevated in mhDISC1 transgenic mice, 1.77-fold in the cerebellum ($P = .01$, power = 0.86) and 1.54-fold in anterior cortical regions ($P = .001$, power = 0.90) as compared to matched controls. The kynurenine concentrations trended towards an elevation in the cerebellum (1.47-fold that of controls, $P = .09$, power = 0.18) but were not significantly elevated in anterior cortical regions of the mhDISC1 transgenics (1.37-fold that of controls, $P = .32$, power = 0.11). These results represent preliminary evidence that the downstream effects of the mutant DISC1 protein include a shift in the regulation of tryptophan concentrations of relevance to changes seen in schizophrenia, but will require additional transgenic animals to confirm whether or not a difference exists for kynurenine. The mechanism of the elevation in tryptophan is unknown, but would be expected to involve gene-expression differences in enzymes or receptors involved in kynurenine pathway regulation.
ID: 549841

DISSOCIABLE EFFECTS OF D-AMPHETAMINE IN LATENT INHIBITION AND LOCOMOTOR ACTIVITY IN D2 RECEPTOR KNOCKOUT MICE

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The purpose of this study was to investigate the role of the dopamine D2 receptor subtype (D2) in latent inhibition (LI), d-amphetamine-induced disruption of LI and locomotor hyperactivity. These effects of amphetamine are reversed by antipsychotic drugs which also enhance LI, and as such are commonly used as animal models to test novel antipsychotic drug activity. LI is a model of information filtering abnormalities seen in schizophrenia and refers to the process whereby prior exposure of a stimulus without consequence impairs subsequent learning of an association to that stimulus. A role for D2 in LI has been suggested by pharmacological studies, however, none of the available DA ligands are receptor subtype specific making it difficult to attribute effects to specific receptor subtypes. We investigated the relative importance of D2 in d-amphetamine-induced disruption of LI and locomotor hyperactivity models using congenic D2 knockout mice (D2KO) backcrossed onto the C57/Bl6 strain. In a standard LI procedure, learning was measured as suppression of drinking upon presentation of an 85dB tone that had previously been paired with footshock in water restricted mice. There were two experimental groups. One group was pre-exposed to the tone 60 times prior to two pairings with a 1sec, 0.38mA footshock (pre-exposed/PE), while one group was exposed to the same conditions but did not receive tone pre-exposure (non-pre-exposed/NPE). Testing was carried out using a 3 day procedure. d-Amphetamine (2.5mg/kg i.p.) was given on days 1 and 2, mice were tested drug free on day 3. LI is reduced learning in PE compared to the NPE group. Locomotor activity was measured in photocell cages over 30 mins, 30 mins following injection. D2KO mice showed clear enhancement of LI. This effect directly parallels antipsychotic drug effects in LI and confirms the importance of the D2 receptor in the enhancement of LI. d-amphetamine (2.5 mg/kg, i.p.) abolished LI similarly in both WT and D2KO mice suggesting that the D2 receptor is not important in d-amphetamine disruption of LI. In contrast, d-amphetamine induced hyperactivity in WT but not D2KO mice suggesting that the D2 receptor is important for d-amphetamine induced hyperactivity. These data suggest that while d-amphetamine disruption of LI and induction of locomotor hyperactivity are both reliably reversed by antipsychotic drugs, the mechanism may be different with respect to the role of the dopamine D2 receptor.
ID: 549630

INTERLEUKIN-6 MEDIATES THE INCREASE IN NADPH-OXIDASE IN THE KETAMINE MODEL OF SCHIZOPHRENIA.

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Acute exposure to N-methyl-D-aspartate receptor (NMDA-R) antagonists, such as ketamine, produces psychosis in humans, and exacerbates symptoms in schizophrenic patients. We recently showed that ketamine, when applied on two-consecutive days in mice, induces the activation of the superoxide-producing enzyme NADPH-oxidase in brain. The superoxide produced leads to a loss of the inhibitory characteristics of a subset of fast-spiking inhibitory interneurons, those expressing the calcium binding protein parvalbumin (PV). This effect was observed only when animals were treated with ketamine on two consecutive days, but absent when brains were analyzed after a single exposure to the NMDA-R antagonist. These results suggest that the first exposure to the NMDA-R antagonist primes the brain such that the deleterious effects only appear upon a second exposure. In search for the neurochemical changes responsible for the induction and activation of NADPH-oxidase upon ketamine exposure we have found that neuronal production of interleukin-6 (IL-6) is necessary and sufficient for ketamine-mediated activation of NADPH-oxidase in brain. Removal of IL-6 in neuronal cultures by anti-IL-6 blocking antibodies, or in vivo by use of IL-6-deficient mice, prevented the increase in superoxide by ketamine and rescued the interneurons. Accumulating evidence suggest that schizophrenia patients suffer from diminished antioxidant defenses, and a recent clinical trial showed that enhancing these defenses may ameliorate symptoms of the disease. Our results showing that ketamine-induced IL-6 is responsible for the activation and induction of NADPH-oxidase in brain suggest that reducing brain levels of this cytokine may protect the GABAergic phenotype of fast-spiking PV-interneurons and thus attenuate the pro-psychotic effects of ketamine.
ID: 549001

PERINATAL ASPHYXIA REDUCES DENTATE GRANULE CELLS AND EXACERBATES METHAMPHETAMINE-INDUCED HYPERLOCOMOTION IN ADULTHOOD

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Obstetric complications (OCs) are considered to be a risk factor for schizophrenia. One of the mechanisms underlying the association is postulated to be a hypoxic process in the brain in the offspring around the time of birth. To clarify such a mechanism and understand pathophysiological changes in the brain caused by hypoxia, we used an animal model of perinatal asphyxia, in which rat pups were artificially exposed to anoxia for 15 min at birth. At 6-week (corresponding to adolescence) and 12-week (corresponding to adulthood) -old, we assessed behaviors of the pups on tests including examination of methamphetamine-induced locomotion (ie, evaluation of any sensitivity in the dopaminergic system). In addition, the hippocampus, a hypoxia-vulnerable brain area and postulated to be a key brain region in relation to schizophrenia, was histopathologically scrutinized by means of stereology. At 12 weeks of age, but not at 6 weeks of age, we found an elevation in methamphetamine-induced locomotor activity. This elevation was confirmed to be associated with an increase of dopamine release in the nucleus accumbens, indicating that exposure to asphyxia at birth is associated with the later development of dopaminergic dysfunction in matured rat brain. At the same age (12 weeks after birth), but not at 6 weeks of age again, there was a reduction of the number of dentate granule cells in the hippocampus, structural and functional abnormalities of which have previously been reported in individuals with schizophrenia, in the rodents exposed to asphyxia. These findings suggest that perinatal asphyxia may lead to disturbed regulation of the dopaminergic system, which become manifest after brain maturation, and it is also related to an aplastic process in the hippocampus. Our findings may provide a

biological basis for understanding the elusive association previously reported between a history of OCs and the risk of the development of schizophrenia.
ID: 548798

THE UTILITY OF ANIMAL MODELS TO EXPLORE THE NEURODEVELOPMENTAL FEATURES OF SCHIZOPHRENIA

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The pioneering studies of Barbara Fish provided us with a deeper appreciation of the altered developmental trajectories that precedes the onset of schizophrenia. Complementing the clues emerging from observational epidemiology, experimental work based on animal models has provided us with clues to the neurobiological correlates of normal and abnormal brain development. This talk will provide a concise summary of the utility of animal models related to schizophrenia. In particular, this presentation will examine if animal models can be used to explore the underlying neurobiological correlates of developmentally-specific surface-level phenotypes. For example, some animal models have behavioural phenotypes (eg, psychomimetic-induced hyperlocomotion) that only emerge in adulthood, while other models display features from neonatal and juvenile stages. Could these models reflect the developmental onset and offset of various intermediate phenotypes of interest to schizophrenia research? We argue that the antecedents of schizophrenia identified by studies such as those of Barbara Fish can help inspire new generations of experimental research based on animal models.
ID: 548539

THE DIFFERENTIAL EFFECT OF CLOZAPINE COMPARED TO OTHER ANTIPSYCHOTIC DRUGS ON CORTICAL AND STRIATAL EGF-ERK CELL SIGNALING: A NOVEL ANTIPSYCHOTIC DRUG MECHANISM?

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Antipsychotic drugs (APD) have limited and variable efficacy in treating positive psychotic symptoms. The atypical APD clozapine appears demonstrably effective in a proportion of these treatment resistant cases. The mechanism through which clozapine exerts this quality is unknown but likely to involve interactions with multiple G-protein coupled receptors (GPCRs) and related signal transduction pathways. A potential candidate is the mitogen activated protein kinase-extracellular signal regulated kinase (MAPK-ERK) cascade that links GPCR and ErbB growth factor signaling systems, thereby regulating synaptic plasticity and connectivity, processes impaired in schizophrenia. We previously reported that clozapine and other APD in vitro acutely inhibited ERK activation but only clozapine stimulated ERK with sustained treatment. This stimulation was mediated by the epidermal growth factor (EGF) receptor (ErbB1) rather than by Gi/o/q coupled receptors and PKA/C signaling systems typically associated with these agents. Here we extend our findings in vivo, to investigate if clo-

zapine, haloperidol, quetiapine and aripiprazole differentially modulate the EGF-ERK1/2 pathway in prefrontal cortex (PFC) and striatum of C57Bl/6 mice following acute treatment. Phosphorylation of the predominant neuronal ERK isoforms, ERK1/2 was measured by immunoelectrophoresis. ERK1/2 phosphorylation was inhibited by clozapine at 20 and 60 min followed by subsequent activation at 8 hrs and normalization of the pERK1 response at 24 hrs. This in vivo clozapine induced ERK activation was significantly reduced by the EGF receptor inhibitor, AG1478, in both brain regions (PFC clozapine 8 hrs: $144.7 \pm 7.4\%$ vs clozapine + AG1478 8 hrs: $46.7 \pm 10.7\%$, $P < .001$). Differential patterns of activation were noted with the other APD tested, in particular, haloperidol significantly stimulated pERK1 in striatum for up to 8 hrs. In contrast, aripiprazole triggered biphasic ERK phosphorylation, with pERK1/2 levels decreased in the PFC at 20 min, increased by 60 min, decreased by 4 hrs and stabilized thereafter with no striatal changes noted, indicating regional ERK specificity. These in vivo data suggest that clozapine action may be uniquely linked to the EGF signaling system which has been implicated in schizophrenia. Therefore clozapine recruitment of ErbB1 signaling to activate ERK1/2 may warrant investigation as a novel therapeutic target for treatment resistant patients.
ID: 550994

MATERNAL INFECTION AND CYTOKINES IN SCHIZOPHRENIA AND AUTISM

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Maternal infection is associated with increased risk of schizophrenia in the offspring. In a mouse model, infection with influenza virus at mid-gestation leads to behavioral abnormalities in the adult offspring that are consistent with abnormalities seen in schizophrenia, have post-pubertal onset, and are corrected by anti-psychotic drugs. The cause of these abnormalities is maternal immune activation (MIA), as evoking an anti-viral-like immune response in uninfected, pregnant mice with the dsRNA, polyI:C, mimics the effects of infection on the offspring. Since infection and polyI:C induce cytokines, we asked whether these proteins mediate the effects of MIA on the fetal brain. Injection of IL-6 in normal pregnant mice causes behavioral deficits in the offspring, while co-injection of anti-IL-6 antibody (but not anti-IFN) with polyI:C in pregnant mice strongly attenuates the effects of MIA on the behavior of the offspring. Moreover, the offspring of polyI:C-treated IL-6 knockout mice do not display behavioral abnormalities. In addition, maternal co-injection of anti-IL-6 with poly(I:C) blocks the transcriptional changes seen in the brains of adult offspring. That is, 90% of the changes in the adult forebrain of MIA offspring are prevented by co-administration of anti-IL-6 with maternal poly(I:C). The MIA model has face and construct validity for schizophrenia, and is useful for exploring the mechanism of how MIA alters fetal brain development and subsequent changes in behavior and gene expression. Supported by the NIMH and the Simons, Autism Speaks, Binational Science, McGrath, and Weston Havens Foundations.
ID: 551881

MATERNAL INFECTION AND CYTOKINES IN SCHIZOPHRENIA AND AUTISM

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Maternal infection is associated with increased risk of schizophrenia in the offspring. In a mouse model, infection with influenza virus at mid-gestation leads to behavioral abnormalities in the adult offspring that are consistent

with abnormalities seen in schizophrenia, have post-pubertal onset, and are corrected by anti-psychotic drugs. The cause of these abnormalities is maternal immune activation (MIA), as evoking an anti-viral-like immune response in uninfected, pregnant mice with the dsRNA, polyI:C, mimics the effects of infection on the offspring. Since infection and polyI:C induce cytokines, we asked whether these proteins mediate the effects of MIA on the fetal brain. Injection of IL-6 in normal pregnant mice causes behavioral deficits in the offspring, while co-injection of anti-IL-6 antibody (but not anti-IFN) with polyI:C in pregnant mice strongly attenuates the effects of MIA on the behavior of the offspring. Moreover, the offspring of polyI:C-treated IL-6 knockout mice do not display behavioral abnormalities. In addition, maternal co-injection of anti-IL-6 with poly(I:C) blocks the transcriptional changes seen in the brains of adult offspring. That is, 90% of the changes in the adult forebrain of MIA offspring are prevented by co-administration of anti-IL-6 with maternal poly(I:C). The MIA model has face and construct validity for schizophrenia, and is useful for exploring the mechanism of how MIA alters fetal brain development and subsequent changes in behavior and gene expression. Supported by the NIMH and the Simons, Autism Speaks, Binational Science, McGrath, and Weston Havens Foundations.
ID: 551594

PHARMACOLOGICAL INTERVENTION ON A MOVING TARGET: ANIMAL MODELS WITH DEVELOPMENTAL RELEVANCE TO SCHIZOPHRENIA

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Introduction: The ideal pharmacological characteristics of effective intervention for individuals exhibiting prodromal symptoms at high risk for first-episode psychosis are not currently known. Data from human studies suggest antidepressant and antipsychotic medications are effective in improving clinical outcome in prodromal adolescents. Enrollment and retention challenges in psychosis prevention trials, however, impede screening diverse interventions. Use of relevant animal models could help circumvent these barriers. Methods: In order to test observations from human studies in a pre-clinical model, we evaluated the effect of atypical antipsychotic medications, and the selective serotonin reuptake inhibitor antidepressant medication fluoxetine, in preventing behavioral abnormalities (locomotor response to amphetamine and MK-801) following prenatal immune activation, a developmental model with relevance to schizophrenia. Results: Significant developmental changes were observed over time in relevant pharmacological intervention targets using this model. Prominent alteration in locomotor response to the NMDA-subtype glutamate receptor antagonist MK-801, suggesting glutamatergic dysregulation, was observed early in development. In contrast, altered behavioral response to the dopamine-releasing agent amphetamine did not appear until later in development. Treatment with the atypical antipsychotic medications risperidone, paliperidone, and aripiprazole during peri-pubertal development each resulted in long-standing corrective impact on altered locomotor responsiveness to amphetamine. Of interest, evidence suggests this may be mediated through serotonergic effects. Treatment with the selective serotonin reuptake inhibitor antidepressant medication fluoxetine during peri-pubertal development also resulted in a protective adaptation to subsequent amphetamine exposure persisting into early adulthood. Conclusions: These data support the observations

in human studies of protective effects of atypical antipsychotic and selective serotonin reuptake inhibitor antidepressant medications for psychosis prevention. In combination, these findings also suggest developmental adaptation to serotonergic intervention may provide a useful pharmacological target for psychosis prevention. Finally, these results highlight the utility of translational research with relevant animal models in the psychosis prevention field.
ID: 551385

MODELLING THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA IN THE SUBCHRONIC PHENCYCLIDINE-TREATED RAT

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In schizophrenia, negative symptoms include alogia, anhedonia, flat affect, avolition and social withdrawal. The development of animal models for these symptoms have proven difficult; some are exclusively 'human' characteristics and thus unsuited, while other behaviours have been modelled but cannot be associated with concurrent brain neurochemical changes. Persistent blockade of NMDA receptor function by repeated phencyclidine (PCP) dosing produces pathophysiological changes that model the cognitive deficits observed in schizophrenia. In this study we evaluate the validity of the sub-chronic PCP rat in modeling behaviours associated with the negative symptoms of schizophrenia. Male Lister-hooded rats administered PCP for 7days followed by a 7day drug free period were evaluated for two behaviours: social interaction and anhedonia. Social behaviour of PCP-injected (2mg/kg bidaily) or saline-injected rats paired with novel saline-injected peers was examined, analysing contact (anogenital sniffing, crawling, and play behaviours), and non-contact (following and proximal sniffing) interaction. In a second study, PCP-administered rats (2 or 5 mg/kg bidaily) and saline-injected controls were assessed for sucrose preference in a two-bottle choice test as a model of anhedonia. Chronic PCP-injected rats exhibited significantly more non-contact interaction than their saline-injected peers after treatment. PCP did not produce a decrease in social interaction but profoundly affected social behaviour, that is, the PCP rats followed or chased their partners much more than did their saline-injected peers. In the two-choice bottle test of anhedonia, PCP administration produced no difference in sucrose intake compared to controls, nor a difference in water intake or total volume of liquid consumed at either time point. These results suggest that sub-chronic PCP is not a valid model for the negative symptoms of schizophrenia, despite the enduring schizophrenia-like deficits in GABAergic neurons and cognitive dysfunction induced by this repeated PCP administration.
ID: 551337

A NEW CELL MODEL TO STUDY THE MECHANISMS OF GENE-ENVIRONMENT INTERACTIONS RELEVANT TO SCHIZOPHRENIA

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The pathogenesis of schizophrenia and related neurodevelopmental psychiatric disorders is likely to involve interactions between genetic vulnerability and environmental factors. Among non-genetic factors, prenatal microbial

infections and ensuing maternal immune response have been associated with the increased incidence of mental diseases. The scarcity of experimental models has impeded mechanistic studies of gene-environment interactions (GEI). We have been characterizing a GEI cell model based on neuronal expression of mutant human Disrupted-In-Schizophrenia-1 (hDISC1) and applications of pro-inflammatory factors to mimic neuroimmune activation due to maternal virus infections during pregnancy. The main goal of the study is to evaluate the neuronal effects of pro-inflammatory soluble factors, expression of which we have found altered in our mice prenatally treated with polyriboinosinic-polyribocytidilic acid (poly IC) to pregnant dams. We evaluated the effects of IL-6 on neurite outgrowth in cortical primary neurons. Consistent with previous results (Pletnikov, 2008), compared to control untreated cortical neurons, untreated cortical primary neurons that express mutant hDISC1 had significantly attenuated neurite outgrowth. Application of 100U/ml of IL-6 did not affect significantly neurite otgrowth in mtant or control neurons. In contrast, adding 1000U/ml of the cytokine led to a significantly greater decrease in neurite outgrowth in primary mutant hDISC1 neurons compared to control cells. These preliminary data seem to indicate greater susceptibility of maturing mutant neurons to adverse effects of pro-inflammatory factors. Investigations are in progress to evaluate the effects of other soluble factors and/or direct applications of poly IC itself (to activate TLR-3 receptors) on neurite outgrowth, synaptogenesis and spine density in cortical or hippocampal primary neuronal or mixed neuron-astrocytes-microglia cultures. We believe that our model of the cellular effects of GEI will facilitate identification of the specific molecular pathways affected by the genetic mutation combined with soluble inflammatory molecules. These models have the potential to advance our understanding of the pathogenesis of schizophrenia and related neurodevelopmental disorders.

ID: 551151

12. 12. Neurochemistry, Clinical

BRAIN GLUTAMATE PREDICTS COGNITIVE FUNCTION IN SCHIZOPHRENIA BUT NOT IN HEALTHY CONTROLS: A PROTON ECHO PLANAR SPECTROSCOPIC IMAGING (PEPSI) STUDY AT 4 TESLA

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Glutamatergic dysfunction related to NMDA hypofunction has been postulated in schizophrenia (SZ). We examined the relationship between glutamatergic metabolism and congnition in SZ. Thirty SZ patients and 28 healthy volunteers (HV) were studied .Two-dimensional spatial mapping was performed using short TE (15 ms)PEPSI with a 4 T MedSpec scanner. Water-suppressed and non-supressed data (8.5 and 1 min, respectively) were acquired with 1 cm3 spatial resolution from a supra-ventricular axial slice parallel to AC-PC. For spectral fitting with LC model, a simulated basis set was used. Automated spectral quality control and selection as follows: FWHM<0.06, SNR>5, CRLB<20 {NAA+NAAG (NAAc), Ins, Cre, Cho, Glu +Glutamine (Glx). This permitted excellent fits in about 130 voxels per subject. T1, T2 and partial volume correction (for CSF, gray and white matter) were performed to obtain milimolal concentrations. A broad neuropsychological battery (18 tests) was completed by both subject groups as well as standard clinical and functional measures by the SZ patients. "Pure" gray (GM) and white matter (WM; regression method) Glx was not different between SZ and HV. However global cognition (factor 1, accounting for 70% of the neuropsychological variance) was directly correlated with WM Glx in the SZ group (r(29) = 0.6, P = .0005) but not in the HV (r(26) = 0.04, P = .83). Furthermore, factor 1 only correlated with two clinical measures: SANS total score (r(29) = −0.4, P = .03) and Employment impairment (r(29) = −0.4, P = .04). Path analyses suggested that Glx and factor 1 share variance as they relate to SANS total. Still, the path goes from factor 1 to SANS total and from SANS total to Employment. Other metabolites differed between the groups, depending on age (same results with duration of illness): "pure" GM NAAc was lower in young (<30 yr) SZ compared to young HVs($F_{1,20}$ = 4.9, P = .04). In older SZ "pure" GM Ins was increased compared to the older HVs($F_{1,34}$ = 11.4, P = .002). Low range (but normal) glutamate levels may interact with NMDA hypofunction to render some SZ's into a functional hypoglutamatergic state with cognitive impairment. Low cortical GM NAAc (with normal cortical volume) in young SZ's, may be evidence of early reduction of dendritic spines. Latter normalization of cortical NAA in older SZ's (with reduced cortical volume) may reflect increased neuronal packing. Elevation in cortical Ins at latter age suggests glial activation.
ID: 550029

TEMPORALLY COHERENT BRAIN NETWORKS ESTIMATED USING ICA MAY BE INTERMEDIATE PSYCHOSIS PHENOTYPES

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Because task-based fMRI studies can be confounded by variable effort and task performance1,2, we have utilized 1). a simple auditory oddball discrimination task (AOD)3 where accuracy does not differ between groups, and 2). resting state studies (RSS)1, requiring only that subjects stay awake with eyes open. We conducted such fMRI experiments with 25 chronic schizophrenia and 12 psychotic bipolar patients and in 18 and 12 of their first-degree relatives respectively, plus 31 healthy controls, to determine if imaging markers could differentiate these groups. We employed two separate analytic approaches: classic SPM and independent component analysis (ICA) designed to identify distinct brain networks exhibiting temporally coherent activity. The SPM analysis showed relatively few differences between patient groups, or between patients and their relatives, although all differed from healthy controls. The ICA analysis was able to identify temporal lobe and "default" mode networks from all participants and distinguished between groups with high sensitivity and specificity. Patterns for both AOD and RSS showed a similar pattern of significantly more low frequency power in controls and significantly more high frequency power in patients (P < .05 FDR corrected for multiple comparisons). These data support the hypothesis that the use of coherent brain networks such as the temporal lobe and default modes, may provide a more reliable measure of disease than conventionally employed fMRI activity. ICA-derived brain networks show promise as a hemodynamic independent phenotypes of schizophrenia and psychotic bipolar disorder.

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ID: 550809

SDF-1 AMONG DRUG NAIVE FIRST PSYCHOTIC EPISODE PATIENTS

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Background: Although it is usually considered primarily a psychotic disorder, schizophrenia is associated with widespread anatomical and metabolic abnormalities, including risk of type 2 diabetes, and possibly early arteriosclerosis. We hypothesized that SDF1, a chemokine central to adult stem cell trafficking, would be decreased in newly diagnosed, antipsychotic-naïve patients with schizophrenia and related disorders. Material and methods: Patients with schizophrenia and related disorders (n = 24) were matched to healthy control subjects (n = 24) on age, gender, body mass index (BMI), and smoking (average number of cigarettes per day); all were European Caucasians. The severity of psychotic symptoms was defined as the sum of the Positive and Negative Syndromes Scale (PANSS) item scores for hallucinations, delusions, and disorganization. Results: SDF1 blood concentrations were lower among psychotic patients, in both direct t-student comparison (1750.0 ng/mL [SD = 306.6] vs. 1926.7 [280.9]; P = .043) and in a multiple regression analysis in which age, gender,

diagnosis, BMI, socioeconomic status and smoking were the independent variables. SDF-1 levels also correlated with the degree of psychosis ($r = 0.54$, $P = .007$). Conclusions: These results suggest that the physiological abnormalities associated with schizophrenia include poor function of the adult stem cell system. Poor reparative processes in the brain may contribute to the widespread central nervous system dysfunction found in schizophrenia.
ID: 550713

IMMUNE PATHOLOGY OF SCHIZOPHRENIA: THE ROLE OF GLIA CELLS

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Recent research has supported a potential role of immune pathology in the etiopathogenesis of schizophrenia. Specific and unspecific evidence has been obtained. In the CNS various viruses (eg, HERV, BDV) were identified in the brains of schizophrenic patients. Pro-inflammatory cytokines were found to be associated with the stage of disease. Microglial cells were reported to be activated in a subgroup of schizophrenic patients in post mortem as well as imaging studies. Until recently, astrocytes were regarded as mere supporters of neurons regulating the environmental milieu. New research, however, has demonstrated that astrocytes play a major role in the immune regulation of the CNS and modulate neuronal proliferation and differentiation. Since neuronal remodelling appears to be a relevant pathogenic factor in schizophrenia the role of astrocytes needs to be evaluated. S100B, a calcium binding astrocyte-specific cytokine, presents a marker of astrocytic activation.
Recent studies showed increased S100B levels in medicated acutely psychotic patients with schizophrenia and drug naïve schizophrenics. A positive correlation between negative symptoms and S100B was described. In a longitudinal approach over 24 weeks a continuously increased S100B concentration was associated with persistency of negative symptoms and deceleration of therapeutic response. In schizophrenic patients increased S100B concentrations are associated with increased myo-inositol, another astrocytic marker measured by MRSpectroscopy. In this presentation new data regarding the relationship between astrocyte activation and cognitive performance is shown. S100B serum concentration, memory performance, and psychopathology were assessed in 40 first-episode and 35 chronic schizophrenia patients upon admission and after four weeks of treatment. Chronic schizophrenia patients with robust high S100B were impaired in cognitive performance compared to chronic schizophrenic patients with low S100B levels and first-episode patients (low S100B). The findings support the hypothesis that astrocyte activation might contribute to the development of cognitive dysfunction in schizophrenia.
ID: 550672

CORTISOL REACTIVITY IN DAILY LIFE: A MECHANISM UNDERLYING PSYCHOSIS

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Background: The tendency to react psychotically to stress might be an essential feature of psychosis, present both in patients suffering from a psychotic disorder, as well as in first-degree relatives of these patients (Myin-Germeys et al. 2005). The present study used a momentary assessment strategy to unravel the underlying biological mechanisms of this increased stress-sensitivity. In a sample of first-degree relatives, it was investigated whether 1) vulnerability for psychosis is associated with changes in hypothalamic-pituitary-axis responsivity, one of the major mediating systems involved in stress responses, and 2) whether altered hpa-responsivity is associated with increases in sub-clinical psychosis in reaction to daily life stress. Method: The sample consisted of siblings of patients with a psychotic disorder ($n = 57$) and healthy control subjects ($n = 66$). The Experience Sampling Method (ESM; a structured diary technique) was used to assess stress and momentary psychotic symptoms in the reality of daily life as well as to sample cortisol in saliva at similar moments. Results: Multilevel analyses revealed significant differences between the two groups in basal cortisol level ($B = 0.24$ (SE = 0.07); $P = .001$) and cortisol reaction to stress ($B = 0.02$ (SE = 0.01); $P = .05$), with larger cortisol reactivity in relatives compared to controls. Furthermore, deviations from the normal daily cortisol curve significantly predicted increases in sub-clinical psychotic experiences ($B = 0.01$, (SE = 0.01); $P = .030$) and this effect was significantly stronger in the siblings compared to the controls ($B = 0.04$, (SE = 0.01); $P = .002$). Discussion: These results demonstrate that momentary assessment strategies might be helpful to increase our understanding of underlying biological mechanisms relevant to psychosis. The data support the hypothesis that vulnerability for psychosis is associated with HPA hyper-responsivity. In addition, the data suggest that HPA hyper-responsivity might be a biological substrate underlying the increase in psychotic symptoms after a stressor, possibly through its association with excessive dopaminergic responses.

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ID: 550652

SUSCEPTIBILITY TO METABOLIC AND OXIDATIVE STRESSES IN LYMPHOBLASTS FROM PATIENTS WITH SCHIZOPHRENIA: SYSTEMATIC COMPARISON OF PERIPHERAL CELLS AND NEURONS FROM THE SAME SUBJECTS

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In order to address molecular pathogenesis of mental disorders, examination of patient tissues and cells in comparison with control subjects is crucial. Autopsied brains are useful to examine molecular profiles, but cannot be utilized for functional assays. Use of blood cells has limitation, because it is uncertain how peripheral cells represent characteristics of neurons. Here we present our new study on possible susceptibility to metabolic and oxidative stresses in lymphoblasts from patients with schizophrenia, which is compared with olfactory neurons obtained from the same set of subjects. Our results in this functional study will be compared with previous studies of molecular profiling with autopsied brains as well as some studies with fibroblasts that have been reported by others. We propose our hypothesis that the major side effects of obesity and type 2 diabetes elicited by administration of atypical neuroleptics is, at least in part, a manifestation of intrinsic susceptibility of schizophrenics to metabolic and oxidative stresses. Consistency and difference of molecular and functional characteristics between blood cells and neurons from the same subjects will be discussed.
ID: 550419

STRESS AND THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY IN FIRST EPISODE PSYCHOSIS

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Background: Hypothalamic-pituitary-adrenal (HPA) axis is the main biological system involved in the stress response. The aim of our study was to evaluate objective and subjective stress together with HPA axis activity in first-episode psychosis patients and healthy controls. Methods: We recruited 40 first-episode psychosis patients (mean ± SEM age: 29.4 ± 1.2 yrs; gender: 35% females) and 30 controls (mean age: 27.4 ± 1.0 yrs; gender: 23.3% females) as part of the large Genetic And Psychosis (GAP) study, carried out in South London. Information about childhood trauma, recent stressful events and perceived stress were collected using validated schedules. Salivary cortisol was obtained at awakening, at 15, 30, and 60 minutes after awakening, and at 12 pm, and 8 pm. We calculated the Areas Under the Curve to investigate the cortisol levels during the day and the cortisol response to awakening. An independent t-test and was used to analyze differences in the stress variables and cortisol secretion. Correlation analyses were run to investigate the association between stress variables and cortisol secretion. Results: First-episode psychosis patients reported more childhood trauma, recent stressful events, and higher perceived stress compared with controls ($P < .001$). Patients showed no significant difference in cortisol levels during the day compared with controls ($P = .2$). However, patients showed a significantly lower cortisol awakening response than controls ($P = .034$). A positive correlation was found between number of recent stressors or perceived stress and cortisol during the day in controls ($r = .377$, $P = .04$ and $r = .321$, $P = .08$). In contrast, a negative correlation between number of recent stressors or perceived stress and cortisol during the day was found in patients ($r = -.413$, $P = .01$ and $r = -.356$, $P = .04$). Conclusions: Our data show that first episode psychosis patients have higher number of stressful events but similar cortisol levels during the day when compared with healthy controls. First episode psychosis patients have an impaired HPA axis response to stress as shown by the blunted cortisol response to awakening and by the negative correlation between measures of recent stress and cortisol secretion during the day. Acknowledgement: This research is funded by NARSAD Mental Health Research Association, British Academy, and NIHR Biomedical Research Centre Institute of Psychiatry (Kings' College London).
ID: 550283

INFLAMMATION MARKERS IN DRUG-NAÏVE FIRST EPISODE OF NON AFFECTIVE PSYCHOSIS PATIENTS.

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A subclinical inflammatory status has been described in schizophrenia, although this relationship might be confounded by antipsychotic treatment, which is associated with weight gain and an increased risk of diabetes. Studies of antipsychotic-naïve patients found an abnormal pulse pressure and an increased risk of diabetes, which are associated with inflammation. We hypothesized that an increase in pro-inflammatory molecules would be present in schizophrenia and related disorders prior to antipsychotic treatment. We measured fasting blood concentrations of interleukin 6 (IL6) and C-reactive protein (CRP) in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis. Patients were categorized into deficit ($N = 23$) and nondeficit ($N = 41$) groups. In a logistic regression model controlling for age, gender, body mass index, smoking, and socioeconomic status, deficit patients had significantly higher IL6 concentrations than did nondeficit patients. In a linear regression model controlling for the same potential confounders, there was no difference in CRP between deficit and nondeficit groups. These findings provide further evidence that patients with nonaffective psychosis have metabolic abnormalities prior to antipsychotic treatment, which may interact with antipsychotics to increase the risk of diabetes and cardiovascular disease. Our findings also provide further evidence that deficit and nondeficit schizophrenia have differing etiopathophysiology.
ID: 551042

IMPAIRED CORTICAL KYNURENINE PATHWAY METABOLISM IN SCHIZOPHRENIA: FOCUS ON KYNURENINE 3-MONOOXYGENASE

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The levels of kynurenic acid (KYNA), a metabolite of the kynurenine pathway of tryptophan degradation, are elevated in the prefrontal cortex of individuals with schizophrenia (SZ) (Biol. Psych., 50: 521, 2001), and this increase is unrelated to antipsychotic medication. Endogenous, ie, nanomolar, concentrations of KYNA, a preferential antagonist of α7 nicotinic acetylcholine and NMDA receptors, reduce the extracellular levels of glutamate and dopamine in the frontal cortex of experimental animals. Therefore, it is conceivable that increased brain levels of KYNA may play a role in the pathophysiology of SZ. We now determined the activity of the enzyme kynurenine 3-monooxygenase (KMO), which appears to control the tissue levels of KYNA, in the prefrontal cortex of patients and well-matched controls ($n = 15$ each), obtained from the Maryland Brain Collection. Compared to controls, KMO activity was reduced (-36% and -38% in Brodmann areas 9 and 10, respectively; $P < .05$ each) in SZ samples. In separate post-mortem samples, we screened microarray expression profiles of several kynurenine pathway genes in 32 frontal cortical tissues (16 from SZ patients) from Brodmann area 6, a cortical area related to eye movement deficits in patients and their relatives, and examined mRNA expression of KMO by RT-qPCR. KMO expression was significantly reduced in SZ ($P < .01$). Taken together, our data demonstrate a distinct, and possibly endophenotype-specific, impairment in cortical KP metabolism in SZ. Our results raise the possibility that the normalization of cortical KP metabolism may constitute a useful new treatment strategy in SZ.
ID: 551863

INFLAMATORY MARKERS IN A PSYCHOTIC CHILDREN CLINICAL IMPLICATIONS FOR PROGNOSIS

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Human and animal studies have suggested an underlying inflammatory mechanism for a variety of neurological disorders, including schizophrenia. To date, all available reports have focused on adult patients with chronic schizophrenia. Knowledge of how inflammation affects the development of schizophrenia remains limited but several studies have identified

inflammatory markers in all stages of disease: acute psychosis, chronic schizophrenia and residual schizophrenia. No studies have evaluated a possible link between inflammation and psychosis in children or adolescents. The purpose of this study is to assess inflammatory markers in a group of psychotic children and adolescents age 12– 18 years old and correlate these findings with clinical variables. To date, 30 patients and 30 healthy controls have been included in the study. Four different groups have created immunological animal models of schizophrenia. Their findings, which examine cytokine levels, mimic those we observed in our preliminary studies of children and adolescents with psychosis. Psychotic patients were diagnosed by a consensus of 2 child psychiatrist. Diagnosis included Psychosis NOS, Schizophrenia, schizophreniform disorder, and schizoaffective disorder following DSM-IV TR criteria. To participate in the study, a patient must have one of 3 core psychotic symptoms (hallucinations, delusions or peculiar fantasies) at admission. To measure the severity of symptoms the standardized SAPS for positive symptoms, the SANS for negative symptoms, and the Brief Psychiatric Rating Scale-Children version has been used. The CGI-Schizophrenia was also used to assess improvement. The level of 4 outcome laboratory measures were taken; These include serum S100Beta, an IL1 beta, IL 6 and TNF alpha as well as routine standard of care laboratory exams for children with first episode psychosis. There are two primary findings in this study. The first is that the initial episode of psychosis in children is associated with changes in immune cells consistent with inflammation. Although both lymphocyte and monocytes absolute levels were increased in psychotic children, this was not simply a consequence of hospitalization or psychiatric illness since these values were less elevated in non-psychotic psychiatric inpatients. The second important outcome is a link between psychiatric illness, inflammation, and BBB disruption, demonstrated by elevation of cytokines and S100β, a peripheral marker of BBB function.

ID: 551691

SSAT GENE EXPRESSION CHANGES IN SCHIZOPHRENIA AND ITS IMPLICATION WITH SUICIDE

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Schizophrenia patients have high rates of suicide. However, only a subset of schizophrenia patients ever attempt or commit suicide. In the past half decade, there have been a number of studies utilizing microarray technology to conduct genome wide screenings of gene expression changes in postmortem brain tissue leading to potential candidate genes for suicide that have not been investigated in the schizophrenia context. The purpose of this study was to investigate if spermidine/spermine N1-acetyltransferase (SSAT) gene expression, a previously confirmed gene for suicide1, plays a role in either schizophrenia or suicide in schizophrenia. We used Affymetrix HG-U133 Plus2, Illumina HumanRef-8 Expression BeadChip, as well as RT-PCR expression data to compare SSAT levels in schizophrenic patients who committed suicide (S-Schz ($N = 4$)), non-suicide schizophrenic patients (NS-Schz ($N = 10$)) and controls ($N = 44$) in the dorsolateral prefrontal cortex (DLPFC). Brain tissue was obtained through the University of California, Irvine Brain Bank following approval by the Institutional Review Board. Analysis was performed correcting in an ANOVA model for demographic variables (age, gender) and quality control parameters (pH and RNA degradation) using PARTEK. SSAT was differentially expressed in both platforms when comparing all schizophrenia subjects to controls and when comparing those schizophrenia subjects who committed suicide (S-Schz) to controls. However, SSAT expression was not significantly different between non-suicides schizophrenia patients (NS-Schz) and controls. We confirmed the schizophrenia and suicide specific results using RT-PCR SYBRGreen expression levels data. In summary, SSAT gene expression is altered in the DLPFC of schizophrenic patients when compared to controls and more specifically in schizophrenic patients who committed suicide. This confirms the previously reported implication of SSAT in suicide and points out to a possible biomarker or therapeutic target for suicide across diagnostics. SSAT is the rate-limiting enzyme in the catabolism of polyamines and this study extends the implication of the polyamine system in suicide in schizophrenic patients.

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ID: 551650

CATION CHLORIDE COTRANSPORTERS: EXPRESSION PATTERNS IN DEVELOPMENT AND SCHIZOPHRENIA

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The biophysical effects of GABA in the brain are dependent upon the relative expression of the cation-chloride cotransporters KCC2 and NKCC1 by GABA-receptive neurons. While early in development GABA has an excitatory post-synaptic effect due to high levels of NKCC1, GABA transitions to an inhibitory neurotransmitter due to increasing levels of KCC2 expression. To assess the expression pattern of these two cation-chloride cotransporters from the second trimester of fetal development through late adulthood, assays were conducted on human frontal cortical tissue using qRT-PCR. Across the second trimester of human fetal development, in frontal cortex, KCC2 mRNA levels rise rapidly while the NKCC1:KCC2 ratios fall. Levels of KCC2 and NKCC1 mRNA continue to rise during childhood and adolescence, leveling off in early adulthood. The ratio of their expression in the DLPFC is relatively constant after birth. Examining multiple brain regions in the adult human brain, KCC2 expression is highest in gray matter, consistent with a neuron-specific pattern of KCC2 expression. NKCC1 expression is highest in cerebellum. Contrasting adult patients with schizophrenia to age-matched normal control subjects, KCC2 expression is significantly lower in the hippocampal formation of patients with schizophrenia, but not in the DLPFC. There were no differences in NKCC1 expression in either brain region. To address the effects of neuroleptic treatment on co-transporters, rats treated with three dose regimens of haloperidol or clozapine for 28 days were compared to saline controls. There were no differences in the expression of either KCC2 or NKCC1 mRNA, in homogenates taken from sections at the level of the hippocampus. This suggests that the difference in hippocampal KCC2 expression in human patient groups is less likely to be a neuroleptic effect. EGR4 is a transcription factor that increases the expression of KCC2. Schizophrenic subjects had significantly lower levels of EGR4 expression in the hippocampal formation compared to controls. Finally, patients with schizophrenia carrying a GAD1 schizophrenia-associated risk allele had significantly lower KCC2 expression, suggesting that the decreased level

of hippocampal KCC2 expression might in part be mediated by decreased GABA neurotransmission in the hippocampus. Alterations in KCC2 expression associated with schizophrenia may be one of the molecular mechanisms underlying hippocampal dysfunction in this disorder.
ID: 551540

A PRIMATE AND BRAIN SPECIFIC ISOFORM OF KCNH2 IS AN ETIOLOGIC AND PATHOPHYSIOLOGIC COMPONENT OF SCHIZOPHRENIA

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Organized neuronal firing is critical for cortical information processing and is disrupted in schizophrenia. Using 5' RACE in human brain, we identified a primate-specific isoform (3.1) of the potassium channel KCNH2 that modulates neuronal firing patterns. Isoform 3.1 mRNA levels are comparable to KCNH2-1A in prefrontal cortex and hippocampus but over 1000-fold lower in heart. Postmortem expression analysis in brains of patients with schizophrenia of multiple ethnicities shows a consistent 2.5-fold increase in Isoform 3.1 relative to KCNH2-1A in schizophrenic hippocampus. A meta-analysis of 5 independent samples constituting a total of 367 families, 1158 unrelated cases, and 1704 controls shows statistically significant association of SNPs in KCNH2 with schizophrenia. Risk-associated SNPs also predict increased isoform 3.1 mRNA expression in postmortem human hippocampus. Protein immunoblotting studies confirm expression in brain and in transfected tissue culture. Structurally, Isoform 3.1 lacks most of the PAS domain critical for slow channel deactivation. Electrophysiological characterization in primary cortical neurons reveals that overexpression of Isoform 3.1 results in a rapidly deactivating K+ current and a high-frequency, non-adapting firing pattern. These results identify a novel KCNH2 channel and strongly support its role in cortical physiology, and psychosis, providing a potential new target for psychotherapeutic drugs.
ID: 551477

CHARACTERIZATION AND GENETIC ASSOCIATION OF NOVEL SPLICE VARIANTS OF DISRUPTED-IN-SCHIZOPHRENIA-1 (DISC1) IN HUMAN BRAIN

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Disrupted-In-Schizophrenia-1 (DISC1) is a promising susceptibility gene for major mental illness, but the mechanism by which the DISC1 gene confers risk for the clinical associations is unknown. Previous studies identified several alternatively spliced DISC1 transcripts. In this study, we searched for novel DISC1 transcripts in adult and fetal human brain and tested whether the expression of novel transcripts is altered in brains of patients with schizophrenia as compared to controls, and associated with the genetic variation within the DISC1 gene. A large number of novel alternatively spliced transcripts were identified, including a group that lack exon 3 (delta3), a group that lack exons 7 and 8 (delta7delta8), and a variant that has an insertion of exon 3 within a known isoform Es (Esv1), all of which would presumably encode truncated DISC1 proteins. We also identified a group of transcripts resulting from intergenic splicing between TSNAX and DISC1. The short isoforms, delta7delta8, Esv1, and delta3 were more abundantly expressed during human fetal development than during the postnatal ages and were expressed at significantly higher levels in the hippocampus of patients with schizophrenia. Importantly, there were significant effects of schizophre-

nia risk-associated DISC1 single-nucleotide polymorphisms [two non-synonymous SNPs rs821616 (Cys/Ser) and rs6675281 (Leu/Phe) and rs821597] on expression levels of delta3 and delta7delta8. Moreover, the same allele at rs6675281 that predicted higher expression in the hippocampus was associated with higher expression of delta7delta8 in lymphoblasts in an independent sample. Our present data suggest a molecular mechanism of genetic risk associated with DISC1 involving alterations in gene processing.
ID: 551455

3-HYDROXYKYNURENINE AND COGNITIVE IMPAIRMENT IN FIRST-EPISODE NEUROLEPTIC-NAIVE PATIENTS WITH SCHIZOPHRENIA

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One branch of tryptophan catabolic cascade is kynurenine (Kyn) pathway, which produces neurotoxic (3-hydroxykynurenine and quinolinic acid) as well as neuroinhibitory (kynurenic acid) compounds. Kynurenic acid acts as a competitive antagonist of the glycine site of N-methyl-D-asparate receptors at high concentrations and as a noncompetitive antagonist of the a-7-nicotinic acetylcholine receptor at low concentrations. Evidence that Kyn pathway may have a functional role in cognitive deficits has implications for the cognitive impairments associated with schizophrenia. Using high-pressure liquid chromatography coupled with a coulometric multi-electrode array system, we examined 13 tryptophan metabolites measured from the plasma of first-episode neuroleptic-naïve patients with schizophrenia ($n = 25$) collected at baseline and 4 weeks after treatment with clinician's-choice antipsychotics. Associations between these metabolites and clinical symptoms measured using standard rating scales (BPRS, SAPS, SANS, GAS, CGI) are the focus of this presentation. Highly significant correlations were obtained between baseline level of 3-hydroxykynurenine (3-OHKyn) and baseline total symptom score (BPRS-18), as well as between this metabolite at baseline and magnitude of change (or improvement) in BPRS-18 at 4 weeks follow-up ($P < .01$). The direction of these associations indicates that increases in baseline 3-OHKyn were related to lower levels of overall symptomatology at baseline (less severe clinical presentation), but reduced magnitude of clinical improvement at follow-up. Moreover, level of 3-OHKyn at baseline was associated with the magnitude of change in symptoms of clinical thought disorder, such as disorganized speech and bizarre thought content and psychosis, including hallucinations and delusions, at 4-weeks follow-up. Direction of these latter relationships indicates that increased levels of 3-OHKyn at baseline were associated with decreased improvement in cognition-related symptoms at 4 weeks. In conclusion, the pattern of relationships between cognitive distortions at follow-up and 3-OHKyn appears in contrast to the pattern observed between overall symptomatology at baseline and 3-OHKyn. If replicable, findings suggest that tryptophan metabolism at baseline may predict clinical presentation, including cognition-related positive symptoms, following short-term treatment with antipsychotic medications. Supported in part by VA Merit Review and MH58141 grants.
ID: 551398

HPA-AXIS ACTIVITY; A PREDICTOR OF TRANSI-TION TO PSYCHOSES IN ULTRA HIGH-RISK PATIENTS?

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This study is a part of the NEURAPRO-E (North America, EURope, Australia PROdrome) study, which is a multicenter controlled trial of Omega-3-fatty acids and cognitive behavioural case management (CBCM) for symptomatic patients at ultra high risk (UHR) for early progression to schizophrenia and other psychotic disorders. In this study we identify UHR patients and offer them 3 month of CBCM and either Eicosapentanoic, an omega-3 essential fatty acid or placebo. We plan to investigate whether intervention with EPA combined with CBCM can reduce the transition rate in prodromal patients, McGorry et al. (2008) An average one-year transmission rate of 36,7 % in UHR subjects who did not receive antipsychotic medicine is reported, using a combination of various studies; Ruhrmann et al. (2003). Different kinds of treatments/intervention offered can delay, if not prevent the onset of psychosis. But still we treat many patients who might never develop psychosis. It would be interesting if we could identify further predictors, ex. biological predictors. Previous studies have identified an increased pituitary volume before the onset of psychosis, Garner et al. (2005). In our study we would like to examine weather it is possible using a HPA axis activity as predictor of transition in UHR subjects. The rational for this approach will be explored.
ID: 551253

DISTURBED SKIN BARRIER FUNCTION IN SCHIZOPHRENIA: RECONSIDERING THE LINK BETWEEN MENTAL ILLNESS AND SKIN PHYSIOLOGY

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Introduction: Associations between mental disorders and skin physiology have been studied for more than five decades. This ongoing interest might be caused by the obvious suitability of the skin for diverse diagnostic testing. Having used a variety of approaches (measurements of skin conductance, skin temperature, dermatoglyphics, skin blood perfusion; several skin stimulation tests), research strongly indicates links between diverse skin physiology parameters and functioning of the central nervous system. Only the diagnostic value is still a matter of debate. Non-invasive biophysical techniques allow the quantitative assessment of skin barrier function as a comprehensive parameter. This is of interest, as the skin barrier is strongly related to the cell regeneration rate in basal layers of the skin and the metabolism of skin lipids. Both, the cell regeneration cycle and lipid metabolism are disturbed in schizophrenia. Method: We investigated 31 neuroleptic naïve first-episode schizophrenia patients (SCH) and 31 healthy age and gender matched control volunteers. Skin barrier function was assessed measuring transepidermal water loss, stratum corneum hydration and skin surface pH values *in vivo*. Skin lipid profiles were measured using a Hexan/Ethanol (2:1) wash out technique and combined HPTL/gas-chromatography. Results: Our data show decreased skin hydration level in SCH patients and dependent on the gender an alteration of skin surface pH values. Analysis of skin lipids is still ongoing. Conclusion: Disturbance of skin barrier function is not previously reported in schizophrenia. Dermatologic

studies are suggestive for links between skin barrier dysfunction and mental stress, deficiency of polyunsaturated fatty acids, eicosanoid metabolism and sex hormone levels. The present alterations in SCH are discussed in the context of current schizophrenia models.
ID: 551953

THE ROLE OF DOPAMINE AND NOREPINEPHRINE IN THE PATHOPHYSIOLOGY OF MOOD DISORDERS

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Evidence from preclinical and clinical investigations supports a role for dysregulation of multiple neurotransmitter systems in the pathophysiology of schizophrenia and mood disorders. The dopamine hypothesis, proposed in the 1970s, implicated elevations of dopaminergic neurotransmission in the pathogenesis of schizophrenia and appeared to explain the efficacy of typical antipsychotics. The development of atypical antipsychotics, which possess a binding profile distinct from typical antipsychotics but offer broadly equivalent efficacy in schizophrenia, supported evidence from other sources implicating serotonin (5-HT) receptors in pathogenesis. More recently, other neurotransmitters have been implicated in the development of schizophrenia, including glutamate and neurotensin. It is increasingly clear that schizophrenia results from pathologic alterations of several, interacting neurotransmitter systems. As in schizophrenia, mood disorders, including major depressive disorder, bipolar disorder, and the mood disorders associated with schizophrenia, may be explained by monoaminergic neuronal dysfunction. Evidence for the involvement of norepinephrine in depression derives from observations including reductions in norepinephrine release and altered adrenoceptor sensitivity in depressed patients, and is supported by the efficacy of norepinephrine reuptake inhibitors in these patients. The involvement of dopaminergic systems in depression is suggested by imaging, postmortem, and biological fluid analyses which have identified reduced receptor binding in the amygdaloid complex and reduced transporter binding in the striatum of depressed patients. In summary, emerging evidence implicates the involvement of multiple, interacting neurotransmitter systems in the etiology of schizophrenia and mood disorders and provides further insights into the mechanism of action of agents with efficacy in these disorders.
ID: 555406

THE CONCEPT OF ATYPICALITY—NEUROPHAR-MACOLOGICAL UNDERPINNINGS AS REVEALED BY MOLECULAR IMAGING

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Growing understanding of the mechanism of action of antipsychotic drugs has implications for the treatment of schizophrenia and mood disorders. The modern pharmacological treatment of schizophrenia began in the 1950s with discovery of the phenothiazine derivative, chlorpromazine. Similar compounds (so-called 'typical antipsychotics') were subsequently developed, but all conferred pronounced adverse effects on the extrapyramidal system. Development of the atypical antipsychotics (eg, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) offered reduced extrapyramidal effects, considered related to their receptor binding profile. While typical antipsychotics act primarily via D2 receptors in schizophrenia, atypical antipsychotics additionally bind to serotonin (5-HT) receptors and, via this pathway, elevate dopamine levels indirectly. Ongoing investigations indicate that disordered dopamine neurotransmission is not solely responsible for the pathogenesis of schizophrenia, and further investigation

of antipsychotics may characterize actions via additional neurotransmitter systems. Novel agents with non-dopamine-related mechanisms of action are also under investigation, with promising results. Continued investigation into the mechanism of action of agents in the antipsychotic drug class has identified the existence of active metabolites, including paliperidone (from risperidone), N-desmethylclozapine (from clozapine), and norquetiapine (from quetiapine). These metabolites may contribute to the clinical efficacy of the parent compound by offering distinct binding characteristics. For example, the major active metabolite of quetiapine in man, norquetiapine (N-desalkyl quetiapine), is similar to quetiapine in its 5-HT2A receptor and D2 receptor binding profile, but is dissimilar in displaying high levels of norepinephrine transporter (NET) occupancy, even at low plasma concentrations. As NET inhibition is a known mechanism of action for conventional antidepressants, norquetiapine may explain the antidepressant and mood stabilizing effects of quetiapine that are observed in clinical trials of schizophrenia, bipolar disorder, and major depressive disorder. In conclusion, antipsychotic agents display differences in receptor binding profile that appear to translate into differences in efficacy profile which are relevant in the treatment of schizophrenia and mood disorders.
ID: 555117

A TRANSLATIONAL PERSPECTIVE ON QUETIAPINE—BEYOND AN ATYPICAL

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Quetiapine fumarate is approved in the USA and other countries for the treatment of schizophrenia, bipolar mania, and bipolar depression, including bipolar maintenance. Additional clinical studies have also shown efficacy for quetiapine in major depressive disorder and generalized anxiety disorder. This broad spectrum of efficacy was not predicted based on initial assessments of preclinical pharmacology, and additional preclinical research has been undertaken to find a potential explanation for these effects. *In vitro* receptor binding studies show that quetiapine has a major active human metabolite, norquetiapine (N-desalkylquetiapine), which has different receptor binding properties than the parent compound. Research by both AstraZeneca and others (Jensen et al. 2008) has shown that norquetiapine has moderate to high affinity for central neuroreceptors including D2 dopamine and 5-HT2A receptors as well as the norepinephrine transporter (NET). Occupancy at the NET is a characteristic not demonstrated for other atypical antipsychotics. In collaboration with the Karolinska Institute, a radioligand for the NET has been developed, (S,S)[18F]FMeNER-D2, enabling positron emission tomography studies in both non-human primates and humans. These have confirmed *in vitro* receptor binding profiles, demonstrating dose-dependent occupancy of D2 and 5-HT2A receptors by quetiapine and norquetiapine, while norquetiapine additionally induces high occupancy at the NET even at low plasma concentrations. In order to understand receptor binding profiles in more detail and explore their potential clinical relevance, theoretical models of receptor occupancy are in development. Modeling studies suggest that neurotransmitter systems may be engaged along different timescales depending on the dose and formulation of quetiapine.

Reference

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ID: 555103

NEUROBIOLOGY—NET INHIBITION AND THE EFFECTS OF ANTIPSYCHOTIC DRUGS

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The dopamine hypothesis of schizophrenia implicates impaired prefrontal dopamine functioning coupled with a hyperactive or hyperreactive subcortical dopamine projection to limbic areas of the brain. Dopamine in the prefrontal cortex is profoundly involved with control of cognition. Rodent studies support the notion that atypical antipsychotics increase dopamine output in the prefrontal cortex, eg, via 5-HT2 receptor antagonism. Further studies suggest that inhibition of the norepinephrine transporter (NET) may augment the efficacy of classical D2 antagonists to increase the availability of dopamine in the prefrontal cortex. By enhancing the efficacy of typical and atypical antipsychotics, adjunctive NET inhibition may reduce the D2 receptor occupancy required for an antipsychotic effect, with potential for less extrapyramidal effects, cognitive and motivational impairment, and weight gain. As selective NET inhibition also exerts an antidepressant effect, an enhanced therapeutic effect on negative symptoms may additionally be achieved. The glutamate hypothesis of schizophrenia and cognitive impairment implicates dysfunctional NMDA receptor subtypes in the prefrontal cortex. In line with animal studies supporting this hypothesis, NMDA antagonists are known to exacerbate psychotic symptoms and cognitive impairment in schizophrenic patients, as well as inducing these symptoms in healthy volunteers. Atypical antipsychotics share a common property of augmenting NMDA-evoked responses in pyramidal cells of the prefrontal cortex, implying facilitation of NMDA receptor-mediated transmission. In analogy with atypical antipsychotics, selective NET inhibitors also facilitate prefrontal NMDA receptor-mediated transmission and, in addition, enhance the effects of atypical antipsychotics in this regard. In short, similar to most atypical antipsychotics, selective NET inhibition facilitates both prefrontal dopaminergic and NMDA receptor-mediated transmission, which provides a neurobiological rationale for a cognitive enhancing action. Consequently, the combination of quetiapine and its active metabolite norquetiapine (N-desalkylquetiapine), which is a NET inhibitor, would be expected to generate an improved effect in schizophrenia, particularly on depressive symptoms and cognitive deficits.
ID: 555084

13. 13. Neuroimaging, Neurochemical

EXTRASTRIATAL AND STRIATAL D2 RECEPTOR BINDING IN A LONGITUDINAL STUDY OF ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE SCHIZOPHRENIC PATIENTS: RELATION TO POSITIVE AND NEGATIVE SYMPTOMS

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Background: Whereas the literature strongly supports that positive psychotic symptoms can be dampened by striatal D2 blockade, the relation between striatal and extrastriatal D2 receptors and negative symptoms—and between extrastriatal D2 receptors and positive symptoms is weaker. We have studies regional baseline D2 binding potentials (BP) as markers for treatment outcome—and the relation between striatal and extrastriatal D2 occupancies and psychopathology after 3 months of treatment in a longitudinal study of 23 antipsychotic-naïve first-episode schizophrenia patients. Methods: Twenty-three neuroleptic-naïve schizophrenic patients were examined with psychopatho-logical ratings and single-photon emission computerized tomography (SPECT) using the D2-receptor ligand [123I]epidepride before and after 3 months of treatment with either the atypical an-tipsychotic drug, risperidone, or the typical antipsychotic compound zuclopenthixol. Results: We found a highly significant correlation between frontal D2 BP in the antipsychotic-naïve state and treatment outcome with regard to the effect of antipsychotic medication on positive symp-toms. After 3 months of treatment the effect on positive symptoms was not, however, correlated with extrastriatal but only with striatal D2 occupancy. In contrast, high frontal D2 occupancy was correlated with more negative symptoms. Discussion: In agreement with our previous report of a relation between frontal D2 BP and positive symptoms (1), high frontal D2 BP seem to be a marker predicting the effects of antipsychotic medication on these symptoms. The results do not, however, support that the effect of antipsychotics on positive symptoms is mediated via blockade of frontal receptors. Instead, they support an association between high frontal blockade and negative symptoms—and in agreement with the literature also between striatal blockade and effect on positive symptoms. Optimal antipsychotic effect seems to depend on a delicate balance between striatal and extrastriatal D2 blockade in the individual patent.
ID: 549577

DOPAMINE D_2 AND D_3 RECEPTOR OCCUPANCY OF CARIPRAZINE IN SCHIZOPHRENIC PATIENTS

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Background: Cariprazine is a novel dopamine D_3/D_2 receptor functional antagonist, that may have antipsychotic properties based on in vitro and animal pharmacological studies. The D_3 dopamine receptor is a possi-ble pharmacological target in part because of its high density in the ventral striatum and its ability to improve cognition in animal models. The addi-tion of significant D_3 antagonism to cariprazine's D_2 antagonism is hypoth-esized to offer reduced potential for extrapyramidal symptoms, cognitive enhancement, and improvement in negative symptoms. This study was designed to determine the D_3/D_2 occupancy at various doses of cariprazine. Methods: To determine the D_2 and D_3 occupancy of cariprazine we con-ducted an open-label, fixed-dose, 2-week trial with up to 4 PET scans obtained at baseline, during dosing, end of dosing period and at the fol-low-up visit in 8 male subjects with a DSM-IV diagnosis of schizophrenia. F-18 Fallypride was the radiotracer used because of its high D_3/D_2 receptor affinity. Subjects received daily dosing of cariprazine for 2 days followed by a higher dose for 12 additional days. The oral doses ranged from 0.5 mg to 3.0 mg QD. Results: D_3/D_2 receptor occupancy in the caudate and putamen was greater than 50% following 14 days of cariprazine 1.5 mg QD, and at least 90% for cariprazine 3mg QD. Conclusions: Cariprazine at doses of 1.5 to 3 mg has D_3/D_2 receptor occupancy within the antipsychotic range pre-dicted by other atypical antipsychotic medications.
ID: 550746

LONGITUDINAL INVESTIGATION OF 3T 1H-MRS AND PSYCHOTIC SYMPTOMS IN UNMEDICATED FIRST EPISODE PSYCHOSIS

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This prospective study used 1H-MRS at 3 Tesla to investigate NAA+NAAG, Cr+PCr, Choline compounds (Cho) and glutamate in the medial prefrontal region of unmedicated young adults with first episode psychosis (FEP). Concentration levels were examined in association with measures of current severity of symptoms. Sixteen patients (22.3 + 3.2 years of age) with FEP and without mitigation from substance abuse were assessed at baseline (while non-medicated), at 2–6 months and at 12 months after initiation of randomized monotherapy with either olanzapine, risperidone or quetiapine. Sixteen matched healthy controls (HC) were also recruited (21.71 + 3.3 years of age). Mixed ANOVAs were computed to assess be-tween-group differences in neurochemical levels at baseline and at fol-low-up scans (averaging repeated follow-up scans for each participant). A marginally significant discrepancy was found between the FEP and HC groups in concentration levels of NAA+NAAG referenced to internal water. Follow-up tests revealed a significant difference solely at follow-up time [$t_{30} = 2.1$, $P = .047$], indicating lower levels in the FEP group. Non-parametric bivariate correlations revealed a significant and negative asso-ciation between baseline Cho levels and scores on the positive scale of the PANSS ($r = -.66$, $P = .006$, $n = 16$). Greater severity of positive symptoms was associated with lower levels of prefrontal Cho. This association was rep-licated in repeated measures with a subsample of patients assessed after two to six months of medication ($r = -.83$, $P = .042$, $n = 6$), but it was not observed at the 12-month follow-up ($r = .07$, $P = .911$, $n = 5$). Reduced frontal NAA+NAAG concentration levels have been previously reported in groups of patients with chronic schizophrenia. We report similar findings in young adults with first episode psychosis, but solely after medication was initiated for a few months. The negative association between prefrontal Cho levels and severity of positive symptoms, which was found at baseline and repli-cated in the early but not later follow-up assessment, might be indicative of a disturbed regional phospholipid turnover in the early stages of the illness, in gradation with the severity of positive symptoms. This research was sup-ported by a CIHR grant.
ID: 550706

GLUTAMATE/GLUTAMINE AND GABA LEVELS IN HIPPOCAMPUS IN SCHIZOPHRENIA: A 3T H-MRS STUDY

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Schizophrenia (SZ) is a debilitating disease with long recognized phenomenology, but only partially understood pathophysiology. The diversity of etiological factors and the variability of clinical presentation diversity leaves an open question as to what brain regions and what neurotransmitter systems are defective in schizophrenia. There is reliable evidence for hippocampus involvement: neuroimaging and postmortem studies have consistently documented hippocampal alterations is schizophrenia. Based upon pharmacological challenge and postmortem chemistry, glutamate transmission decrease appears to be one of the prevailing mechanistic explanations of the disease. Using 3T H-MRS, we measured glutamate, glutamine, NAA and GABA levels in a cohort of 15 subjects with schizophrenia (SZ) in comparison with their matched normal controls (NC). Data was collected from a single voxel of 50/15/15 mm that was placed over the left hippocampus. Experiments were carried out on a whole-body Philips 3T scanner (Philips Medical Systems). A standard birdcage head RF coil was used for transmission and signal reception. MP-RAGE (magnetization prepared rapid gradient echo) images were used for voxel positioning. The data were corrected for field drift using the NAA singlet during the post-acquisition processing. LCModel software was used for spectral fitting of the data. Triple refocusing was used for Gln-Glu measure. An additional 180° pulse that refocused resonances between 1.7 and 3.3 ppm was applied within PRESS. The three subecho times were optimized for simultaneous detection of Gln and Glu signals. The total echo time was 193 ms, which gave a minimum signal of the NAA aspartate moiety at $\sim$2.45 ppm where a small Gln peak is generated. The Glu peak at $\sim$2.35 ppm was suppressed to enhance the selectivity of a neighboring Gln signal. GABA was measured using scalar difference editing (MEGA). All reported values were normalized to creatine. We found no difference between the groups with respect to glutamine (NC = 0.51 ± 0.05; SZ = 0.51 ± 0.05; $P = .98$), glutamate (NC = 1.61 ± 0.05; SZ = 1.53 ± 0.05; $P = .35$), or GABA (NC = 0.22 ± 0.01; SZ = 0.20 ± 0.01; $P = .31$) concentrations. We did found a significant decrease in NAA in the schizophrenia group (NC = 1.57 ± 0.04; SZ = 1.38 ± 0.04; $P = .0035$). In our opinion, the NAA decrease represents most probably a treatment effect.
ID: 550496

DECREASED FRONTAL 5-HT2A RECEPTOR BINDING IN ANTIPSYCHOTIC-NAIVE FIRST EPISODE SCHIZOPHRENIA PATIENTS

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The purpose of this study was to assess in vivo brain 5-HT2A receptor binding in a large sample ($n = 30$) of first episode, antipsychotic-naïve schizophrenic patients and age and gender matched healthy controls and relate the binding with psychopathology. In vivo brain 5-HT2A receptor binding was measured using [F-18]altanserin Positron Emission Tomography (PET) in a bolus infusion approach. The binding potential of specific tracer binding was used as the outcome parameter. Psychopathology was assessed using the Positive and Negative Symptom Rating Scale (PANSS). Schizophrenic patients had significantly lower frontal cortical 5-HT2A binding ($t = -2.16$, $df = 61$, $P < .05$) as compared to controls. There was a significant negative correlation ($r = -.571$, $P = .007$) between frontal 5-HT2A binding and positive psychotic symptoms in the male patients. Our results suggest that frontal 5-HT2A receptors are involved in the early stages of schizophrenia.
ID: 549656

POSITRON EMISSION TOMOGRAPHY IMAGING OF AMPHETAMINE-INDUCED DOPAMINE RELEASE IN THE HUMAN CORTEX: A COMPARATIVE EVALUATION OF THE HIGH AFFINITY DOPAMINE $D_{2/3}$ RADIOTRACERS [^{11}C]FLB 457 AND [^{11}C]FALLYPRIDE

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The use of PET and SPECT endogenous competition binding techniques has contributed to the understanding of the role of dopamine in schizophrenia. An important limitation of these imaging studies is the fact that measurements of acute changes in synaptic dopamine have been restricted to the striatum. The ligands previously used, such as [^{11}C]raclopride and [^{123}I]IBZM, do not provide sufficient signal to noise ratio to quantify D_2 receptors in extrastriatal areas, such as cortex, where the concentration of D_2 receptors is much lower than in the striatum. Given the importance of cortical DA function in cognition and the cognitive deficits observed in schizophrenia, a method to measure cortical dopamine function in humans would be highly desirable. The goal of this study was to compare the ability of two high affinity DA D_2 radioligands [^{11}C]FLB 457 and [^{11}C]fallypride to measure amphetamine-induced changes in DA transmission in the human cortex. D_2 receptor availability was measured in the cortical regions of interest with PET in 12 healthy volunteers under control and post amphetamine conditions (0.5 mg kg-1, oral), using both [^{11}C]FLB 457 and [^{11}C]fallypride (four scans per subject). Kinetic modeling with an arterial input function was used to derive the binding potential (BP_{ND}) in eight cortical regions. Under control conditions, [^{11}C]FLB 457 BP_{ND} was 30 to 70% higher compared to [^{11}C]fallypride BP_{ND} in cortical regions. Amphetamine induced DA release led to a significant decrease in [^{11}C]FLB 457 BP_{ND} in six out the eight cortical regions evaluated. In contrast, no significant decrease in [^{11}C]fallypride BP_{ND} was detected in cortex following amphetamine. The difference between [^{11}C]FLB 457 and [^{11}C]fallypride ability to detect changes in cortical D_2 receptor availability following amphetamine is related to the higher signal to noise ratio provided by [^{11}C]FLB 457. These findings suggest that [^{11}C]FLB 457 is superior to [^{11}C]fallypride for measurement of changes in synaptic dopamine in cortical regions, including the dorsolateral prefrontal cortex, a region hypothesized to be a key node in the cognitive impairments observed in schizophrenia.
ID: 549619

ASSESSMENT OF HUMAN BRAIN GLUTAMATE USING A HYPEROSMOLAR PROBE AND 1H-MRS

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Converging evidence suggests that glutamatergic abnormalities play a role in the pathogenesis of schizophrenia, but validation of these abnormalities in vivo remains to be determined. Thus, we developed a novel method to assess the change in glutamate concentrations in response to a hyperosmolar probe using 1H-MRS based on preclinical data that have shown that in addition to being the most abundant neurotransmitter, glutamate is a major osmolyte, which accumulates in brain tissue with sustained hyperosmolality. Methods: To induce sustained hyperosmolality, first we developed a water restriction paradigm (WRP). WRP was safe and effective. Healthy controls ($N = 8$) completed 1H-MRS scans before and after WRP on a 4T Bruker system to examine the link between sustained hyperosmolality and cortical glutamate concentrations. We have also obtained preliminary data from patients ($N = 2$) using WRP and MRS. Occipital 1H MRS was performed with a spin-echo acquisition (TE/TR = 68 ms/2500 ms) with ISIS and outer volume suppression, using a surface coil with outer volume suppression. GABA measurements were obtained from J-edited difference spectra. Results: The WRP was effective in inducing sustained hyperosmolality [$F_{4,32} = 2.8$, $P = .04$] and there was no significant group effect [$F_{1,7} = 2.1$, $P = .18$] suggesting that it was effective in both groups. A significant increase in glutamate concentrations was found in healthy controls using both water ($t = 3.5$, $df = 7$, $P = .01$) and creatine ($t = 3.4$, $df = 7$, $P = .01$) referencing. Consistent with the animal literature, in healthy controls, sustained hyperosmolality was associated with increased cortical glutamate concentrations ($r = .69$, $P = .05$). In healthy controls, the other measured molecules (NAA, GABA, glutamine, myoinositol, and choline) did not show significant changes (all $P > .05$). Patients did not show significant changes in the concentrations of any of the molecules measured (all $P > .05$). Discussion: We have shown that sustained hyperosmolality is associated with increased cortical glutamate concentrations in healthy humans, as predicted from the preclinical literature. Our preliminary findings in the patients suggest that schizophrenia may involve abnormal regulation of the glutamatergic system in relation to water metabolism.
ID: 550872

A COMBINED FMRI AND 1H-MRS STUDY OF THE ACC AND THE HIPPOCAMPUS IN PATIENTS WITH SCHIZOPHRENIA AND MATCHED HEALTHY VOLUNTEERS

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Our previous imaging studies in schizophrenia have revealed that limbic brain networks, such as the anterior cingulate cortex (ACC) and the hippocampus (HIP), are related to psychosis. In this study we use fMRI together with proton magnetic resonance spectroscopy (1H-MRS) to contrast the physiological and biochemical properties of the ACC and HIP in patients with schizophrenia (SZ) and matched healthy volunteers (HV). We hypothesized that greater BOLD response to cognitive tasks known to activate the ACC (Stroop) and the HIP (episodic memory) as

well as greater N-acetyl-aspartate (NAA) and GLU metabolite measurements in these regions would be seen in HV vs. SZ. All scans were acquired with a Siemens 3T scanner. fMRI: BOLD data were acquired with single-shot gradient echo planar imaging (TR = 2.1sec, TE = 40msec, Flip angle = 70 degrees, slice thickness = 2.5mm, 1mm gap, FOV = 240mm) during a Stroop and an episodic memory task. An event-related design was used with 3 runs of 88 trials each for the Stroop and 2 runs of 60 word presentations for the memory task. The preprocessed fMRI data were analyzed using SPM5. The mean percent signal change was found for the cluster of maximum activation in the ROIs for which the contrasts of incongruent > congruent (Stroop) and encode (episodic memory) were significant as calculated by MarsBar. 1H-MRS: Water-suppressed spectra were acquired with a point resolved pulse sequence (PRESS) (TR = 2000ms, TE = 80ms, 2000 HZ spectral width) from voxels prescribed in the left HIP and the bilateral dorsal ACC. Combined fMRI and 1H-MRS scans were acquired in HV ($n = 9$) and SZ ($n = 8$). Significant activation in dorsal ACC/medial PFC (Stroop) was seen in HV (MNI: -2, 16, 42; $t = 8.15$) and SZ (6, 26, 44; $t = 4.17$) and in left HIP (Memory encode) in HV ($-20, -32, -10$; $t = 4.02$) and SZ ($-34, -34, -2$; $t = 2.02$). There was a trend level ($P = .07$) decrease in the NAA/Cr ratio in SZ vs. HV in the ACC. In the ACC, there was a positive correlation ($r = 0.53$, $P = .16$) between percent signal change (Stroop) and NAA/Cr ratio in SZ but not in HV. The data suggest that, in SZ, there is a loss of neuronal integrity in the ACC. In addition, the combined fMRI/1H-MRS data in that region suggest that, in SZ, there is a tighter relationship between functional activity and neuronal integrity. These data show the feasibility of combining fMRI and 1H-MRS to investigate the function and the biochemistry of the ACC and the HIP.
ID: 551490

D2/D3 RECEPTOR BINDING IN STRIATAL AND EXTRASTRIATAL REGIONS IN SCHIZOPHRENIA STUDIED WITH PET AND [18F]FALLYPRIDE

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Background: Alterations in dopamine (DA) D2/D3 receptor binding have been reported in schizophrenia, showing a modest elevation in baseline radioligand binding in striatum. New radioligands now allow the assessment of these receptors in extrastriatal regions, and several studies have been reported with variable findings. We used [18F]fallypride PET imaging to evaluate these receptors in both striatal and extrastriatal regions in schizophrenia. Methods: Twenty-one patients with schizophrenia and 22 group-matched healthy controls were scanned with [18F]fallypride and an HR+ camera. Each scan was acquired over 240 min in 3 sessions of 50, 60 and 40 min with breaks. Arterial blood was collected for metabolite-corrected plasma input function. Regions of interest were drawn on each subject's MRI and transferred to the coregistered PET. Regional data were analyzed by kinetic modeling using reference tissue and 2 tissue compartment models. Binding potential outcome measures BPND, BPP, and BPF were compared with 2-tailed t tests. Results: Mean regional BPND values were nonsignificantly elevated in striatum in schizophrenia as in prior literature, although no striatal or extrastriatal region showed significantly altered BPND. For example, mean regional BPND values in patients and controls respectively were 20.2 ± 4.0 and 19.5 ± 2.9 in whole striatum, 18.7 ± 3.9 and 18.3 ± 3.1 in dorsal caudate, 1.8 ± 0.4 and 2.0 ± 0.4 in amygdala, and 2.2 ± 0.5 and 2.1 ± 0.3 in thalamus ($P > .05$ in all cases). While BPP regional values were significantly lower in patients in several regions, both plasma free fraction of radioligand and nondisplaceable distribution volume assessed in the cerebellum were lower in the patient group,

resulting in absence of significant regional differences in BPND or BPF in any brain region. Discussion: In this study, we did not find significant alterations in D2/D3 receptor expression levels in schizophrenia. These results are consistent with some but not all previous studies of extrastriatal D2/D3 receptors. Assessing DA function in extrastriatal regions, such as with stimulated release or DA depletion paradigms, may be a more productive approach to understanding the role of these regions in the pathophysiology of the illness, as previously shown for the striatum. Acknowledgment: This work was supported by NIMH 1 P50 MH066171.
ID: 551379

THALAMIC GLUTAMATE AND THE TRANSITION TO PSYCHOSIS

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The thalamus is central to the NMDA receptor dysfunction hypothesis of schizophrenia. Functional impairment of thalamic NMDA receptors is thought to give rise to a disinhibition of thalamocortical projection neurons, potentially leading to cortical dysfunction, excitotoxicity and grey matter loss. Reduced thalamic glutamate prior to the development of psychosis is one mechanism by which this might occur. We tested the hypotheses that subjects at ultra high risk of psychosis (UHR) have reduced thalamic glutamate and that this reduction correlates with reductions in cortical grey matter volume. 27 healthy controls and 27 UHR subjects were recruited. All subjects underwent magnetic resonance spectroscopy (MRS) and structural SPGR MRI scanning on a 3T Signa GE MRI scanner. The MRS acquisition employed a PRESS sequence with a 30ms TE, with a 2 x 2 x 1.5cm voxel placed on the left thalamus. SPGR images were segmented into grey matter, white matter and CSF using SPM. MRS data were analysed using LCModel, with water-scaled values being corrected for voxel CSF content. Voxel-based morphometry (VBM) analysis relating thalamic glutamate levels to cortical grey matter changes were preformed using XBAMM. 10 of the healthy controls and 8 UHR subjects were rescanned after 1 year or after transition to psychosis. Thalamic glutamate was significantly reduced in UHR subjects ($n = 26$; $P = .017$) and directly correlated with grey matter reductions in the left prefrontal, insular and temporal cortical regions most robustly affected in schizophrenia ($n = 26$; $P = .007$). Transition to psychosis in 2 subjects was associated with a further decrease in thalamic glutamate levels (reduction of 30%, $n = 2$, SD = 15%), whereas other ARMS subjects and controls showed a small increase in thalamic glutamate levels between the two time points (increase of 6%, $n = 6$, SD = 23%; and increase of 7%, $n = 10$, SD = 25%, respectively). These results indicate that central glutamate dysfunction predates the onset of schizophrenia and may underlie the neuroanatomical abnormalities associated with the disorder. The findings suggest that enhancement of thalamic glutamate function represents a potential therapeutic target for novel compounds, particularly in the early phase of psychosis.
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NICOTINIC ANTAGONIST EFFECTS ON FUNCTIONAL ATTENTION NETWORKS

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Cognitive impairments like attention deficits are core symptoms of people with schizophrenia, which may be related to nicotinic receptor deficits. Correspondingly smoking prevalence in schizophrenia is increased possibly for self-medication reasons. Complementary co-therapies of novel nicotinic ligands are being developed to add to antipsychotic therapy in order to treat the cognitive impairment of schizophrenia. Therefore we assessed the underlying functional mechanisms of cholinergic attention modulation (1) by functional Magnet Resonance Imaging (fMRI) in healthy subjects while performing the Attention Network Task (ANT) under pharmacological treatment with mecamylamine, a non selective nicotinic antagonist, placebo, or Scopolamine a muscarinic antagonist. The ANT operationalises Alertness, Orienting and Executive Control, the three attentional networks as described by Posner and Petersen (2). Twelve healthy, male, right handed nonsmokers were assessed with fMRI in intervals of at least one week in a single blind, double dum¬my, cross-over- design three times. Prior to each scanning session they received in a randomized order either Mecamylamine or Scopolamine plus placebo or exclusively Placebo. The functional brain activation was assessed during the ANT as operationalised for the fMRI environment by Fan et al. (3). During the placebo trial the orienting and executive control network activations were in line with Posner and Petersens hypothesis (2), resulting in bilateral activations in predominantly frontal and subcortical areas in the orienting trial and in bilateral activations in the anterior cingulum, the precuneus and occipital areas of the left hemisphere in the executive control trial. In both conditions both antagonists effectively disrupted these activation patterns with more extensive disruptions by the nicotinic antagonist. This selective modulation has implications on cognitive enhancements in schizophrenia. Supported by the Deutsche Forschungsgemeinschaft (KFO 112).

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ID: 551981

INHALATION OF Δ9-TETRAHYDROCANNABINOL INDUCES STRIATAL DOPAMINE RELEASE IN HUMANS: AN [11C]RACLOPRIDE PET STUDY

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The use of cannabis increases the risk for developing schizophrenia and worsens its clinical outcome. In schizophrenia, enhanced striatal dopamine function has been consistently demonstrated. Further, in animal models, cannabinoid substances such as Δ9-tetrahydrocannabinol (THC), the main psychoactive component in cannabis, stimulate striatal dopamine neurotransmission by activating cannabinoid CB1 receptors. However, it is not known whether THC affects the human striatal dopamine system. Therefore, as a first step to unravel the role of the endogenous cannabinoid

system in schizophrenia, the purpose of the present study was to investigate whether THC can induce dopamine release in the striatum of healthy human subjects. Seven male subjects were included in this double-blind, randomized, placebo-controlled, cross-over study. They underwent two PET scans after inhalation of either 8 mg THC or placebo using a Volcano® vaporizer. Scanning sessions were separated by two weeks and all subjects were incidental cannabis users. Dopamine release in striatal subregions was assessed by determining changes in binding potential (BPND) of the dopamine D2/D3 receptor ligand [11C]raclopride. In addition, behavioral and subjective effects of THC were assessed using the Brief Psychiatric Rating Scale (BPRS) and Visual Analogue Scales. Venous blood samples were withdrawn to determine THC plasma concentrations. [11C]raclopride BPND was significantly reduced in ventral striatum and precommissural dorsal putamen, but not in other striatal subregions, after inhalation of THC compared with placebo (see table). This is consistent with increased dopamine release in these striatal subregions after THC administration. In addition, THC induced well-known significant behavioral, subjective and physiological effects. Plasma concentrations of THC showed a maximum of 143 ± 91 ng/ml five minutes after inhalation, decreasing rapidly thereafter. These findings indicate that the endogenous cannabinoid system is involved in regulating striatal dopamine release. This allows new directions in research on the effects of THC in schizophrenia.

Table.

Region	BP_{ND} Placebo	BP_{ND} THC	Difference (%)	P-values
Ventral striatum	1.40 ± 0.24	1.35 ± 0.24	-3.43 ± 3.70	0.029 *
Precommissural dorsal caudate	2.18 ± 0.25	2.12 ± 0.13	-2.09 ± 6.44	0.355
Precommissural dorsal putamen	2.75 ± 0.24	2.64 ± 0.16	-3.88 ± 4.07	0.042 *
Postcommissural caudate	1.62 ± 0.19	1.55 ± 0.15	-4.12 ± 7.14	0.157
Postcommissural putamen	2.74 ± 0.29	2.69 ± 0.20	-1.50 ± 4.42	0.329
Striatum	2.28 ± 0.22	2.21 ± 0.12	-2.57 ± 4.42	0.153

ID: 557778

GLUTAMATE INCREASE IN THE ASSOCIATIVE STRIATUM OF PATIENTS WITH SCHIZOPHRENIA: A HIGH-FIELD PROTON MAGNETIC RESONANCE SPECTROSCOPY LONGITUDINAL STUDY

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Glutamate (Glu) has been implicated in the pathophysiology of schizophrenia. Its receptor blockers can induce schizophrenia-like symptoms. There is evidence of a complex interaction between dopamine (DA) and Glu neurotransmission in schizophrenia; but, little is known about the role of Glu in a dense DA innervated region like the associative-striatum. Proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive neuroimaging technique for measuring *in vivo* metabolite concentration such Glu and creatine (Cr). The aim of this study was to compare the Glu levels in patients with schizophrenia, before and after antipsychotic treatment (Risperidone), with appropriate controls in the

associative-striatum (anterodorsal caudate) and in a negligible DA region (cerebellar cortex). Fourteen patients with schizophrenia (age: 24.9 ± 5.9, 7-males) and nineteen healthy controls (age: 26.6 ± 5.9, 13-males) were included. The patients were during an acute psychotic episode (PANSS = 87.8 ± 19.8); drug free for at least one month; and able to consent the procedures involved. They were treated with Risperidone for 6-weeks and the doses (3.43 ± 1.45 mg/day) were adjusted based on clinical judgment (PANSS-post treatment = 56.2 ± 12.6). Concomitant medications were not allowed during the study. Patients underwent two 1H-MRS studies, one before treatment and other after 6-weeks of daily Risperidone treatment. Controls underwent one 1H-MRS study. 1H-MRS were performed on a 3.0-T GE scanner using a PRESS pulse sequence with TR = 1500 ms, TE = 35 ms, 128 repetitions in 4ml voxels (2x2x1 cm) localized on the anterodorsal caudate and cerebellar cortex. All metabolite concentrations were normalized by the relative concentration of Cr. Our results indicate that the increase of Glu in the associative-striatum in schizophrenia is related to the illness and does not change after 6-weeks of antipsychotic treatment. Moreover, the lack of change in the cerebellum suggests that the increase of Glu in schizophrenia is not ubiquitous within the brain and may be associated with DA target regions. The results might tie with the glutamatergic hypothesis of schizophrenia; which propose a disinhibition of dopamine and glutamate subcortical activity due to hypofunction of the cortical NMDA-receptor.
ID: 554585

[11C]GSK931145: A NEW PET LIGAND FOR GLYCINE TRANSPORTER1

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Introduction: NMDA receptors possess recognition sites for the two obligatory co-agonists glutamate and glycine. Enhancing glycine levels at the NMDA site may reverse impaired NMDA function in schizophrenia and glycine transporter1 (GlyT-1) inhibitors are under investigation for its treatment. The development of a GlyT-1 PET radioligand would allow for quantification of GlyT-1 density, determination of drug-induced receptor occupancy and allow researchers to examine the role of GlyT-1 in healthy volunteers and patients with schizophrenia. In this study, [11C]GSK931145 was evaluated as a PET ligand for GlyT1 in animals and translated to humans. Methods: Animals (pig, $n = 2$ and baboon, $n = 2$) were scanned following i.v. administration of [11C]GSK931145 at baseline and following pre-treatment with pharmacological doses of selective GlyT-1 inhibitors (GSK565710 or GSK931145). Dynamic data were quantified using a two tissue compartment model to derive estimates of the distribution volume (VT). Two further primates were scanned for the purpose of obtaining dosimetry estimates. [11C]GSK931145 was then transitioned to humans and healthy volunteers ($n = 6$) were studied following tracer injection. Further ($n = 4$) healthy volunteers underwent whole body PET-CT scans to confirm preclinical dosimetry estimates. Results: In both pig and baboon [11C]GSK931145 demonstrated a heterogeneous uptake with regional distribution volumes consistent with known GlyT1 distribution: brainstem $\sim$ thalamus > cerebellum > cortex. The kinetics were reversible and brain uptake was reduced to homogenous levels

following blockade (pig: VND = 1.81, baboon: VND = 1.53 ± 0.19) and allowing estimation of binding potentials (Table). In humans, the tracer demonstrated reversible kinetics and maintained binding ratios, although a reduced uptake, as compared to preclinical species was observed. Dosimetry data in baboons (ED: 4.5μSv/MBq) was confirmed in humans (ED: 4.1μSv/MBq) with the liver being the dose limiting organ. Conclusion: [11C]GSK931145 is a novel PET ligand for imaging of GlyT-1 which may be used to support clinical development of GlyT-1 inhibitors and to investigate the role of GlyT-1 in the pathogenesis of schizophrenia.

Table. [11C]GSK931145 Binding Potentials in different brain regions

BPND	Brainstem	Thalamus	Cerebellum	Cortex
Pig	1.94(0.16)	1.96 (0.36)	0.97 (0.01)	0.52 (0.01)
Baboon	2.80 (0.59)	2.55 (0.04)	2.28 (0.28)	1.37 (0.10)

Values are mean (SD)
ID: 552010

14. 14. Neuroimaging, Functional

AN AGFCTIVATION LIKELIHOOD ESTIMATION META-ANALYSIS OF FACIAL EMOTION PROCESSING IN SCHIZOPHRENIA

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Background: Although there is a consensus of behavioural findings that patients with schizophrenia have certain deficits in perceiving and expressing facial emotional expression, interpretation of imaging findings is complicated by the range of experimental design and differences in the clinical characteristics of the patient samples recruited may contribute to inconsistencies in the results. Aim: The current study adopted a relatively recent voxel-wise technique, activation likelihood estimation (ALE) to consolidate the existing evidence of the neural basis of facial emotional perception in schizophrenia. Method: Fifteen articles meeting inclusion criteria were recruited for the meta-analysis. 7 articles reported coordinates from patients with schizophrenia alone, 12 articles reported coordinates from patient-control contrasts were included. The ALE analyses were conducted in the Talairach space. Results: The healthy controls activated six distinct brain regions. These regions included large portions of the bilateral fusiform gyri (Brodmann areas [BA] 19, 37), and amygdala, right inferior frontal gyrus (BA47), parahippocampal gyrus (BA28) and cerebellum and the left insula (BA 13). Compared to the controls alone analysis, analysis of schizophrenia samples alone generated more extensive activation of left insula, and also included the right insula and more ventral portions of BA 28 (corresponding to the uncus). Healthy subjects activated prefrontal areas more than patients, in particular medial regions of BA 6, 8, 9 and 10. Patients with schizophrenia activated multiple widespread regions which were relatively limited in extent compared to the cluster sizes generated by previous analyses. Apart from small clusters in dorsolateral prefrontal lobe, the clusters reported were mostly in posterior brain regions: medial aspects of the left fusiform gyrus (BA 20), right inferior occipital gyrus (BA 18), bilateral parahippocampal gyri (BA 35), right posterior cingulate (BA 29, 30), ventral striatum, mid-brain and bilateral cerebellum. Conclusions: ALE meta-analyses showed that when processing facial expressions of emotions, patients with schizophrenia activated some similar regions as controls, namely the bilateral amygdala, bilateral fusiform gyri and insula. However, the extent of activation in these regions was general much more limited in the schizophrenia samples.
ID: 538250

HIPPOCAMPAL HYPERACTIVITY IS ASSOCIATED WITH POSITIVE SYMPTOMS

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Our studies show that overactivity of the hippocampus is associated with positive symptoms in schizophrenia. We previously demonstrated the presence of medial temporal lobe hyperperfusion in separate subgroups of schizophrenia patients who had distinct regions of hypoperfusion (Malaspina 2005). In a new study focused on the hippocampus, we confirmed resting hippocampal hypermetabolism, showing it was restricted to outflow tracks in CA1 and the subiculum. This activation was associated with positive symptoms of the disease. We propose that hippocampal hyperfunction could be a primary defect that drives dysfunction in other cortical and subcortical areas. Among hippocampal outflow sites, we found strong associations of CA1 activity to OFC cerebral blood volume ($F = 5.0$; $P = .015$). CA1 activity was not related to DLPFC activity. OFC itself stimulates a broad range of downstream areas, including subcortical dopamine, and subcortical emotion and cognitive processing regions. Blocking dopamine with antipsychotic medications may decrease psychotic symptoms, but not ameliorate other cognitive and emotional effects that are also driven by the hippocampal dysfunction. CA1 particularly interacts with the amygdala. Increased CA1 and subiculum hippocampal activity is proposed to be a principal driver of psychosis in schizophrenia.
ID: 550739

INDEPENDENT COMPONENTS ANALYSIS OF WORKING MEMORY NETWORKS IN SCHIZOPHRENIA

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Functional activity during performance of neurocognitive tasks differs between patients with schizophrenia and normal controls. One of the most consistent cognitive deficit findings suggests that patients show impairments in the executive functions involved in working memory (Reichenberg and Harvey, 2007). In addition, abnormal functional connectivity within or between neural networks in the brain has been suggested to contribute to the symptoms of schizophrenia and may also be related to the cognitive functioning of patients. Functional activation within these networks has been shown to discriminate between patients with schizophrenia and controls (Calhoun, Maciejewski, Pearlson, and Kiehl, 2007). This study examines differences in functional networks during working memory performance in both patients and controls. Methods: Independent components analysis (ICA) was used to identify networks associated with working memory activity in patients with schizophrenia and normal controls. The networks most strongly associated with task were identified by correlating the time course within individual components with the time course of the task. The two groups were then compared in order to identify any group differences in the maximum and average task/component correlation. Results: Correlations between task and activity within the component with the highest task association ranged from .21–.87 (mean = .546, SD = 0.178) in patients with schizophrenia and from .27–.87 (mean = .594, SD = 0.138) in controls. While patients with schizophrenia tended to have a slightly lower task/component correlation and a greater variability of task/component correlation, there was not a significant difference between groups ($P = .389$, effect size = .297). Conclusions: These results suggest that patients with schizophrenia activate a working memory network associated with task to the similar degree as controls. Thus, differentiating groups using functional activity during working memory performance likely relies on overall strength of activation and/or overall pattern of activation.

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ID: 550659

AN EVENT-RELATED FMRI STUDY OF BIOLOGICAL MOTION PERCEPTION AND SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Schizophrenia (SZ) patients have difficulty processing dynamic visual stimuli (eg, motion). SZ is also characterized by social dysfunction such as impaired Theory of Mind (ToM). Biological motion (BM) refers to movements generated by living beings. The visual system rapidly extracts socially-relevant information from BM and a deficit in BM perception may lead to detrimental consequences for social information processing. Our past work indicates that BM perception deficit in SZ is associated with reduced social functioning. The present study aimed to identify the neural underpinnings of impaired BM perception in SZ and to further specify the relationship between BM perception and social deficits. We measured brain activation using event-related fMRI in SZ and healthy controls (CO) during a BM perception task which required participants to decide whether a point-light stimulus display looked like a human or not. Three types of stimuli were presented (BM, scrambled, and partially scrambled motion). Clinical symptom ratings and ToM tests were also administered. Signal detection analyses showed a reduced sensitivity in SZ compared with CO on BM detection, which was due to higher false-alarm rates ('biological' response to scrambled motion) rather than lower hit rates ('biological' response to BM). The fMRI results from CO indicated that the posterior superior temporal sulcus (STSp) is strongly activated by BM, but not by scrambled motion. Interestingly, strong STSp activation was also observed for scrambled or partially scrambled motion when the participant perceived it as BM. STSp activation in SZ was not selective to BM, resulting in relatively greater activation to scrambled motion compared to CO. Furthermore, this abnormal STSp activation was associated with ToM deficits and positive symptoms. In CO, STSp activation in relation to BM perception interacted with observer's response regardless of the stimulus, highlighting the influence of top-down processing on perceptual experience. SZ's increased false-alarm rates and accompanying elevated STSp activation to non-BM indicate that BM perception deficit is due to misperception of non-BM as biological rather than a failure to perceive BM. Overall, these results suggest an intricate interaction among subjective perceptual experience, STS activation, psychotic symptom, and social deficits. This study was supported by NARSAD.
ID: 550653

NEUROINFLAMMATION IN SCHIZOPHRENIA: A POSITRON EMISSION TOMOGRAPHY STUDY

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Schizophrenia is a chronic and disabling brain disease with unknown etiology. It has been suggested that neuroinflammation plays a role in the pathophysiology of schizophrenia. Neuroinflammation is characterized by activated microglia cells that show an increase in the expression of the peripheral benzodiazepine receptor (PBR). The isoquinoline (R)-PK11195 [(R)-N-methyl-N-(1-methylpropyl)-1-(2-chlorophenyl)isoquinoline-3-carboxamide)] is a PBR ligand and can, after labeling with carbon-11, be used for imaging of neuroinflammation with positron emission tomography (PET). Neuroinflammation was hypothesized to be more profound during psychosis and therefore 7 schizophrenic patients were included that had a score of at least 5 on the positive item of the PANSS, or a score of 4 on two items. The patients were compared to 8 age-matched healthy controls. A dynamic PET scan of 60 minutes was acquired after a bolus injection of 404 ± 49 MBq of [11C]-(R)-PK11195. During the PET scan, whole blood activity was monitored using an automated sampling system. In addition, blood samples were taken 20, 45 and 60 minutes after tracer injection to correct for metabolites. All subjects underwent a T1-weighted MRI scan. The T1-weighted MRI image was co-registered with the PET image of the

same subject and both the MRI and PET images were normalized to a T1-template in SPM[2]Automated regions of interest were used to generate time-activity curves of the PET image, which were fitted to a two-tissue compartment model to calculate the binding potential (BP) per region of interest. The whole brain BP was non-significantly higher in patients (1.81 ± 0.61) as compared to the healthy controls (1.36 ± 0.39). A statistically significant higher BP of [11C]-(R)-PK11195 was found in the hippocampus (2.07 ± 0.42 vs. 1.37 ± 0.30; $P = .004$), midbrain (2.63 ± 0.40 vs. 1.68 ± 0.60; $P = .009$) and pons (2.85 ± 1.42 vs. 1.54 ± 0.32; $P = .014$) of patients as compared to healthy volunteers. In the basal ganglia an almost significant increase in BP was found in patients as compared to healthy volunteers (1.82 ± 0.59 vs. 1.39 ± 0.28; $P = .054$). No abnormalities were found on the MRI images. In a small group of patients, the present study showed that neuroinflammation may play an important role in schizophrenia, especially during psychosis. This neuroinflammation may precede brain atrophy. This study was funded by the Stanley Medical Research Institute. ID: 550619

DIFFERENTIAL WORKING MEMORY DYSFUNCTION IN DEFICIT AND NONDEFICIT SCHIZOPHRENIA: AN FMRI STUDY

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Numerous neuroimaging studies suggested that working memory (WM) dysfunction is a core component of schizophrenia. However, the extreme heterogeneity among patients hindered to yield a consistent WM dysfunction model. The aim of the present study was to compare the brain activation patterns of deficit schizophrenia (DS) and nondeficit schizophrenia (NDS) under parametric increasing WM load, and investigate the relationship of WM-dysfunction, cerebral activation, and diagnostic specificity. We used functional magnetic resonance imaging (fMRI) and a parametric n-back WM task ($n = 0, 1, 2$) to examine 10 DS patients, 10 matched NDS patients and 10 healthy controls. In all three groups, we found increasing reaction times (RT) and decreasing accuracy with increasing load. Schizophrenic patients performed worse and slower than controls, while only the differences between DS and controls on the 2-back task achieved significant. Compared with controls, patients with schizophrenia showed more activation in frontoparietal network and subcortical regions, whereas the 2 schizophrenia subtypes differed in the activity or recruitment with increasing load. At each WM load level, NDS patients showed more activation in prefrontal cortex than that of controls, which recruited ventrolateral prefrontal cortex (VLPFC) to a significantly greater degree. However, DS patients showed more activation in dorsolateral prefrontal regions (DLPFC) than that of controls at load 1 and significant hypofrontality at load [2]In addition, the DS patients showed more activation in inferior parietal cortex than that of controls at each WM load level. The results indicated that peak activation of the WM-system is reached at a lower processing load in schizophrenic patients than in healthy controls. Compared with controls, NDS patients used greater prefrontal resources (ie, hyperfrontality) and achieved lower but relatively normal accuracy (ie, physiological inefficiency), which reflect a compromised neural strategy for handling information mediated by the prefrontal cortex. However, DS patients failed to sustain the prefrontal network and achieved significant lower accuracy, even with the compensatory recruitment of inferior parietal

cortex. The present study provided further support for that deficit schizophrenia may have characteristic impairment of prefrontal lobe. This research was supported by grants from NSFC (30700236) and RFDP (20070533067).
ID: 550593

TASK RELATED ACTIVATION DEFICITS IN SCHIZOPHRENIA ARE DUE TO AN AROUSAL-COGNITION DECOUPLING: *AN EEG-FMRI STUDY*

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Introduction: Because cognition is correlated to social and occupational status, it is a target to therapeutic interventions. Among the latter, many of the procognitive drugs target arousal systems. This study attempts to test for the rational of arousal targeted intervention to improve cognition. Are most hypoactive regions sensitive to arousal? If it is the case, then are hypoactive regions also merely hypo-aroused or is it that cortical arousal is no more properly converted in cognitive activity, ie, not correctly coupled?. Methods: Seventeen right-handed patients and the same number of controls took part in the study. Participants performed a Sternberg-like visual working memory paradigm during the EEG-fMRI acquisition. Because the low frequencies in the EEG (5-9.5 Hz) are well correlated with cortical arousal, this measure allows to map cortical regions sensitive to it. All main effects maps had a threshold of $P < .001$, and masked group difference at $P < .01$ (ext. 800 mm3 in both). The overlap between the hypoactive and arousal sensitive regions was evaluated by a mutual information measure and its statistic by bootstrapping. The arousal-cognitive coupling was evaluated by the slope of the regression line between the arousal effect and the task effect for the voxels belonging to the same region. Results: Quite all the voxels that were hypoactive in the patient group were sensitive to arousal (MI = 0.03, $P < 10$-5). All correspond to a prefronto-parietal network. Although there were less than expected arousal sensitive voxels that were not hypoactive in patients, these still correspond to a substantial group covering the posterior visual regions. Patients' hypoactive regions did not show a reduction of their arousal sensitivity, neither could we observed a global reduction of arousal using behavioral or EEG measures. Conversely, the arousal-cognition coupling index was largely decreased in the hypoactive areas ($P = .005$). Conclusion: Arousal targeted procognitive drugs might well help in reducing patients cognitive deficit since all task-related hypoactive regions are arousal sensitive. However, they would do so just by optimizing arousal which is not different from controls in this stabilized treated group. Nevertheless it would not target the core of the problem, ie, the conversion of arousal triggered activity increase in a coherent cognitive activity. Such arousal modulating or potentiating interventions remain to be invented.
ID: 550565

REPRODUCIBILITY OF FMRI ACTIVATIONS IN PATIENTS WITH SCHIZOPHRENIA

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Longitudinal functional Magnetic Resonance Imaging (fMRI) studies of schizophrenic patients might be of great interest in evaluating brain response to therapeutic interventions. However, it is crucial to assess the reliability of fMRI paradigms. Indeed, it has been suggested that schizophrenic patients present unreliable activations (Manoach et al., 2001). The aim of this study was to evaluate reproducibility of fMRI activations in schizophrenic patients. Ten right-handed (RH) patients (DSM IV) and 10 RH controls were scanned 21 months apart during a story listening paradigm. This paradigm involved 2 conditions (French narrative versus Rest and French narrative versus Tamil). The former text was easier to understand while the second needed more integrated language processes. Task performances were evaluated through a post session comprehension questionnaire.Two indices of reproducibility were used: the intersession overlap percentage of activation maps and the intersession relative standard deviation (RSD) computed on a voxel-wise basis. Individual RSD maps were entered in a SPM analysis comparing patients and controls. In both conditions, patients had lower comprehension scores than controls. Regarding the Text versus Rest condition, patients and controls did not differ significantly neither for the overlap percentage (65.37 ± 8.28 vs 60.50 ± 7.04) nor for the RSD, and task performances did not impact on reproducibility. Concerning the Text minus Tamil condition, patients had a significantly lower overlap percentage (30.65 % ± 15.81%) than controls (47.00 % ± 11.59 %, $P = .005$) and, in comparison with controls, patients intersession variability assessed with the RSD was significantly higher ($P < .001$, uncorrected) in 3 left hemispheric regions: the posterior part of the middle temporal gyrus, the pars triangularis of the inferior frontal gyrus and the medial part of the superior fontal gyrus. However, when controlling for task performances, these differences were no longer significant. In patients with schizophrenia, activations were as reliable as in healthy subjects for a task targeting automatic cognitive processes. When more integrated cognitive processes were involved, the reproducibility of activations was decreased in patients probably due to worse task performances. Hence, longitudinal fMRI studies might be suited for patients with schizophrenia but the effect of task performances should be carefully assessed.
ID: 550527

AN FMRI STUDY OF PREDICTIVE MOTOR MODELS IN SCHIZOPHRENIA

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Introduction: Patients with schizophrenia with positive symptoms can mis-attribute their own actions to an external source; this labelling of an action as ones own is hypothesized to depend on a match between the predicted and actual sensory consequences of the action. Previously, we have shown that there are sensory prediction deficits in patients with schizophrenia2 and we now examine the underlying neural basis of this phenomenon using functional magnetic resonance imaging (fMRI). Methods: A fMRI study of 20 patients with schizophrenia, and a matched group of controls, examined while performing a sensorimotor force matching task on a 3T scanner. Data were analysed using SPM5 with analyses of main effect of group and task and an interaction between these factors. Activation was assessed for correlation with the positive symptoms of psychosis. Results: Performance was matched between the groups, as assessed by equivalent force generated and perceived during the task. The fMRI results demonstrated a significant interaction between group and task evident in the right postcentral gyrus (Brodman Area 3; Talairach coordinates 57, −12, 48). This sensory region demonstrated activation in the control subjects only when a force was being applied to their left index finger; but in patients also showed activation when a force was anticipated, on the basis of a predictive motor model, but no force was actually being applied to this finger. There were no correlations with composite scores

on positive symptom scales. Discussion: The results show that self-generated forces showed less attenuation within the post central gyrus in the patient group, suggesting a dysfunction in their ability to predict the sensory consequences of their actions. Although most of the patients were treated with antipsychotic medication, the absence of any difference between patients and healthy volunteers in the force levels applied during the experiment suggests that there is no systematic effect of medication upon motor performance; indeed there was no significant correlation between the chlorpromazine dose equivalents of medication and the degree of functional attenuation demonstrated by patients. The present study provides support for the presence of a dysfunctional sensory predictive mechanism based in the sensory cortex in schizophrenia.
ID: 550457

OPPOSITE NEURAL EFFECTS OF THE MAIN PSYCHOACTIVE INGREDIENTS OF CANNABIS ON THE NEURAL SUBSTRATE FOR PSYCHOSIS

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The cannabis plant has many psychoactive ingredients. Delta-9-THC, the main psychoactive ingredient of cannabis, impairs memory and induces anxiety and psychotic symptoms acutely and increases the risk of psychotic disorders in regular cannabis users. There is increasing interest in the therapeutic potential of Cannabidiol (CBD), the second most abundant component of Cannabis. CBD does not impair memory, may have anxiolytic and possibly antipsychotic effects. Hence, we compared directly the acute neural effects of these two active ingredients of cannabis, by combining pharmacological challenge with fMRI in 15 healthy volunteers with minimal exposure to cannabis and other illicit drugs. Using a double-blind, repeated measures, within subject design and oral challenge with 10mg of delta-9-THC, 600mg of CBD or placebo, we examined whether delta-9-THC and CBD have opposing effects on the neural substrates of verbal memory and whether they also have opposing effects on the neural substrates of psychotic symptoms induced by delta-9-THC. Delta-9-THC induced psychotic symptoms acutely but there was no change in psychotic symptoms with CBD. During the memory task, delta-9-THC and CBD had opposing effects on activation in the anterior cingulate and the striatum bilaterally. While delta-9-THC attenuated striatal activation, CBD increased activation in the striatum bilaterally. Effect of delta-9-THC on striatal activation was inversely correlated with the psychotic symptoms induced by it concomitantly. Thus, the modulation of striatal activation by delta-9-THC may underlie the psychotogenic effects of cannabis. Opposing effects of CBD on striatum and anterior cingulate, key neural substrates for psychotic symptoms may suggest possible therapeutic role of CBD in countering the adverse psychological effects of cannabis and more specifically cannabis-induced or cannabis use related psychotic disorders. Funding: Psychiatry Research Trust, UK.
ID: 550414

OBJECT-LOCATION SOURCE RECOGNITION IN WORKING MEMORY: AN FMRI STUDY

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Source monitoring is suggested to be an important aspect of the episodic memory system, integrating different contextual information related to the specific memory. The purpose of the study was to investigate a previous studied network implicating the posterior precuneus, left ventro-lateral frontal cortex and left dorsal inferior frontal cortex in an event related source monitoring working memory fMRI paradigm. Lundstrom et al. (2005) suggested a two step process in this system were the left ventro-lateral frontal cortex is associated with the search of relevant information and working in tandem with the posterior precuneus for regeneration of rich contextual information. Secondly, areas in the dorsal inferior frontal cortex were suggested to be important for selection of correct information. fMRI BOLD data were acquired on a 3 T General Electric Signa HDx scanner. Twenty healthy subjects completed a working memory source monitoring paradigm. In each trial subjects were instructed to remember several neutral pictures and their location. Memory test (recognition) of object by location was collected immediately after encoding of each trial. Memory load were varied between three to five units in eight possible different locations. Preliminary results showed that all conditions of load activated the areas of interest. Posterior precuneus and the ventro-lateral frontal cortex were activated bilaterally whereas the dorsal inferior frontal cortex was activated on the left side only. Using a linear contrast on memory load a trend towards increasing activation in posterior precuneus and right ventro-lateral frontal cortex with load was obtained, while the left dorsal inferior frontal cortex showed a declining activation with increasing memory load. The previously suggested network by Lundstrom et al. (2005) was activated in a source monitoring working memory task. Future studies will be conducted where the modulation of this network in a source monitoring working memory task in patients with schizophrenia will be investigated.
ID: 550408

NEURAL CHANGES ASSOCIATED WITH SUCCESSFUL RELATIONAL LEARNING IN SCHIZOPHRENIA

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Relational learning and memory, processes dependent upon medial temporal lobe (MTL) function, may be particularly vulnerable in schizophrenia. This study investigated neural changes with fMRI before and following training on a relational learning paradigm, transverse patterning (TP), in schizophrenia volunteers (SV) and healthy volunteers (HV). Diffusion tensor imaging (DTI) was also used to investigate the integrity of the fornix, a major hippocampal white matter tract. Proton magnetic resonance spectroscopy (1H-MRS) was acquired from the hippocampus to assess neurochemistry. Seventeen SV and 15 HV participated in this study. MR scanning was conducted on a 3T Philips MR scanner at the Kirby Imaging Center, Kennedy Krieger Institutes. The imaging protocol consisted of hippocampal single-voxel 1H-MRS, and DTI; fMRI scans were acquired during initial TP learning and following training. The fMRI results reveal different patterns of neural activity between groups despite similar performance. For HV, MTL activity was present during the initial stages of TP learning, but was not present following training. After training HV parietal lobe activity was prominent. In contrast, SV exhibited no MTL activity but instead engaged the anterior cingulate and cuneus during initial TP learning, and visual cortical regions following training. Fornix fiber tracking results revealed reduced fractional anisotropy (FA) in SV compared to HV, and 1H-MRS revealed a trend toward elevated

hippocampal glutamate+glutamine in SV compared to HV. HV engaged the MTL and parietal regions, which are part of a neural network commonly associated with relational learning. These experience dependent activation patterns support the hypothesis that the MTL is important for encoding information, but additional brain regions are used for memory retrieval. These results also show that successful relational learning in SV is accomplished through alternative brain networks that include frontal and visual circuits. The reduced fornix FA in SV suggests compromised connections to/from the hippocampus, and altered glutamate+glutamine in SZ suggests compromised hippocampal function. The DTI and MRS changes may help to explain why MTL activity, commonly observed during relational learning in HV, is not observed in SV.
ID: 550369

SEX DIFFERENCES IN THE PROCESSING OF POSITIVE AND NEGATIVE AFFECT IN SCHIZOPHRENIA: AN FMRI AND ERP STUDY

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Introduction: We have demonstrated recently disturbed normal sexual dimorphism in cerebral function of schizophrenia patients during exposure to aversive pictures (Mendrek et al., 2007), as well as during emotional memory processing (Guillem et al., 2008). The present study was designed to extend these preliminary findings by including appropriate control groups, studying both negative and positive affect, and combing functional magnetic resonance imaging (fMRI) with event-related potentials (ERP). Methods: The fMRI (BOLD 3T) and ERP (56 EEG electrodes) data were collected on separate days during presentation of unpleasant-high arousal, unpleasant-low arousal, pleasant-high arousal and pleasant low arousal pictures. The data of schizophrenia men (SZ-M) and schizophrenia women (SZ-W) were compared to healthy control men (HC-M) and healthy control women (HC-W). Results: fMRI: there were no differences between sexes during exposure to pleasant stimuli either in patients or in controls, though overall HC-M and HC-W exhibited more activations in the inferior frontal, parietal and temporal cortex, as well as the thalamus and amygdala. In contrast, during exposure to negative pictures both HC-M and SZ-W activated occipital, orbitofrontal and middle frontal cortex, cerebellum and caudate, while HC-W and SZ-M showed significant activations only in the occipital region. ERP: both SZ-M and SZ-W presented significantly reduced late positive component (LPC) at the anterior and central regions relative to controls. However, while the SZ-W showed smaller LPC amplitude and were less reactive to emotional valence than to the arousal content of the image, the SZ-M showed the opposite pattern with smaller LPC amplitude and less reactivity to the arousal content than to the emotional valence of the images. Conclusion: Present results reveal disturbed sexual dimorphism in cerebral function associated with emotion processing in schizophrenia and suggest that affect might be mediated by different neural mechanisms in men and women patients. Moreover, the data point to the importance of considering sex of tested participants in neurophysiological investigations of cognitive, perceptual and emotional processing. Acknowledgements/Funding: Canadian Institute of Health Research (CIHR), Fonds de recherche en Santé Quebec (FRSQ), participants.
ID: 550343

DOPAMINE EFFECTS ON REWARD ANTICIPATION AND REVERSAL LEARNING IN SCHIZOPHRENIA

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In those diagnosed with schizophrenia, dopamine dysfunction may interfere with an error feedback signal that encodes surprising reward or presentation of reward-indicating, conditioned stimuli. Functional brain imaging shows that unmedicated schizophrenics display reduced activation of the ventral striatum during reward anticipation, ie, after presentation of a conditioned stimulus that predicts reward. Furthermore, reduced activation of the ventral striatum interferes with behavioral adjustment after unexpected outcomes. In healthy controls, learning of a probabilistic reversal task is driven by the connectivity between the substantia nigra and dorsal striatum, which may reflect dopaminergic input. To further explore the interaction between dopaminergic neurotransmission, reward anticipation and reversal learning, we used a multimodal imaging approach that combines positron emission tomography and functional magnetic resonance imaging. The radioligand 18-F-DOPA was used to measure dopamine synthesis capacity in the brainstem, dorsal and ventral striatum. The results were correlated with functional activation elicited by a probabilistic reversal task and a reward anticipation task in unmedicated schizophrenic patients and healthy controls. The schizophrenic group's dopaminergic dysfunction diminishes the group's ability to learn quickly and precisely. They are, however, able to compensate for those neural errors by engaging alternative circuits.
ID: 550316

FUNCTIONAL MAGNETIC RESONANCE IMAGING OF INNER SPEECH IN SCHIZOPHRENIA

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Auditory verbal hallucinations have been linked to defective monitoring of one's own verbal thoughts. Previous studies have shown that patients with auditory verbal hallucinations show attenuated activation of brain regions during the monitoring of inner speech. Fifteen patients with schizophrenia and 12 healthy controls were studied using functional magnetic resonance imaging while listening to sentences or imagining sentences. Significant interactions between group (controls vs. patients) and task (listening vs. inner speech) were seen for the left superior temporal gyrus, left posterior cingulate, right sub-gyral of the temporal lobe, and bilateral cingulate gyrus. Attenuated activation of the left superior temporal gyrus in schizophrenia patients during the processing of self-generated speech may indicate deficits in self-monitoring.
ID: 550300

M100 PHASE-LOCKING IN SCHIZOPHRENIA: ASSOCIATIONS WITH SYMPTOMS AND MEDICATION

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Electroencephalographic (EEG) and magnetoencephalographic (MEG) studies have observed an abnormally small 100 ms auditory evoked response (N100/M100) in patients with schizophrenia (Sz), which could be the result of decreased low-frequency phase locking (PL). Associations between low-frequency PL, medication status, and patient symptoms are largely unexamined and may shed light on mechanisms contributing to the abnormal response and options for treating it. The present study examined whether left or right superior temporal gyrus (STG) PL differs as a function of medication or patient symptoms. Dense-array MEG from 45 controls and 45 patients with Sz administered a standard paired-click task produced left- and right-hemisphere 100 ms STG PL measures. Patients on typical antipsychotics (haldol and prolixin) showed less STG theta-band PL than controls and patients on atypical antipsychotics (aripiprazole, olanzapine, risperidone, quetiapine). Quadratic associations indicated that the more patients' STG theta-band PL values diverged from the mean PL value observed in controls, the more impaired was the patient (higher PANSS/SANS scores). As MEG primarily reflects the activity of cortical pyramidal cells, PL abnormalities may be the result of problems timing the interaction of these cell types (perhaps dysfunction of glutamatergic input to inhibitory interneurons as well as dysfunction of $GABA_A$-receptor mediated hyperpolarization). Findings indicate that several atypical antipsychotics may normalize STG theta-band activity and that normalization of theta-band PL would be a promising target of treatment in patients.
ID: 550276

VELOCITY RELATED MECHANISMS OF SMOOTH PURSUIT EYE MOVEMENTS (SPEM) IN SCHIZO-PHRENIC PATIENTS. AN EVENT RELATED FMRI STUDY

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In about 50% of schizophrenic patients the SPEM velocity is reduced compared to healthy subjects. In this study we wanted to find out velocity-related regions which show different activations in the patient group. Methods: We included 19 schizophrenic patients and 20 healthy subjects (all right handed males). Medication was: Quetiapine (7), Amisulpride (5), Olanzapine (4), Ziprasidone (2), Aripiprazole (1). Exclusion criteria were: medication with Risperidone, Clozapine, Lithium, Benzodiazepines and Carbamazepine. We presented ramps with different SPEM-velocities (5, 10, 15, 20°/s) in a range of 40° from right to left. An event related design was used to analyze the fMRI data with spm2. Eye movements were registered in the scanner environment. Velocity of the targets were correlated with the BOLD (MRT: 3 Tesla, 38 x 3 mm, 158 Volumes *4 sessions, TR 2.62) Results / Discussion: In both groups the frontal eye fields the intraparietal sulcus, V1 and V5 were activated. Comparing the patients with the healthy subjects revealed lesser activation in the Putamen and the supplementary eye field (SEF) of the patient group. Since the SEF is related oculomotor prediction and learning, reduction of SEF activation seems to be in line with previous findings of frontal dysfunction in the patients. Reduced activation in the Putamen seems to repre-

sent a deficit in the feedback loop from the FEF -> Putamen -> Thalamus -> FEF.
ID: 550274

FDG-PET AND MRI IMAGING OF THE EFFECTS OF TYPICAL AND ATYPICAL NEUROLEPTICS ON THE THALAMUS AND STRIATUMI IN SCHIZOPHRENIA

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Twenty-two never-previously medicated psychotic adolescents received an anatomical MRI and FDG-PET scans at baseline and after 8–9 weeks of a randomized double-blind trial of either olanzapine or haloperidol and 15 adult patients with schizophrenia received an MRI and FDG-PET scans after 6 weeks of a randomized double-blind trial of either sertindole or haloperidol. Adults were then crossed to the other treatment and scanned again at week 12. Caudate nucleus, putamen and globus pallidus were traced on the MRI. Younger adolescents (13–15) treated with haloperidol had a significant increase in the relative metabolic rate of both the caudate nucleus and putamen at dorsal levels while treatment with olanzapine generally decreased metabolic rates. The difference between the two medications was most marked anteriorly. Similarly, in the adult sample we found that the metabolic rates of the caudate nucleus and the putamen were significantly higher with haloperidol than with sertindole.
ID: 550232

DIFFERENTIATING VOLITION FROM HEDONIA USING A MONITARY REWARD TASK DURING FMRI

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Reward paradigms are useful in understanding volition and hedonia. Few studies have examined both motivational aspects of reward circuitry or have compared fMRI activity to reports of motivation and hedonia. Studying this circuitry in relation to self report measures may provide insight into the relationship between these states and psychopathology. Seven healthy subjects performed a monetary reward task during event related fMRI. Subjects responded to one of two cues that signified increasing score for a correct and fast response after a variable delay. After a second delay, subjects received feedback on their accuracy. All subjects also completed self report measures of volition and hedonia: the TEPS, MEI and Chapman Questionnaire. fMRI data were analyzed using GLM in FSL. Cues activated visual cortex, supplemental motor area (SMA), anterior cingulate, primary motor and sensory cortex (SMC; thresholded at Z > 1.6, cluster $P < .05$). Activity in the nucleus accumbens (NuAc) was modulated by reward magnitude. During the first delay prior to responding, activity was found in the insula, striatum, cingulate, pre-SMA, and SMC. Activity in the SMA, striatum and anterior cingulate was modulated by reward magnitude. SMC, thalamus, inferior frontal lobe, orbital frontal cortex, striatum, anterior cingulate, and inferior parietal lobe were active during response. Self reports of social motivation correlated with reaction time on the no reward condition ($r = -.67$, $P = .045$) and mental motivation correlated with social pleasure ($r = -.71$, $P = .03$). The TEPS correlated with activity during the cue in the putamen ($r = -.80$, $P = .03$), NuAc ($r = -.93$, $P < .003$) and SMA ($r = -.85$, $P < .02$). Task activated circuitry

related to regions of motor planning, action and reward anticipation. Reward magnitude modulated activity of the NuAc during the cue and activity in regions of motor planning before response, suggesting reward modulates volitional action and reward anticipation. Lower reports of hedonia were associated with greater activity in regions modulated by reward magnitude and self reported motivation was reflected in faster reaction time. This study is one of the first to explore and link motivation as a state and behavior and their circuitry. Such work may be the first step towards understanding avolition and anhedonia in psychiatric disorders like schizophrenia, where normal consummatory hedonia does not overcome inaction and anticipatory anhedonia. Irving Center NIH CTSA Pilot Award.

ID: 550012

ALTERED HIPPOCAMPAL NEURONAL ACTIVITY AND PERFUSION IN SCHIZOPHRENIA

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Alterations in the function of hippocampus (hipp.) and medial temporal lobe (MTL) have been described in schizophrenia (SZ). The hipp. shows elevated basal perfusion and decreases in task-stimulated activations in SZ, especially in the anterior hipp. Aim: We will examine predictions of the metaplasticity and SZ model that hipp. subfield activations and perfusion will differ in the three populations, NV, SZ-on and SZ-off, especially in DG and CA3. The model of pathophysiology we have proposed in MTL invokes distinct activations in hipp. subfields and distinct correlates between the subfields and SZ symptoms. We will carry out high resolution (hi-res) imaging for perfusion with VASO and activation with fMRI BOLD (the latter using MTL encoding and relational memory tasks). Vascular Space Occupancy (VASO) will be used to assess hi-res rCBV (measure of perfusion) focused on hippocampal subfields during rest. Then, using fMRI BOLD with high resolution, we will describe hipp. subfield activations in SZ alone (SZ-off) and in SZ treated (SZ-on) both contrasted with NV's. With respect to perfusion, we predict a reduction in DG perfusion and an increase in CA3 perfusion. We predict a reduction in task-associated activation in DG and CA3. In the SZ-off, we predict a direct correlation between psychosis and CA3 perfusion and a loss of that correlation in the SZ-on. Methods: High resolution fMRI images (1.5x1.5x1.5 mm3) and T2w images (0.5x0.5 mm2 in-plane resolution, 2mm thick slices) have been acquired so far on 1 NV, 2 SZ-ON and 2 SZ-OFF. BOLD images were co-registered to the T2w image; subfields DG, CA1, CA3 and subiculum were drawn on the T2w image, fMRI analysis was performed and % BOLD signal change extracted. Results and conclusion: This early data analysis was focused on providing high-res. subfield rCBV results for CA3 in the three groups and an initial look (noting the low subject number) at a correlation between rCBV and BOLD activation. In CA3 we see an increase in rCBV in the SZ-OFF 1.69 (0.69) compared with NV 1.38 and SZ-ON 1.49(0.50), however this CA3 increase in the SZ-OFF was only apparent in the anterior CA3 and did not obtain in the posterior CA3. The outcomes correspond to our predictions in these subjects. Subfield high-res. fMRI BOLD results were correlated with rCBV data; while numbers are clearly too low to demonstrate a correlation, the direction of the association in both the patient groups is inverse.

ID: 549965

SCHIZOPHRENICS LEARN A VISUAL MATCH-TO-SAMPLE TASK BY USING THE PREFRONTAL CORTEX FOLLOWING INFORMATIVE ERROR FEEDBACK

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Neither healthy volunteers (NV) nor research participants diagnosed with schizophrenia (SZ) can quickly learn a difficult perceptual matching task without informative feedback. But in the presence of feedback both groups improve quickly in their accuracy. This report examines how these two diagnostic groups successfully adapt to informative feedback. The brain activity characteristics of each group, before and after feedback, are also presented. Those findings demonstrate how each group responds to the task initially, before learning, and subsequently, after learning. This fMRI study lasted about sixty minutes and consisted of three consecutive twenty minute stages. Each stage provided forty-eight match-to-sample trials that required the subject to judge whether the height of the first rectangle was identical to the height of a second rectangle. Feedback, only provided during the second stage of the study, consisted of an icon that indicated the subject's trial accuracy. Subjects who improved by 7% or more during stage-2 were classified as learners. 12 out of 21 NV, and 10 out of 18 SZ met "learner" criteria. Correct trials in all stages were classified in one of two ways, correct-following-correct (CC) or correct-following-incorrect (IC). IC and CC trials were assessed in each stage. IC versus CC contrasts were also generated for each group at each stage. IC-minus-CC contrasts were significantly different between stages and between groups. NV IC-minus-CC contrasts: Stage-one contrasts revealed significant changes in orbital frontal cortex, dorsal medial frontal cortex, parietal cortex, ventral striatum, caudate, and globus pallidus. Stage-two (feedback) contrasts revealed significant changes in amygdala, hippocampus, ventral striatum, globus pallidus, putamen, dorsal medal frontal cortex and parietal cortex. Stage-two (uniquely) contained significant habenular activity for IC and CC trials. Stage-three contrasts revealed significant changes in amygdala, hippocampus, globus pallidus, and putamen. SZ IC-minus-CC contrasts: Stage-two contrasts provided significant change clusters in the left dorsolateral prefrontal cortex. No other significant changes were observed. Healthy volunteers engage an extensive subcortical system when confronted with this implicit learning task. Parietal, orbital and medial frontal systems also participate. These findings emphasize the SZ group's ability to "solve" a difficult perceptual problem through cortical systems.

ID: 549802

SCHIZOPHRENICS LEARN A VISUAL MATCH-TO-SAMPLE TASK BY USING THE PREFRONTAL CORTEX FOLLOWING INFORMATIVE ERROR FEEDBACK

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Neither healthy volunteers (NV) nor research participants diagnosed with schizophrenia (SZ) can quickly learn a difficult perceptual matching task without informative feedback. But in the presence of feedback both groups improve quickly in their accuracy. This report examines how these two diagnostic groups successfully adapt to informative feedback. The brain activity characteristics of each group, before and after feedback, are also presented. Those findings demonstrate how each group responds to the task initially, before learning, and subsequently, after learning. This fMRI study lasted about sixty minutes and consisted of three consecutive twenty minute stages. Each stage provided forty-eight match-to-sample trials that required the subject to judge whether the height of the first rectangle was identical to the height of a second rectangle. Feedback, only provided

during the second stage of the study, consisted of an icon that indicated the subject's trial accuracy. Subjects who improved by 7% or more during stage-2 were classified as learners. 12 out of 21 NV, and 10 out of 18 SZ met "learner" criteria. Correct trials in all stages were classified in one of two ways, correct-following-correct (CC) or correct-following-incorrect (IC). IC and CC trials were assessed in each stage. IC versus CC contrasts were also generated for each group at each stage. IC-minus-CC contrasts were significantly different between stages and between groups. NV IC-minus-CC contrasts: Stage-one contrasts revealed significant changes in orbital frontal cortex, dorsal medial frontal cortex, parietal cortex, ventral striatum, caudate, and globus pallidus. Stage-two (feedback) contrasts revealed significant changes in amygdala, hippocampus, ventral striatum, globus pallidus, putamen, dorsal medal frontal cortex and parietal cortex. Stage-two (uniquely) contained significant habenular activity for IC and CC trials. Stage-three contrasts revealed significant changes in amygdala, hippocampus, globus pallidus, and putamen. SZ IC-minus-CC contrasts: Stage-two contrasts provided significant change clusters in the left dorsolateral prefrontal cortex. No other significant changes were observed. Healthy volunteers engage an extensive subcortical system when confronted with this implicit learning task. Parietal, orbital and medial frontal systems also participate. These findings emphasize the SZ group's ability to "solve" a difficult perceptual problem through cortical systems.
ID: 549802

NEURAL BASIS OF HUMOUR APPRECIATION AND UNDERSTANDING OTHERS' INTENTIONS IN SCHIZOPHRENIA: AN FMRI STUDY

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Individuals with schizophrenia have social cognition deficits which affect their ability to recognise humour and understand others' intentions. It remains unclear how humour appreciation interacts with understanding of others' intentions in patients. Using fMRI, we compared the neural response for the interaction of these two processes between patients with schizophrenia and healthy controls. We hypothesised that the lateral prefrontal cortex of patients with schizophrenia would be underactivated compared to that of healthy controls. Nineteen right-handed individuals with DSM-IV diagnosis of schizophrenia (mean age = 37.4 ± 10.7) and 22 right-handed healthy controls (mean age = 36.8 ± 10.4) underwent fMRI scans (Philips Intera 3T system; TR = 3 sec; 576 time points; 32x4mm transverse slices). Subjects in the scanner viewed two separate runs of 15-second silent coloured video clips (36 clips per run). These previously validated clips, which were arranged in a 2x2 factorial block design, included probes of understanding others' intentions (necessary or not necessary) and humour (present or absent). After each clip, participants indicated whether the clip was funny or not. The imaging data were preprocessed and analysed using Statistical Parametric Mapping (SPM5) (second level random effect analysis; $P < .001$ uncorrected; extent threshold over 35 voxels). Results for the interaction between humour appreciation and understanding of others' intentions showed that patients with schizophrenia had less activation than the controls in the left dorsolateral prefrontal cortex (DLPFC) [Brodmann's area 9]. This finding indicated that, in patients, there were significant increases of activation in the DLPFC when only one of the two processes occurred (ie, humour present without the need to understand others' intentions and humour absent but understanding of others' intentions was necessary). The activation was not significantly increased when both phenomena were present together (ie, humour present and understanding of others' intentions were needed).

On the contrary, in controls, the activation at the DLPFC was significantly increased only when both processes were present together, but not when either humour appreciation or intentions understanding occurred on their own. Though preliminary, these findings suggest that the left DLPFC may be involved in the integration of emotion and cognition and its dysfunction may contribute to the social cognition deficits in schizophrenia.
ID: 549789

STRUCTURE AND FUNCTION IN SCHIZOPHRENIA PATIENTS, NON-PSYCHOTIC RELATIVES, AND COMMUNITY CONTROLS

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Diffuse structural and functional brain abnormalities are commonly found in schizophrenia patients and have recently reported in patients' first-degree non-psychotic relatives. Previously, we reported structural abnormalities in the cingulate and temporal cortices and functional abnormalities in the prefrontal cortex in the non-psychotic relatives of patients compared to controls. The goal of the present study was to recruit a new sample of schizophrenia patients, non-psychotic relatives, and community controls to investigate in tandem, structural and functional correlates of the schizophrenia diathesis at varying genetic loads. To date, imaging data has been collected on 26 patients, 20 relatives, and 30 controls. Functional imaging was conducted during a context-processing task that required the active suppression of a prepotent tendency to complete a weaker task-relevant response. Analysis of behavioral data demonstrated all groups had more difficulty overriding a prepotent response evidenced by longer mean reaction times on these trials compared to prepotent response trials. Schizophrenia patients demonstrated more difficulty inhibiting prepotent responses compared to non-psychotic relatives and controls, whereas, there was no difference between non-psychotic relatives and controls. Neuroimaging data will be analyzed to determine the neural correlates of context-processing difficulties in schizophrenia patients. In relatives, we will analyze whether the neural correlates found to be aberrant in schizophrenia patients are also disrupted and whether any compensatory neural mechanisms exist that enable normative performance. Multiple indicators of brain structure, such as cortical thickness, surface area, and volume will be examined. Lastly, we will investigate whether there is any correspondence between the location of abnormalities in form and function.
ID: 549783

THE NEURAL BASIS OF SELF-INHIBITION IN THEORY OF MIND IN PSYCHOSIS PRONENESS: AN FMRI STUDY

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Previous research on the functional and neural basis of perspective taking has shown that the prefrontal cortex and the temporo-parietal junction play a role in this so called Theory of Mind (TOM) capacity. This TOM capacity can be subdivided into two perspective taking components: (1) self-perspective inhibition and (2) other-perspective taking (Samson et al., 2005, Brain). In this study, we looked at differences between psychosis prone subjects (PP) and healthy control subjects (HC) in networks

processing TOM, using functional MRI. The task consisted of short movie clips differing in demands regarding self-perspective inhibition and other-perspective taking. Conditions with a similar demand in other-perspective taking, but a differing demand in self-perspective inhibition were compared. In HC we found activation of the left inferior prefrontal cortex for self-perspective taking, which has also been implicated in simple response inhibition (eg, Rubia et al., 2001, Schizophrenia Research). Furthermore, we found activation of the middle temporal gyrus when conditions similar in other-perspective taking demand were compared to a baseline condition. This confirms the subdivision of TOM into self-perspective inhibition and other-perspective taking. We did not find behavioural differences between groups, however PP showed stronger activation in left IFG, DLPFC, MTG and SFG in PP in self-perspective taking. Thus, in order to perform as well as HC, PP excessively addressed these self-perspective taking networks. Finally, we found deactivation in the PCC and mPFC in false belief reasoning versus baseline, which was stronger in HC than in PP. Possibly the IFG inhibits self-perspective by deactivating the mPFC and increasing TPJ activation, implying that less deactivation in mPFC reflects more difficulty in this inhibition process. The results suggest that PP—in order to equal the behavioural performance of the HC—have to compensate by excessively activating TOM networks. This paradigm could reveal interesting results in psychotic patients lacking insight in illness. These patients may have difficulty inhibiting their own perspective resulting in more difficulties in taking someone else's perspective. Being unable to observe themselves through the eyes of others and critically reviewing their own behaviour, might result in problems in adapting their own self-image to reality, namely that they suffer from a psychotic disorder.
ID: 549593

CORRELATION BETWEEN PREPULSE INHIBITION AND CORTICAL PERFUSION DURING AN ATTENTIONAL TEST IN SCHIZOPHRENIA

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Background: Processes underlying cortical hypoactivation in schizophrenia are poorly understood but some evidence suggests that a deficient sensory filtering is associated to with the condition. This filtering deficit can be studied by using measures of prepulse inhibition (PPI) of the startle reflex. Objective: To evaluate the contribution of sensory filtering deficits to cortical hypoperfusion during an attention test in schizophrenia. Method: PPI measurements of the startle reflex and perfusion during the performance of a Stroop test (assessed with single-photon emission tomography) were obtained in 10 acutely treated schizophrenia patients (6 with recent onset, RO) and 16 control subjects. These measurements were compared between patients and controls and the correlation between PPI and perfusion was evaluated within each group using Statistical Parametric Mapping. Results: In comparison with normal subjects, the patients exhibited lower PPI, although the difference was not statistically significant. Perfusion was significantly lower in the prefrontal and premotor regions of the patients. In the patient group, there was a statistically significant correlation between PPI and perfusion in the parietal, premotor and cingulate regions. When the associations were analyzed in the RO alone, a positive correlation was also found between prefrontal perfusion and PPI, and anterior hippocampal perfusion was inversely related to PPI. Conclusions: These results support the notion that deficient sensory-motor filtering is associated with decreased cortical task-related activation in schizophrenia.
ID: 549591

DECODING COMPLEX BEHAVIOR BY MEANS OF RAPID CEREBRAL HEMODYNAMIC MODULATION IN HEALTHY SUBJECTS AND PATIENTS WITH SCHIZOPHRENIA

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Rapid cerebral hemodynamic modulation substantially correlates with non-routine spatial planning. This finding contrasts missing or erroneously reported brain behavior relationships with functional imaging techniques during planning. In the following investigation, we did not only expand the above findings to a minute analysis of routine and non-routine spatial planning in schizophrenia, but we applied this novel measure to the Wisconsin Card Sorting Test (WCST). Healthy subjects and patients with chronic schizophrenia performed a spatial planning task and the WCST while rapid cerebral hemodynamic modulation was measures by means of functional transcranial Doppler sonography. Uni- and multivariate analyses of variance and correlation analyses were applied. Slowing during set shifting of WCST showed a shared variance of 80.5% ($P = .0004$) with early modulation of cerebral hemodynamics in a normal sample. Healthy subjects rapidly adjusted cerebral hemodynamic modulation to the respective phases of the planning task ($P < .01$), whereas patients failed to do so. Rapid cerebral hemodynamic modulation is a major correlate of complex behavior, and there is evidence of impairment in schizophrenia. Pathophysiological mechanisms and a review of relevant functional imaging literature are included in this presentation.
ID: 549579

ELEVATED FUNCTIONAL CONNECTIVITY IN A CORTICOSTRIATAL LOOP AND THE MECHANISM OF AUDITORY/VERBAL HALLUCINATIONS IN PATIENTS WITH SCHIZOPHRENIA

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The pathophysiology of auditory/verbal hallucinations (AVHs) in patients with schizophrenia is poorly understood. We tested the hypothesis that elevated functional connectivity linking the superior temporal gyrus (STG) to sites in the left inferior frontal gurus (IFG) leads to emergence of AVHs. Functional connectivity estimates were extracted from correlations between "steady-state" time-course of fMRI-generated BOLD signal across brain regions. Thirty-two patients with schizophrenia and active AVHs, 23 similarly diagnosed patients without AVHs, and 22 healthy controls were studied. Groups were well-matched in terms of age, gender, education. The two patient groups were well-matched in terms of positive symptoms, chronicity and antipsychotic medication dosage. Functional connectivity was calculated relative to a bilateral superior temporal gyrus (STG) reference region shown to be involved in the genesis of AVHs in a prior fMRI study. As predicted, ROI analysis revealed significantly greater functional connectivity referenced to STG in subregions of the left IFG among hallucinators compared to nonhallucinating patients. This finding emerged in the context of reduced functional connectivity linking the STG reference region to other, diverse cortical regions—as well as increased functional connectivity linking the STG reference region to a large subcortical region—when both patient groups were compared to healthy controls using a voxel-based analysis following FDR correction. This subcortical region consisted of the thalamus, the dorsal striatum, and midbrain monoamine centers. A follow-up region-of-interest analysis identified a functional loop of heightened

functional connectivity linking IFG, STG, and the dorsal striatum in hallucinators. Eliminating from the analysis those patients with frequent AVHs during scanning demonstrated that functional connectivity elevations in hallucinators were not a consequence of waxing/waning co-activation coincident with AVHs, but instead reflected a sustained vulnerability factor. These findings suggest that AVHs arise from relatively heightened functional connectivity linking sites in IFG and STG that produce language representations possibly triggered by the striatum. Parallel elevations in functional connectivity linking STG to thalamic and/or midbrain dopamine centers may gate resulting, spurious language representations into consciousness as hallucinated speech. Research supported by NIMH R01MH067073.
ID: 549435

ALTERED STRUCTURAL AND FUNCTIONAL CONNECTIVITY OF COGNITIVE CONTROL NETWORKS IN SCHIZOPHRENIA

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Disruption of executive cognitive control has been implicated in the pathophysiology of schizophrenia. Our findings from a series of fMRI studies in schizophrenia patients are suggesting altered cortico-cortical and fronto-striatal networks (Schlösser et al. 2003, 2008; Koch et al. 2007, 2008) and a correlation between frontal DTI fractional anisotropy (FA) reduction and fMRI activation (Schlösser et al. 2007). However, the relationship between white matter structural integrity and functional connectivity parameters within these networks remains largely unknown. In the current study thirteen patients with schizophrenia and 13 controls were studied with DTI and fMRI while performing a short-term memory task associated with increasing overlearning of stimulus material. Functional connectivity was investigated by analyses of psychophysiological interactions (PPI). DTI analyses were based on voxel-based and ROI-based statistics. Results revealed significant ($P < .05$, FDR) task-related modulation of functional connectivity between the left DLPFC and a network including the right DLPFC, left VLPFC, parietal cortex, left and right cerebellum. A significant correlation between task-dependent prefrontal interhemispheric functional interaction (PPI-analysis) and FA of the corpus callosum (DTI) could be found in schizophrenic patients. The findings are demonstrating structure-function relationships with regard to interhemispheric and frontal-subcortical circuitry. The combined analysis of DTI and BOLD fMR provides complementary information supporting the notion of schizophrenia as a cortical-subcortical connectivity disorder.

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ID: 549364

TEMPORAL MODELING DEMONSTRATES PRESERVED OVER LEARNING PROCESSES IN SCHIZOPHRENIA: AN FMRI STUDY

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Working memory impairment is a central component of the cognitive dysfunction seen in schizophrenia. However, whether this impairment must be regarded as a trait marker of the disorder or can be positively modified by practice has scarcely been investigated. Therefore, the present study aimed to quantify and model the neural substrates of continuous overlearning of short-term memory information to investigate patients ability to profit from practice. Thirteen schizophrenic patients and 13 healthy volunteers were studied with fMRI while performing a Sternberg overlearning paradigm. Because previous findings in healthy subjects demonstrated that short-term practice, in the context of working memory, was associated with exponential activation decreases, the practice-associated changes were modelled according to an exponential signal decay. We found that short-term learning was associated with significant individual performance improvements and exponential signal decreases in a fronto-parieto-cerebellar network both in schizophrenic patients and healthy volunteers. Patients exhibited stronger signal decreases relative to controls in anterior cingulate (BA 32), middle and superior temporal (BA 37, BA 22), superior frontal (BA 8/9, BA 6) and posterior parietal regions (BA 40). A relative hyperactivation in the patient group was observable only at the beginning of the learning process when task demands were high and decreased with continued practice. Our data indicate a gradual reduction of recruited neuronal resources and a practice-associated activation normalization in patients with schizophrenia. Inefficient working memory function and associated activation abnormalities in schizophrenia do not seem to constitute stable characteristics of the disorder but might be modified by adequate practice and experience.
ID: 549272

ASSESSING INTRA-AMYGDALA ACTIVITY TO AFFECTIVE FACES IN SCHIZOPHRENIA OFFSPRING: IMPLICATIONS FOR DISORDERED BEHAVIOR DURING ADOLESCENCE

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Abnormal affective processing in structures such as the amygdala may underlie disordered affective function in offspring of schizophrenia patients (Scz-Off; Phillips and Seidman, 2008). The amygdala contributes to the processing of affect, and its critical sub-nuclei (Centro-medial: CM; Basolateral: BL; Superficial: SF) play different roles in relaying affective information to other cortical and sub-cortical centers. Abnormal response of regions such as the CM that project to autonomous centers in the brain (McDonald, 2003) may result in blunted behavioral responses to rewarding (positive) stimuli in Scz-Off. To assess this we used fMRI, to estimate intra-amygdala activity (Eickhoff et al., 2007) to negative, neutral and positive affect in adolescent (age:10–20 yrs) controls (HC) and Scz-Off. Twenty one

HC (8 females; mean age:14.7 yrs) and 14 Scz-Off (5 females; mean age:14.7 yrs) performed a jittered event-related affective working memory task (Bruker MedSpec 4Tesla; 345 EPI scans; TR = 2s; 24 slices; 3.8x3.8x4mm). Subjects viewed faces (Ekman and Oster, 1979) in sequence to assess if the emotion conveyed on the current face matched that on the preceding one. fMRI data were processed and analyzed used SPM[2]Regions of interest (ROI) were created by overlaying maximum probability maps of amygdala nuclei (Eickhoff et al., 2005) with amygdala masks (Tzourio-Mazoyer et al., 2002). BOLD percent signal change to different affective valences were computed for ROIs from unsmoothed fMRI images (to preserve relative localization of signal). Data for each emotion were analyzed in separate repeated measures ANCOVA's. A significant group x region x hemisphere interaction was observed for both positive, $F_{2,62} = 4.26$, $P < .02$, MSe=.05, and neutral faces, $F_{2,62} = 5.64$, $P < .01$, MSe = .04. Further pairwise tests revealed, hypo-activity in the left CM in Scz-Off relative to HC to positive stimuli, $t_{33} = 2.37$, $P < .02$. The CM integrates signals from other nuclei (Pitkanen et al., 1997), and recent studies indicate the value of the amygdala in modulating responses to rewarding stimuli (Baxter and Murray, 2002). Though preliminary, our data suggesting hypo-activity of the CM sub-region to positive stimuli in Scz-Off, may reflect reduced sensitivity to reward eliciting stimuli. This in turn may blunt the salience of positive social cues, impairing social cognition and interaction in Scz-Off. These intriguing links between amygdala activity and behavior will need further investigation.
ID: 549140

THE EFFECT OF NEUREGULIN1 ON NEURAL CORRELATES OF EPISODIC MEMORY ENCODING

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Neuregulin 1 (NRG1) has been found associated with schizophrenia. Impaired performance in episodic memory tasks is an often replicated finding in this disorder. In functional neuroimaging studies, this dysfunction has been linked to signal changes in prefrontal and medial temporal areas and could possibly constitute an endophenotype. Therefore, it is of interest whether genes associated with the disorder, such as NRG1, modulate episodic memory performance and the neural correlates of memory encoding. 85 healthy individuals performed an episodic memory encoding task while brain activation was measured with functional MRI. All subjects were genotyped for the single nucleotide polymorphism (SNP) in the NRG1 gene, SNP8NRG221533 (rs35753505). The effect of genotype on brain activation was assessed with fMRI during an episodic memory encoding task. While there were no differences in performance, brain activation in the right cingulate gyrus (BA 24) and the bilateral middle frontal gyrus (BA 9) was positively correlated with the number of risk alleles in NRG1. NRG1 genotype does modulate brain activation during episodic memory in key areas for memory encoding. The results suggest that subjects with risk alleles show hyperactivations in areas associated with elaborate encoding strategies in order to improve task performance.
ID: 549025

GENETIC VARIATION IN THE SCHIZOPHRENIA-RISK GENE NEUREGULIN 1 CORRELATES WITH

BRAIN ACTIVATION AND IMPAIRED SPEECH PRODUCTION IN A VERBAL FLUENCY TASK IN HEALTHY INDIVIDUALS

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Impaired performance in verbal fluency tasks is key finding in schizophrenia. In functional neuroimaging studies, this dysfunction has been linked to signal changes in prefrontal and temporal areas. Since schizophrenia has a high heritability, it is of interest whether susceptibility genes for the disorder, such as NRG1, modulate verbal fluency performance and its neural correlates. 429 healthy individuals performed a semantic and a lexical verbal fluency task. A subsample of 85 subjects performed an overt semantic verbal fluency task while brain activation was measured with functional MRI. NRG1 (SNP8NRG221533; rs35753505) status was determined and correlated with verbal fluency performance and brain activation. For the behavioral measure, there was a linear effect of NRG1 status on semantic but not on lexical verbal fluency. Performance decreased with number of risk-alleles. In the fMRI experiment, decreased activation in the left inferior frontal and the right middle temporal gyri as well as the anterior cingulate gyrus was correlated with the number of risk-alleles in the semantic verbal fluency task. NRG1 genotype does influence language production on a semantic level in conjunction with the underlying neural systems. These findings are in line with results of studies in schizophrenia and may explain some of the cognitive and brain activation variation found in the disorder. More generally, NRG1 might be one of several genes that influence semantic language capacities.
ID: 549020

GENETIC VARIATION IN THE SCHIZOPHRENIA-RISK GENE NEUREGULIN1 CORRELATES WITH DIFFERENCES IN FRONTAL BRAIN ACTIVATION IN A WORKING MEMORY TASK IN HEALTHY INDIVIDUALS

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Working memory dysfunctions are a prominent feature in schizophrenia. These impairments have been linked to alterations in prefrontal brain activation with studies reporting hypo- and hyperactivations. Since schizophrenia has a high heritability, it is of interest whether susceptibility genes modulate working memory and its neural correlates. The aim of the present study was to test the influence of the NRG1 schizophrenia susceptibility gene on working memory and its neural correlates in healthy subjects. 429 healthy individuals performed a verbal and a spatial working

memory task. A subsample of 85 subjects performed a 2-back version of the Continuous Performance Test (CPT) in a functional MRI study. The NRG1 SNP8NRG221533 (rs35753505) carrier status was determined and correlated with working memory performance and brain activation. There were no effects of genetic status on behavioural performance in the working memory tasks in the 429 subjects and in the fMRI task (n = 85). A linear effect of NRG1 SNP8NRG221533 carrier status on neuronal activation emerged in the fMRI experiment. Hyperactivation of the superior frontal gyrus (BA 10) was correlated with the number of risk-alleles. NRG1 carrier status did not have an influence on working memory performance on the behavioural level. The fMRI data however suggest that performance measures between groups did not differ due to a compensational activation of BA 10 in risk-allele carriers. Our results are in line with functional imaging studies in patients with schizophrenia, which also showed a differential activation in lateral prefrontal areas.
ID: 549019

THE DIFFERENCE IN CEREBRAL ACTIVITY BETWEEN AUDITORY VERBAL HALLUCINATIONS AND INNER SPEECH

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The pathophysiology of Auditory Verbal Hallucinations (AVH) is largely unknown. Several functional imaging studies have measured cerebral activation during AVH, but sample sizes were relatively small (1–8 subjects) and findings inconsistent. In this study cerebral activation was measured using fMRI in 24 psychotic patients while they experienced AVH in the scanner and, in another session, while they silently generated words. All patients were right handed and diagnosed with schizophrenia, schizo-affective disorder or psychosis NOS. Group analysis for AVH revealed activation in the right homologue of Broca's area, bilateral insula, bilateral supramarginal gyri and right superior temporal gyrus. Broca's area and left superior temporal gyrus were not activated. Group analysis for word generation in these patients yielded activation in Broca's and Wernicke's area and to a lesser degree their right-sided homologues, bilateral insula and anterior cingulate gyri. Lateralization of activity during AVH was not correlated with language lateralization, but rather with the degree to which the content of the AVH had a negative emotional valence. The main difference between cerebral activity during AVH and activity during normal inner speech appears to be the lateralization. The predominant engagement of the right inferior frontal area during AVH may be related to the typical low semantic complexity and negative emotional content of AVH.
ID: 548933

NEURAL CORRELATES OF THE SUBJECTIVE EXPERIENCE OF REWARD IN SCHIZOPHRENIA

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In many experimental studies of emotion in schizophrenia (SZ), patients have reported finding pleasant stimuli as rewarding as controls. Nonetheless, patients generally show a diminished capacity to initiate and sustain goal-directed behavior, motivated by potential rewards. The relative inability of rewards to drive behavior in SZ suggests that responses to rewards, at the physiological level, may be abnormal, and possibly disconnected from the reported experience of them. In healthy volunteers, the subjective experience of a food reinforcer has been been linked to neural responses in ventral prefrontal cortex (PFC). We hypothesized that, relative to controls, SZ patients would show a reduced correspondence between subjective ratings of reinforcer pleasantness, and neural responses in ventral PFC. In a 3-T MRI scanner, we administered 18 patients and 18 matched controls 600-μl boluses of the juice of their choice (apple, grape, or fruit punch; juice was delivered at a rate of 1 ml/s). Subjects were administered 78 total squirts (46.8 ml), separated by intervals of approximately 20 seconds, over the course of 3 runs of 26 squirts each. Between runs of the fMRI experiment, subjects were prompted to rate, on a visual analog scale, their enjoyment of the juice. For each individual subject, we identified reward-evoked BOLD signal changes, using juice delivery times as regressors. Neural responses corresponding to individual ratings of juice pleasantness within a group were then assessed using voxel-wise whole-brain analyses (regression analyses performed with AFNI). We corrected for multiple comparisons based on cluster size (a minimum cluster size of 424 ml extent, for a voxel-wise threshold of $P < .002$, was determined by a Monte Carlo simulation). Patients and controls did not differ in their average ratings of juice pleasantness [t_{34}=1.25; $P > 0.10$]. Regression analyses revealed that, within the group of control subjects, BOLD activity in both mesial and lateral areas of PFC tracked subjective ratings of rewards. No such correspondences between MRI responses and subjective ratings were observed in patients. These results support previous findings in healthy volunteers, and suggest that patients with schizophrenia do not show the same correspondence between PFC physiology and the subjective experience of rewards. These findings may contribute to our understanding of hedonic deficits in SZ, and inform our treatment of negative symptoms.
ID: 548832

DISORDERED FUNCTIONAL MATURATION OF THE AMYGDALA DURING ADOLESCENCE: FMRI STUDIES OF AFFECTIVE JUDGMENT IN SCHIZOPHRENIA OFFSPRING

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Adolescent offspring of schizophrenia patients (Scz-Off) are an important group in whom to assess impaired functional brain development associated with affective function (Phillips and Seidman, 2008). Maturation of affective processing and of brain regions such as the amygdala is particularly dynamic during adolescence (Herba and Phillips, 2004). Further, Scz-Off show increased incidence of behavioral impairments related to dysfunction and dysmaturation of limbic regions. We assessed developmental trends in fMRI-estimated amygdala function in a group of controls (HC) and Scz-Off using a continuous affective judgment task. In particular, we were interested in whether amygdala response to negative stimuli attenuates with age in HC but not Scz-Off. Fourteen Scz-Off (5 females, mean age = 14.7 yrs) and 20 HC (8 females, mean age = 14.9 yrs) were assessed. During fMRI, faces (Ekman and Oster, 1979) and distorted faces (control stimuli) were presented (3s/face) in sequence. Subjects judged if the affect depicted on a face was identical to that on the previous face (irrespective of identity). Stimuli were presented in a jittered event-related design. fMRI was

conducted on a Bruker MedSpec 4T system (345 EPI scans; TR = 2s; 24 slices; 3.8x3.8x4mm). Analyses were performed in SPM2. Stimuli were modeled as 3s events; Contrast images (faces>distorted; negative valence>distorted) were submitted to intra group regression to assess age-related effects on valence-related activation. Analyses were restricted to the amygdala (Maldjian et al., 2003). In HC, a significant inverse correlation was observed between age and amygdala response to all faces (t_{18} = 4.57, p_{FWE} < .05, x = 32, y = −1, z = −22). This effect was largely modulated by an age-related decrease in amygdala response to negatively valenced faces (t_{18} = 3.05, p_{FWE} < .05, x = 30, y = −3, z = −20). Age-related associations were absent in Scz-Off (P > .1). To account for differences in sample size, HC analyses were replicated in a sub-sample of HC that were age- and gender-matched to the Scz-Off subjects (t_{12} = 3.60, p_{FWE} <.05, x = 26, y = −8, z = −10). Positive correlations were absent. HC trends are consistent with previously published data (Kilgore et al., 2001) and may reflect increased age-related modulation of the amygdala by cortical regions. Such age-related modulation may be absent in Scz-Off, suggesting a cortico-sub-cortical mechanism underlying behavioral disorders in these subjects. ID: 548739

PET IMAGING OF CANNABINOID RECEPTORS IN SCHIZOPHRENIA

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The CB1 cannabinoid receptor is of considerable interest in schizophrenia (SZ) (as well as Alzheimer's, obesity and drug abuse). Here, we present data from the first human study with [11C]OMAR in SZ. We previously showed OMAR has specific binding in regions consistent with the known distribution of CB1. PET were carried out on 7 controls (HC; mean age = 29) and two 45 year old subjects with DSM-IV criteria for SZ with no history of cannabis abuse or drug dependence. Dynamic PET scans of 90 min after IV injection of high specific activity OMAR (6 -8 Ci/micro mole; mean dose of 19 mCi) with radial arterial blood sampling and HPLC metabolite analysis. Each subject had an SPGR MRI for definition of volumes of interest. Total distribution volume (VT) was estimated in brain regions by the Logan plasma reference graphical analysis (PRGA) and a 2 tissue compartment model with constraint with 5 parameters (TTCM-5C). The brain time-activity curves of OMAR peaked at approximately 20 minutes post injection (% SUV ranged from 136 to 207% in putamen) and decreased gradually thereafter to reach a SUV between 80 and 117% at 90 min. The average parent ligand in plasma was 41% at 60 minutes by HPLC. The average VT for brain regions in HC ranged between 1.0 and 1.7 in multiple cortical and subcortical regions. The highest binding was observed in cingulate, globus pallidus and putamen, all CB1 rich areas. The first of the two SZ subjects had increases in VT ranging from 3.7 to 13.1% above the mean and from 4% to 13% above the upper 95% confidence limit of the HC group. The greatest differences were seen in the frontal cortex, cingulate and globus pallidus. The other subject with SZ was within the confidence limits. Interestingly enough the subject with elevated CB1 receptors had a higher BPRS total score (32 vs. 22), with a greater score on the psychosis subscale; 7 vs. 3; anxiety subscale; 8 vs 4; and hostility subscale 5 vs 3, and was generally considered to be clinically more affected. OMAR has characteristics for studying in human brain including neuropsychiatric disorders such as SZ. It has reversible kinetics during the 90 minute PET .These early findings of elevations in multiple brain regions of CB1 receptors in subjects with more severe SZ symptoms will be expanded to a series of at least 6 patients. These studies could have important implications for the role of CB1 in the pathophysiology of SZ and possible novel treatments. ID: 548716

CORTICAL ACTIVITY DURING VISUAL-PERCEPTUAL BINDING IN SCHIZOPHRENIA AS REVEALED BY FMRI

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Background: Behavioral and electrophysiological studies of schizophrenia have consistently demonstrated impairments in the integration of visual features into unified perceptual representations. Specific brain regions involved in this dysfunction, however, remain to be clarified. The purpose of this study was to examine, using fMRI, the relative involvement of visual cortex areas involved in form perception, and parietal and frontal regions involved in attention, in the visual integration impairment in schizophrenia. Methods: Fourteen patients with schizophrenia and 14 healthy controls were compared on behavioral performance and data acquired via fMRI while completing a contour integration task that had previously been used to identify a visual integration deficit in schizophrenia. Results: Schizophrenia patients demonstrated poorer visual integration than controls. Analyses of peak signal change indicated that while the groups were equivalent in area V1, the schizophrenia group demonstrated reduced signal in areas V2-V4, which are the earliest regions sensitive to global configurations of stimuli. Moreover, whereas the control group demonstrated greater recruitment of prefrontal and parietal areas during perception of integrated forms compared to random stimuli, the schizophrenia group demonstrated greater recruitment of frontal regions during perception of random stimuli. The groups differed on brain regions involved in form perception even when they were matched on accuracy levels. Conclusions: The visual integration disturbance in schizophrenia may involve both deficient basic visual processes (beginning at least as early as occipital region V2), as well as reduced feedback from visual attention regions that normally serves to amplify relevant visual representations relative to irrelevant information. ID: 548683

THE NEURAL BASIS OF RESPONSE SELECTION IN SCHIZOPHRENIA: A POTENTIAL ENDOPHENOTYPE

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The search for genes conferring liability for schizophrenia may be aided by the identification of endophenotypes. Response selection is a heritable cognitive function that is impaired in patients with schizophrenia and their unaffected siblings. The abnormalities in cerebral function that presumably underlie the deficit in patients and unaffected siblings remain to be elucidated. We employed fMRI to examine cerebral neurophysiology during performance of a 4-choice reaction time (CRT) task in 25 patients with schizophrenia (15 medication free first episode (FEP) and 10 chronic

patients), 32 controls, and 12 unaffected siblings of individuals with schizophrenia. CRT was impaired in both medication free FEP and chronic patients with schizophrenia, and unaffected siblings. FEP patients, chronic patients, and unaffected siblings demonstrated greater BOLD response in the right dorsolateral prefrontal cortex (dlPFC) during CRT task blocks. Functional connectivity analysis revealed marked reductions in connectivity between the right dlPFC and multiple brain regions in both patient groups and, to a lesser degree, unaffected siblings. The magnitude of connectivity between right dlPFC and inferior parietal lobule correlated with task performance in the combined patient/unaffected siblings group, but not controls suggesting that the network of brain regions recruited to perform the task differed as a function of genetic liability for schizophrenia. Altered activity and connectivity of the right dlPFC appears to be related to genetic vulnerability for schizophrenia and may represent a potential endophenotype of the disorder. Consequently, genes linked to behavioral performance and cerebral activity, including regional connectivity, associated with response selection may be related to schizophrenia vulnerability.
ID: 548421

FUNCTIONAL NEURAL CORRELATES OF PHYSICAL ANHEDONIA IN NON-CLINICAL INDIVIDUALS AND IN PATIENTS WITH SCHIZOPHRENIA

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The persistent nature of negative symptoms in schizophrenia has led to the investigation of neural abnormalities underlying such symptoms. Inter-individual variability in anhedonia severity is likely to be multi-determined. It may be explained by basic neural abnormalities present prior to the onset of the illness, as well as by other factors that have emerged following illness onset. In the current study, we proposed to better characterize the brain abnormalities associated with anhedonia in schizophrenia. Anhedonia potentially affects emotional processing and fMRI is a well-suited technique to explore the relation between emotional processing and neural activity as a function of anhedonia severity. In an event-related functional MRI study, we used an emotional picture viewing task to identify in 26 non-clinical individuals and 30 people with schizophrenia the brain regions whose activity significantly correlated with physical anhedonia severity during hedonic processing. A conjunction analysis identified the neural correlates of anhedonia common to both groups. An interaction analysis identified the neural correlates of anhedonia specific to schizophrenia. We found anhedonia severity to be inversely correlated with the activity of visual attention-related cortical regions in both groups. The orbitofrontal cortex, insula, and putamen/ventral striatum activity was negatively correlated with anhedonia severity in people with schizophrenia only. The data first suggest that basic neural abnormalities associated with trait anhedonia and potentially representing a neural marker of vulnerability for schizophrenia involve a poor modulation of perceptual and attentional brain regions during the processing of hedonic information. Alternatively, the orbitofrontal/anhedonia link found in schizophrenia could reflect the specific impairment of indirect factors, such as reward anticipation deficits, that influence the measurement of anhedonia severity through self-report questionnaires.
ID: 548006

A MULTIMODAL IMAGING STUDY OF THEORY OF MIND FUNCTIONING IN A JAPANESE SAMPLE OF SCHIZOPHRENIA PATIENTS

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There is empirical evidence from functional imaging studies that during performance of Theory of Mind (ToM)-tasks (ability to infer other's thoughts and intentions) schizophrenia patients activate certain brain areas less than healthy controls. In the rare Diffusion Tensor Imaging (DTI) studies published so far, white matter analyses focusing on the superior temporal junction and the basal temporal regions have shown a reduction of white fibers. In our study we implemented a sophisticated ToM-paradigm first used by Abell et al. (2000; Research group Uta Frith, UC London) in a functional Magnetic Resonance Imaging (fMRI) design and combined these analyses with DTI in a sample of schizophrenia patients. We hypothesized, that a reduced activation pattern during ToM-task performance should be related to a reduction of white matter integrity of ToM-relevant brain areas. This is an innovate approach that has not been performed for ToM-tasks yet. 11 schizophrenia patients and 12 healthy controls have been assessed with the functional MRI-paradigm (3T), comprising short video animations with geometrical, moving shapes acting in social, sometimes ToM-related patterns. DTI was additionally applied to assess white matter integrity. Also, psychopathology, neuropsychological data and behavioral ToM-data were obtained. First analyses of the fMRI data indicate differential activation patterns in schizophrenia patients compared to controls in cortical areas that have been related to the proposed ToM neuronal network. Interestingly, while performing ToM-tasks, certain brain areas, eg, the ACC and the temporal lobes, were more activated in schizophrenia patients than in healthy controls. First results of white matter tract investigations revealed lower FA-values in the left arcuate fasciculus and right deep white matter of the temporal lobes in schizophrenia patients. Our functional MRI results of the ToM-paradigm imply a compensatory stronger activation of ToM-related areas in schizophrenia patients, whereas former studies reported reduced activations in these ToM related brain areas. Lower FA-values indicate disturbed white matter integrity in the temporal lobes. Further analyses of our data in combination with clinical performance and neuropsychological results might help to amplify our understanding of the neurobiological basis of social cognition deficits. The study was supported by a research fellowship of the Japan Society for the Promotion of Science (JSPS).
ID: 546817

AUDITORY-VERBAL HALLUCINATIONS AND MENTAL IMAGERY COMPETE FOR SHARED NEURAL RESOURCES: AN FMRI STUDY

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Auditory-verbal hallucinations (AVH) are a cardinal feature of schizophrenia. Cognitive models have suggested that AVH are related to abnormal mental imagery processes. Specifically, it has been hypothesized that the production of inner speech, and its subsequent misattribution to an external

source may give rise to AVH. Using a behaviorally controlled auditory mental imagery task in an fMRI setting, Aleman et al. (2005, Cereb Cortex) showed that secondary auditory processing areas, namely posterior superior temporal sulcus, as well as speech production areas (inferior frontal gyrus), were activated during imagery in healthy subjects. Interestingly, similar areas are found to be activated when schizophrenia patients observe AVH (Shergill et al., 2000, Arch Gen Psychiatry). We hypothesized that if auditory imagery processes and AVH compete for the same neural resources, differential activation patterns will be observed during an auditory imagery task. Specifically, we expected an attenuation of the neural response in hallucinating patients. Functional MR images were obtained from 25 right-handed males subjects (8 patients with AVH, 8 patients without AVH and 9 healthy controls, group-matched for age and education level), who performed a metrical stress evaluation task, which requires the formation of an auditory mental image of a visually presented word, in order to generate the correct stress pattern. Active task blocks were interspersed with 30 second rest periods. Whole brain EPI images were acquired on a 3T Phillips System. Compared to healthy controls, hallucinating patients showed increased activation in the left middle and superior temporal gyrus, the left middle cingulate gyrus and the left postcentral gyrus during auditory imagery compared to baseline. Alternatively, reduced activation was observed in the right superior temporal gyrus. When compared to non-hallucinating patients, right middle cingulate gyrus was more activated. Right superior temporal gyrus, which has previously been found to activate during AVH, showed reduced responsivity to auditory imagery in hallucinating schizophrenia patients. Alternatively, patients showed increased activation in left temporal areas, possibly as a compensatory mechanism. This finding is interpreted as resulting from competition for shared neural resources, and implicates auditory imagery processes in the genesis and/or maintenance of AVH.
ID: 543930

CEREBRAL ACTIVATION ON FMRI DURING PROCEDURAL LEARNING IN UNMEDICATED FIRST EPISODE PSYCHOSIS

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Using fMRI, we have previously identified abnormal activity in the cerebral cortex and basal ganglia during procedural learning in individuals with chronic schizophrenia and in unaffected siblings, suggesting dysfunction of distributed cortical-subcortical circuitry with potential relevance to an endophenotype of schizophrenia. To assess this further we examined unmedicated patients experiencing a first episode of psychosis. Method: Seventeen unmedicated individuals suffering their first episode of psychosis (FEP) were recruited from the Edmonton Early Psychosis Intervention Clinic (EEPIC). They were 22 years of age (mean = 21.94 years, SD = 3.99), ill for 5 months (mean duration of illness = 0.38 years, SD = 0.27), and had minimal prior exposure to neuroleptic treatment (mean prior exposure = 17.87 days, SD = 25.38; four were neuroleptic naïve). An age- and gender-matched healthy control (HC) sample was recruited through campus advertising. The HC sample was also 22 years of age (mean age = 22.12, SD = 3.19). All subjects completed an embedded series Serial Reaction Time (SRT) task while undergoing fMRI on a 1.5T scanner Results: The FEP and HC groups exhibited comparable procedural learning, but the FEP group exhibited less left hemisphere cortical activity in the DLPFC (BA 46 and 9), the premotor cortex (BA 6) and the superior temporal gyrus (BA 22). The HC group also exhibited significant activation of bilateral anterior cingulate cortex that was not apparent in the FEP group. Sub-cortically, significant activation of the basal ganglia was evident during procedural learning in both the FEP and HC groups. Conclusions: Cortical but not subcortical pathology was apparent in this unmedicated first episode sample. Previously we reported similar cortical anomalies in unaffected siblings of patients. We also reported cortical and subcortical anomalies in medicated individuals with chronic schizophrenia. fMRI appears sensitive to (1) a cortical anomaly of the left hemisphere that may represent an endophenotype marker for schizophrenia, and (2) a subcortical anomaly that may result from prolonged illness and/or pharmacotherapy. Delineation of an endophenotype marker for schizophrenia would facilitate premorbid identification and early intervention. Recognition of anomalies caused by prolonged illness or treatment is essential to the development of safe and effective treatments for schizophrenia.
ID: 540726

EFFECTS OF EYE GAZE DIRECTION ON AMYGDALA ACTIVATION TO THREAT RELATED EXPRESSIONS IN SCHIZOPHRENIA

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Emotion recognition deficits are well documented in schizophrenia and are associated with abnormal amygdala functioning. This is pronounced for threat related emotions, and previous work has demonstrated that the threat relatedness of stimuli modulates amygdala activity in healthy controls with lesser effects in individuals with schizophrenia. We sought to examine whether eye gaze direction of threat related faces, a factor shown to modulate amygdala activation in healthy controls, would evoke differential amygdala responses in schizophrenia. Neural activity was measured using BOLD fMRI in 21 healthy controls and 22 schizophrenia patients during emotion recognition. Faces displaying anger, fear or no emotion were presented. Half were shown with direct gaze so that they appeared to be looking straight at the participant, and half were averted by 8° so that they appeared to be looking slightly away from the participant. Analysis of performance revealed a gaze by emotion interaction such that both patients and controls were more accurate for direct gaze anger than averted gaze anger and for averted relative to direct gaze fear. Analyses of neural activation demonstrated that patients showed reduced activation in a network of neural regions associated with face processing including left amygdala and bilateral fusiform gyrus. Examination of percent signal change in the left amygdala revealed a significant 3-way interaction of group, emotion, and gaze. Controls showed greater activation for direct anger than averted anger, and comparable levels of activation for averted anger and direct and averted fear. Patients, however, showed a reverse pattern with greater amygdala activation to averted anger and direct fear than their opposite gaze counterparts. These results demonstrate that patients with schizophrenia show modulation of amygdala activation in an opposite pattern to that of controls and to their pattern of behavioral performance, with poorest performance in conditions inducing greatest amygdala activation. The results are consistent with previous work suggesting that increased amygdala activation in patients may interfere with the top-down cognitive processes necessary for accurate emotion recognition. They also suggest that the increased ambiguity of averted anger and direct fear may be perceived by patients as more threatening than direct anger and averted fear expressions. Support provided by NIMH grants R01-MH060722 and T32-MH019112.
ID: 550829

INFLUENCE OF EMOTIONAL PROCESSING ON WORKING MEMORY IN SCHIZOPHRENIA

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Schizophrenic patients seem to be equally sensitive to the emotional content of stimuli than controls. But how do they further process this information while they perform a cognitive task? We compared the influence of emotion on working memory in patients and healthy controls using behavioral measures and fMRI. 38 patients and 32 controls performed a nonverbal 2back working memory task while being scanned. To manipulate the emotional content in the task, faces displaying happy, neutral or fearful expressions were presented in blocks so that positive, neutral and negative conditions were created. Repeated measure ANOVAs indicated that patients, but not controls, were significantly more accurate in the negative as compared to neutral condition. Neither group showed a difference in accuracy between positive and neutral conditions. In both groups, RTs in the negative condition were significantly longer than in the neutral or happy conditions. A number of brain regions, including the basal ganglia, lingual and fusiform gyri, hippocampus, superior temporal cortex, as well as regions in the DLPFC and cerebellum showed a significant interaction between condition and group in whole brain analyses, with patients tending to have greater activation in the negative condition, and controls in the neutral condition. A ROI analysis of areas involved in signaling stimulus salience showed that amygdalar activation was significantly higher in the negative condition in patients, but did not significantly differ among conditions in controls. The lenticular and caudate nuclei were more active in the neutral than emotional conditions in controls, but more active in the negative than neutral or positive conditions in patients. Regions thought to be associated with emotion regulation (such as DLPFC and hippocampus) demonstrated significantly greater activity in the neutral than negative and positive conditions in controls. Patients, however, demonstrated significantly greater activation in the negative condition in anterior DLPFC regions and hippocampus, and no difference in activation among conditions in more posterior DLPFC regions. These results suggest that patients experience an enhanced influence of negative emotion on cognition, which potentially increases the engagement of areas involved in emotion regulation. In the context of a working memory task, this enhanced influence of negative emotion may facilitate encoding of the stimuli and thus more accurate performance.
ID: 551888

ABNORMAL CORTICAL-THALAMIC-CEREBELLAR RECRUITMENT DURING SUCCESSFUL MEMORY RETRIEVAL IN SCHIZOPHRENIA

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Declarative memory deficits are a prominent feature of schizophrenia. Previous studies have demonstrated that patients with schizophrenia engage less in conscious recollection of details and rely more on a sense of familiarity for retrieval of information. In the present study, we employed a slow event-related fMRI design using a Remember-Know paradigm to study the neural basis of episodic and semantic memory in schizophrenia. Eighteen male schizophrenia and 15 matched healthy control participants learned 108 words and then were presented with a randomized list of the original and 28 novel words while undergoing functional neuroimaging. Participants initially decided whether words were previously learned or new and then indicated whether they remembered details of the encoding experience (Remember = R) or if they simply recognized the word (Know = K). Behavioral performance (overall hit rate) was assessed during the old/new

and R/K judgments. We used a mixed-effect model in SPM5 to compare brain activation ($P < .05$, corrected) during correct recognition (hits versus misses) and episodic memory (hit-R versus hit-K) between groups. Schizophrenia patients were less accurate when remembering the previously learned words (overall hit rate), but this difference was not significant. We did not find evidence for selective impairments of episodic or semantic memory in our sample of schizophrenia patients: all groups had similar hit-R rates (0.46 in controls; 0.42 in schizophrenia patients) and hit-K rates (0.27 in controls; 0.21 in schizophrenia patients). In the context of equivalent recognition performance, the control group exhibited significantly greater activation compared to schizophrenia patients in five brain regions: cerebellum, thalamus/caudate, precuneus, left medial frontal gyrus, and bilateral superior frontal gyri. The schizophrenia group did not exhibit any areas of significantly greater activation compared to the control group, and there were no group differences when comparing hit-R and hit-K events. In contrast to previous behavioral studies, the current slow event-related fMRI study could not confirm selective episodic memory deficits in schizophrenia. However, we found compelling evidence for impaired recruitment of a cortico-thalamic-cerebellar network during successful memory retrieval in schizophrenia. This provides the opportunity to explore further the neural basis of memory function in schizophrenia.
ID: 551885

EVALUATION OF MEDIAL TEMPORAL LOBE STRUCTURES IN SCHIZOPHRENIA USING BOLD FMRI DURING NOVELTY DETECTION WITH MULTIPLE STIMULI

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Alterations of declarative memory in schizophrenia implicate aberrant mechanisms of processing within medial temporal lobe (MTL) structures, namely, the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex. Examination of differential activation along the rostrocaudal axis affords multiple regions of interest (ROI) for evaluation. Using 3T T2* high-resolution blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI), we employed a block design of categorically related stimuli to contrast neural responses of normal and schizophrenic subjects. Statistical parametric mapping (SPM2) and ROI analysis, with manual generation of ROIs for the aforementioned regions, is ongoing. Preliminary analysis of the normal control group using SPM2 confirms a posterior localization of activation with novel scene stimuli, an anterior localization with novel faces, and combined A-P involvement with novel word stimuli, whereas the schizophrenia group demonstrates significant variation of activation. Moreover, a subject's deviation from normal activation correlates with their degree of psychosis. These results evidence a modular architecture for the MTL structures involved in encoding memory and suggests the MTL is one of the sites of dysfunction associated with psychosis in schizophrenia.
ID: 551884

ABERRANT FUNCTIONAL CONNECTIVITY IS ASSOCIATED WITH HALLUCINATIONS DURING SOURCE MONITORING

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Previous research suggests that the dysfunctional cognitive operations underpinning hallucinations in schizophrenia overlap with those leading

to inner/outer (ie, self/other) confusions in source memory. Specifically, associations are observed between internal-to-external source misattributions (ie, externalizations) and hallucinations. In the current study we investigated the neural underpinnings of this association using functional magnetic resonance imaging (fMRI). 10 hallucinating and 14 non-hallucinating patients with schizophrenia alternated between saying and hearing words prior to scanning. During scanning, each of these words was displayed visually, and subjects were required to indicate, by key-press, whether they had previously said or heard the words. A control condition was included that involved task monitoring. For this, subjects alternated between reading and providing a semantic associate to words prior to scanning. During scanning, each of these words was displayed visually, and subjects were required to indicate, by keypress, whether they had previously read or associated the words. Constrained principal component analysis for fMRI (CPCA for fMRI) was used to identify connected neural networks that differed between hallucinating and non-hallucinating patients. The importance of each component in each peri-stimulus scan and in each condition of interest was computed, and these values were compared across patient groups in a mixed-model repeated measures ANOVA in SPSS. A component involving the right hippocampus and superior temporal cortex followed a different time-course for hallucinating compared to nonhallucinating patients, and the difference between the patient groups also depended on whether they were carrying out the source monitoring or task monitoring (control) condition. These results suggest that the association between externalizations and hallucinations in schizophrenia may result from differences in functionally connected networks involving the right hippocampus and superior temporal cortex. These findings concur with previous research describing significant activation of the right temporal cortex in schizophrenia patients during hallucinations, and while making external misattributions.
ID: 551879

DELUSIONS OF REFERENCE AND ABNORMALITIES IN SOCIAL COGNITION

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Certain classes of delusions- including delusions of reference and persecutory delusions may be characterized by abnormalities in social cognition- such as the misinterpretation of ambiguous but potentially self-relevant stimuli or a misunderstanding of the intentions of others. Both these processes require metacognitive evaluations of external socially relevant stimuli. A growing body of research has begun to examine the neural systems underlying the appraisal of the self and others and implicates a number of regions including the medial prefrontal cortex, anterior and posterior cingulate cortex and precuneus (collectively known as the cortical midline structures- CMS), and a number of sub-cortical areas including striatal, limbic and paralimbic regions. We hypothesized that patients with delusions of reference would show abnormal neural activity in processing socially relevant information-particularly when they are required to make metacognitive evaluations about others. In the current fMRI study schizophrenia patients with prominent delusions of reference ($N = 13$) and healthy controls ($N = 15$) were presented with trait adjectives and were asked to make yes/no judgments in three different conditions: a self referential evaluation (SE), where participants had to judge whether the trait words were

true of them, a significant other-evaluation (OE), where participants had to judge whether the traits were descriptive of a significant other, and a non-referential semantic positivity evaluation. We hypothesized that both referential conditions (SE and OE) would evoke activity along the CMS, and that patients with delusions would show differential activity in processing information about significant others. As predicted, both referential conditions showed robust activity along the CMS in both groups. As per our second hypothesis, the significant other versus self evaluation contrast revealed that deluded patients showed greater activity in the amygdala and other limbic structures, while controls showed greater activity in the mPFC and cortical structures relative to the patients. We hypothesize that these differences in neural activity-particularly increased activity in the limbic system (which is intimately connected to the CMS) in the patient group during the metacognitive evaluation of other people might play a role in the misinterpretation of external social stimuli, thus leading to delusional ideation.
ID: 551869

ABNORMAL NEURAL SYNCHRONY OF CORTICAL SOURCE SIGNALS DURING SPATIAL WORKING MEMORY TASK IN SCHIZOPHRENIA PATIENTS

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Schizophrenic symptoms have been known to be associated with functional integration deficits in neural dynamics. It has been posited that the gamma frequency band power reflects functional integration in local neural circuits involved in specific cognitive functions. On the other hand, the synchronous neural activity across distant cortical regions has received much attention as an index of long-range functional integration, in which distant neurons coordinate to generate various complex cognitive functions. It has been found that schizophrenia patients exhibit both diminished gamma band power and synchrony while they perceive complex visual objects. We have found that schizophrenia patients exhibit reduced gamma band power modulation associated with spatial working memory (SWM) task performance over dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC). To investigate aberrant neural synchrony of gamma activity between these cortical regions, we acquired 248 sensor magnetoencephalography (MEG) signals from schizophrenia patients and nonpsychiatric control subjects while they perform SWM task. Cortical source time series signals of these regions were generated by consecutive inverse problem solving with individual structural magnetic resonance image (MRI) and minimum norm algorithm, which were applied for every time points of the MEG sensor signals. With the cortical source signals, we computed phase synchrony estimates between cortical regions involved in SWM for 5 frequency bands (delta, theta, alpha, beta, and gamma). To yield uniform resolution of phase synchrony across brain regions we applied a novel reduced interference distribution method to avoid the trade-off between time and frequency evident in wavelet analysis. Analyses revealed that schizophrenia patients failed to exhibit gamma synchrony modulation between left DLPFC and right PPC and between left DLPFC and right inferior frontal cortex according to SWM load. These results will be discussed regarding the role of gamma synchrony in SWM deficits and schizophrenic symptoms.
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DEVELOPMENT OF RESTING STATE NETWORKS FROM BIRTH TO AGE 2 YEARS

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People with schizophrenia have evidence of abnormal resting state networks. To better understand the development of these networks in humans, we used resting functional MRI to depict brain regions exhibiting temporal synchronization, also known as resting brain functional connectivity (rfc), to determine the temporal and spatial patterns of rfc in healthy children between 2wks and 2yrs old. Resting brain functional connectivity was performed on 85 children: 38 neonates (2–4 wks), 26 1yr olds and 21 2yr olds. All subjects were imaged while asleep; no sedation was employed. Six regions-of-interest (ROIs) were chosen, including the primary motor, sensory, and visual cortices in each hemisphere. Mean signal of each ROI was used to perform correlation analysis pixel-by-pixel throughout the entire brain, identifying regions with high temporal correlation. Functional connectivity was observed in all subjects in the sensorimotor and visual areas. The percent brain volume exhibiting rfc and the strength of rfc increased from 2wks to 2yrs. The growth trajectories of the percent brain volume of rfc appear to differ between the sensorimotor and visual areas while the z-score is similar. The percent brain volume of rfc in the sensorimotor area is significantly larger than that in the visual area for 2wks ($P = .008$) and 1yr ($P = .017$) olds but not for the 2yr olds. These findings suggest that rfc in the sensorimotor precedes the visual area from 2wks to 1yr but becomes comparable at 2yrs. In contrast, the comparable z-score values between the sensorimotor and visual areas for all age groups suggest a disassociation between percent brain volume and the strength of cortical rfc. Ongoing studies of the development of the default network will also be presented.
ID: 551783

ALTERED PREFRONTAL-PARIETAL PHYSIOLOGY DURING OLD-NEW ITEM RECOGNITION IN SCHIZOPHRENIA: A MULTIMODAL NEUROIMAGING INVESTIGATION

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Prefrontal-parietal networks are essential to many cognitive processes, including the ability to differentiate new from previously presented items. Given the well-documented recognition memory performance decrement in patients with schizophrenia (compared to healthy individuals), we hypothesized that these patients might demonstrate task-related abnormalities in prefrontal and parietal physiology as measured by both functional magnetic resonance imaging (fMRI) and magnetoelectroencephalography (MEG). A total of 18 medicated outpatients with schizophrenia and 18 age-matched healthy control subjects participated. Subjects underwent an old-new item recognition paradigm during scanning with both fMRI (using a 1.5 T Siemens Avanto whole-body clinical scanner) and MEG (using a dc-SQUID Neruomag Vectorview system). During encoding blocks, participants saw and heard 26 words and identified the gender of the recorded voice using a keypad button. Immediately following encoding, participants were presented with 52 words (26 previously presented and 26 new) and were asked to specify whether each word was new, or previously presented

by a male or female voice. While controls exhibited strong, bilateral activation of prefrontal and posterior parietal regions during successful identification of old versus new items, patients showed markedly attenuated activation of the right prefrontal and parietal cortices. However, among the patient group, those with better performance activated more strongly these right-sided regions, and unlike in controls, old-new effect-related activations in frontal and parietal regions were tightly correlated. As seen with the finer temporal resolution of MEG, control subjects—but not patients—exhibited a sequential pattern of old > new electrical activity in the left posterior parietal cortex and then right prefrontal cortex; however, patients uniquely exhibited old > new activity in right temporal cortex, a region not usually implicated in old-new item recognition processing in healthy subjects. Collectively, these findings point to markedly different distributions of regional specialization necessary to complete the old-new item recognition task in patients versus controls. Inefficient utilization of prefrontal-parietal networks, with compensatory activation in temporal regions, may thus contribute to deficient old-new item recognition in schizophrenia.
ID: 551767

DISTINGUISHING EFFECTS OF SCHIZOPHRENIA AND IQ DECLINE ON BOLD FMRI ACTIVATION

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Many previous fMRI studies examining functional brain differences in schizophrenia are confounded by differences in intelligence score (IQ) between patients and healthy controls. Patients' IQ is often below 100, whereas those of age and education matched controls are usually much higher. Using a variation of the Wisconsin Card Sorting Test (WCST), a standard neuropsychological test (modified for use in fMRI), we investigated brain activation in a group of high functioning schizophrenia patients and two groups of healthy controls that were matched either in terms of their current IQ or premorbid IQ. The results have significant implications for any researchers trying to distinguish which BOLD fMRI differences relate to IQ decline or schizophrenia itself. 12 patients with diagnosis of schizophrenia were matched to 12 healthy controls on the basis of premorbid (WTAR) IQ, and to another 12 on current (WASI) IQ estimates. Age, education, sex, and SES were matched between groups. All subjects then performed the modified WCST during fMRI. BOLD fMRI (TR = 3s; FA = 90; matrix = 64 x6 4; FOV = 192 x 192; 780 volumes of 32, 3 mm slices acquired parallel to AC-PC plane) was performed on a 1.5 T Siemens Symphony MRI scanner. Motion correction, 8 mm FWHM smoothing, and Talairach transformation was performed prior to random effects general linear modeling using FIR deconvolution (BrainVoyager QX v1.10, Brain Innovation, Holland). Voxels above threshold (corrected $P < .05$) were considered significant. Significant group differences were found in several regions, including dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex. In these regions, hypoactivity was found for low IQ relative to high IQ subjects. Previous fMRI studies have noted DLPFC hypoactivity for schizophrenics (in whom IQ is lower) relative to healthy controls (with higher IQ). The present study therefore raises the possibility that DLPFC hypoactivity, which was previously ascribed to schizophrenia, may instead simply reflect reduced intellectual function in these patients. Caution is therefore needed when interpreting fMRI studies with patients in whom IQ may be affected. To avoid potential confounds, stricter IQ matching is required.
ID: 551752

THE DEVELOPMENT OF AN AUTOMATED TOOL FOR THE DETECTION OF FMRI ACTIVITY PATTERN ASSOCIATED WITH SCHIZOPHRENIA

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Background: The development of objective, laboratory based diagnostic tools would significantly augment our ability to accurately identify individuals suffering from or at high risk of developing schizophrenia. Here we report on our efforts to use automated multivariate pattern analysis to differentiate fMRI activation patterns from individuals with schizophrenia from healthy subjects. Method: 25 patients with first episode schizophrenia and 24 demographically matched healthy control subjects underwent fMRI scanning while they completed the AXCPT. A non-linear neural network based pattern classifier analyzed DLPFC seeded functional connectivity maps of the contrast between B Cue (high cognitive control) and A Cue (low cognitive control) conditions. Training and testing was conducted using a jack-knife or n-1 cross-validation procedure in which the subject's data to be tested (classified) was excluded from the training set in an iterative manner. Results: The pattern classifier achieved overall diagnostic accuracy of 75.5%, identifying 72% of patients and 79% of controls correctly. Conclusion: Automated diagnosis based on fMRI activation pattern analysis achieved fairly high accuracy, suggesting that this procedure is a viable method to assist in the assessment and diagnosis of individuals with or thought to be at risk for schizophrenia.
ID: 551750

PRACTICE-INDUCED CHANGES IN NEURAL CIRCUITRIES SUPPORTING SACCADE PERFORMANCE IN SCHIZOPHRENIA: AN FMRI STUDY

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Decreased prefrontal cortex (PFC) function is hypothesized as a key deficit in people with schizophrenia. PFC circuitry supports higher level executive control processes such as inhibition. A simple test of inhibition is provided by an antisaccade task, which requires a glance to the mirror image of a peripheral cue. People with schizophrenia make more antisaccade errors towards the cue and have lower PFC activity than healthy participants. The extent to which PFC activity may be enhanced to possibly improve executive control in schizophrenia is uncertain. Recent studies from our laboratory showed that in healthy people daily antisaccade practice improves antisaccade performance, while daily prosaccade practice disrupts antisaccade performance. These behavioral changes are accompanied by quantifiable changes in brain activation. The current study was designed to determine whether neural pathways supporting antisaccade performance in schizophrenia are modified across time. People with schizophrenia and healthy comparison subjects took part in a 2-week trial. Testing evaluated anti- and pro-saccade performance in a 3-Tesla fMRI environment at 3 time points, each separated by a week; 1) Pre-Test, 2) Mid-Test, and 3) Post-Test. Subjects were assigned to a practice group (either antisaccades or prosaccades) and between fMRI testing sessions completed daily practice sessions on the assigned task. The behavioral results were similar to previous studies; at Pre-Test, participants with schizophrenia had normal prosaccade performance, but made more antisaccade errors. The imaging results across groups illustrated typical saccadic circuitry including: supplementary eye fields (SEF), frontal eye fields (FEF), posterior parietal cortex (PPC), visual cortex, cingulate gyrus and caudate, with thalamus and prefrontal cortex (PFC) observed in the antisaccade task. The schizophrenia group, however, showed brain activation patterns that differed from comparison subjects. For instance, signal associated with task performance was modified differentially over the three time points. Group differences were observed in SEF, FEF, PPC, and PFC. This study may have implications for understanding the malleability of activity in PFC and its associated circuitry in people with schizophrenia. This research was supported by a grant from the National Institute of Mental Health (MH076998).
ID: 551744

PERCEIVED REALITY AND LOUDNESS OF AUDITORY VERBAL HALLUCINATIONS IS ASSOCIATED WITH REDUCED CONNECTIVITY BETWEEN THALAMUS AND AUDITORY CORTEX: AN FMRI STUDY IN SCHIZOPHRENIA PATIENTS

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Auditory hallucinations (AVH's) are a prominent and often disabling symptom of schizophrenia, that may interfere with social functioning. There may be considerable differences between patients in terms of severity of AVH's, however. The neural correlates of phenomenal aspects such as loudness and perceived reality of hallucinations has not been studied as yet. In this study we investigated whether perceived reality and loudness of auditory verbal hallucinations would be associated with abnormal functional connectivity between thalamus and auditory cortex, which are key nodes in the auditory system. Eighteen schizophrenia patients with active hallucinations in the week prior to scanning underwent a resting state fMRI scan (TR = 2.3 s; 200 volumes). All patients filled out the Auditory Hallucinations Rating Scale (AHRS). Regions of interest were delineated with help of a brain atlas, and included the thalamus and auditory cortex. The Pearson's correlation coefficient was calculated between both areas for each hemisphere seperately, and converted to Z-scores. The frequency, reality and loudness items of the AHRS were correlated with the Z-scores using the nonparametric Spearman's rho. The results revealed that Z-scores of right thalamus—right auditory cortex connection were negatively correlated with the reality ($\rho = -0.585$; $P < .011$) and loudness ($\rho = -0.617$; $P < .008$) item. Thus, our findings show that decreased connectivity between right thalamus and auditory cortex are associated with more realistic and louder voices. We hypothesize that a disconnection between these regions can lead to reduced bottom-up control of the thalamus over spurious auditory activation.
ID: 551734

ELEVATED ACTIVITY WITHIN THE POSTERIOR CINGULATE CORTEX IN SCHIZOPHRENIA DURING SELF-REFLECTION

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Background: Schizophrenia is characterized by abnormalities in social cognition and self-reflection. Functional neuroimaging studies in healthy

subjects have found that social cognitive processes that require reflection on the self or familiar others lead to activation of medial prefrontal and posterior cingulate cortices. Results of previous studies in healthy participants have suggested a role for the posterior cingulate cortex in episodic memory processes, and involvement of the medial prefrontal cortex in semantic aspects of self-reflection. However, it is not known whether one or both parts of this network function abnormally during self-reflective processes in schizophrenia. Methods: We measured activity within this network in 17 patients with schizophrenia and 18 demographically-matched control subjects. Participants underwent functional MRI scanning while adjectives representing desirable or undesirable personality traits (eg, "honest," "lazy") were presented. During scanning, participants were asked to judge whether each word described themselves. In additional blocks, participants were asked to judge whether an adjective described a familiar other (the participant's mother), and whether an adjective represented a good or bad quality (a valence judgment). Activation elicited by the two social reflection tasks was compared to activation elicited by the valence judgment task within the medial prefrontal and parietal cortices within and between subject groups. Results: The control and schizophrenia groups did not differ in their pattern of response types during scanning. Also, both the control and schizophrenia group exhibited activation of the medial prefrontal cortex during social reflection. However, during both social tasks, the patients with schizophrenia exhibited significantly greater activation within the right posterior cingulate cortex than the healthy control subjects. Conclusion: Greater engagement of the posterior cingulate cortex in schizophrenia during social reflection may reflect an increased reliance on (or inefficient processing of) episodic, autobiographical memory. Follow-up studies will determine whether dysfunction of the posterior cingulate cortex in schizophrenia is associated with impairment in social cognition and real-world functioning.
ID: 551722

ABNORMAL BRAIN ACTIVATION DURING A - VISUAL DISCRIMINATION FMRI TASK IN INDIVIDUALS WITH SCHIZOPHRENIA AND THEIR FIRST-DEGREE RELATIVES

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1st degree relatives of individuals with schizophrenia (F) exhibit cognitive abnormalities similar to those found in individuals with schizophrenia (SZ). Previous PET studies have shown that SZ exhibit abnormal cingulate activation during matched-performance on auditory discrimination tasks, but it is unclear whether F might also show similar patterns. This study investigated brain activation found in SZ during a matched-performance visual discrimination task and examined whether these patterns represent a marker of cognitive dysfunction that is also found in F. fMRI was used to compare 10 SZ, 5 F, and 8 controls (C) who engaged in a matched-performance visual discrimination task. The fMRI session consisted of 8 runs (20 trials/run; 12 task conditions and 8 control presentations). The task condition consisted of 1 of 6 discrepancy levels. A correct response was a decision of equivalence or nonequivalence between the two blocks. The control condition consisted of a block that was offset to the left or right of the screen. A correct response was selection of the offset side of the block. Preprocessed fMRI data were analyzed in SPM5 by using a whole-brain approach in a mixed-effects design. The task > control contrast during the decision period was greater in SZ compared to controls in the bilateral superior Medial Frontal Gyrus (MFG), right Superior Temporal Gyrus (STG), right inferior frontal gyrus/operculum, left middle frontal gyrus, and left insula. C showed similar activation in MFG and STG during the time period preceding the decision compared to SZ. F showed greater activation during the decision period in left postcentral gyrus, left precuneus, and left caudate compared to C. C showed significantly greater activation in left caudate and right MFG during the time period preceding the decision. Compared to C, SZ and F have different patterns of brain activation during a visual discrimination task, despite similar performance on the task. Assuming the pattern of activation found in C reflects an efficient decision-making strategy; hypoactivation during the period preceding the decision may indicate a less efficient strategy for decision-making in SZ and F. The widespread activation during the decision period in SZ, but not F, compared to C reflects the greater magnitude of dysfunction in this group. The abnormal pattern of brain activation during the decision period may be a viable candidate as an Imaging Marker of cognitive dysfunction for SZ.
ID: 551719

SEMANTIC MEMORY RETRIEVAL BRAIN ABNORMALITIES IN SCHIZOPHRENIA: STATE VS. TRAIT?

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The neural basis of Formal Thought Disorder (FTD) in psychoses is unknown. An influential hypothesis is that FTD results from impaired semantic memory processing. Using a functional MRI (fMRI) semantic object retrieval task (SORT), we previously showed that chronic, stable schizophrenia patients have impaired activation in semantic brain areas when compared to healthy controls (HC). Furthermore, we found a correlation between the rostral anterior cingulate cortex (ACC) activation and patients' FTD severity (Assaf et al. Biol Psychiatry, 59: 452–9). However, it is not yet known if these findings are related to state vs. trait of the disease. In the current study we used the SORT to explore the neural correlates of semantic memory retrieval in chronic schizophrenia patients who were either stable (S-SZ; $n = 13$) or in a matched group of acute relapsing phase (RL-SZ; $n = 14$) compared to matched HC ($n = 17$). SORT requires participants to determine whether word pairs describing object features combine to retrieve an object. One-way ANOVA demonstrated a group difference in reaction time, such that HC were significantly faster than S-SZ, who were faster than RL-SZ. Functionally, an ANCOVA (controlling for full scale estimated pre-morbid IQ) demonstrated significant group differences in several brain areas, including: bilateral inferior parietal lobule (IPL), dorsolateral prefrontal cortex, posterior cingulate cortex and ACC, and left middle temporal cortex, such that HC had greater activation than all schizophrenia patients ($P < .01$). Of these areas, only the IPL showed a significant difference between the two schizophrenia groups, such that S-SZ showed greater activation (ie, were less abnormal) than RL-SZ. These results suggest that while some brain abnormalities are related to the general trait of the illness, IPL activation depends on illness phase. The relationship of our findings to patients' symptoms will be discussed.
ID: 551718

FRONTO-TEMPORAL HYPOACTIVATION DURING PERFORMANCE OF A VIRTUAL WATER MAZE TASK IN SCHIZOPHRENIA

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In the current study, we applied fMRI BOLD methods to investigate differences in brain activation in a group of schizophrenic patients compared to a group of healthy control subjects during completion of a hippocampal-dependent virtual water maze task. We focused on frontal and medial temporal lobe (MTL) structures because previous studies have identified memory processing deficits as part of the core cognitive symptoms of schizophrenia. These deficits could be mediated by NMDA receptor hypofunction in fronto-temporal areas (Tsai and Coyle 2002). NMDA receptors in the hippocampus and associated MTL structures are essential for spatial learning and memory and that pharmacological blockade of NMDA receptors impairs spatial navigation. Imaging data was acquired on a 3.0 Tesla Varian MRI scanner. Fourteen schizophrenic patients (mean age 40.3 years; 3 females, 11 males) and fourteen age and gender matched controls were included in the study. The water maze task consisted of 3 conditions: encoding, retrieval, and motor. During encoding, subjects swam to a visible platform that was always in the same spatial location and were instructed to remember the location of the platform. During retrieval, the platform was hidden and subject had to navigate to the correct location. The motor condition tested the ability of subjects to navigate in the maze. Imaging data was motion corrected and analyzed in SPM 5 (height threshold $P < .005$, extent k=20 voxels). Contrasts were created using the motor condition as a control condition. Our preliminary results showed lower activation in the hippocampus, and dorsal and posterior cingulate cortex during the encoding task. During the retrieval of spatial information, the decrease in activation was more widespread in schizophrenic patients, and included the cerebellum, superior and inferior frontal gyri, middle temporal gyrus, dorsal cingulate cortex, and posterior parahippocampal gyrus. These findings suggest that memory deficits in schizophrenic patients could be related to hippocampal deficits during encoding of information. Further it suggests that spatial learning and recall in schizophrenia are associated with dysfunctional fronto-temporal networks, rather than abnormalities in a single region.

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ID: 551694

IMPAIRED METACOGNITIVE EVALUATIONS AND HYPOACTIVITY OF THE NEURAL CIRCUITRY OF SELF-OTHER AWARENESS IN EARLY SCHIZOPHRENIA

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Background: The neural correlates of deficits in metacognitive evaluations (MEs) of self and others in schizophrenia are incompletely understood. In healthy controls (HCs), self-other awareness activates the medial prefrontal cortex, the posterior superior temporal sulcus (STS), and the temporal poles bilaterally. We used functional magnetic resonance imaging (fMRI) to evaluate differences in brain activity during an ME task involving self-other awareness in patients in the early phase of schizophrenia (EPS) and HCs. Methods: Eleven EPS subjects (diagnoses based SCID interviews/DSM IV criteria for schizophrenia) (7 males; mean age 26.6 ± 8.0) and 10 HCs (4 males; mean age 29.6 ± 8.4) were recruited at Wayne State University. fMRI scanning was obtained using a full body Brucker MedSped 4.0 T scanner and imaging data was processed with statistical parametric mapping (SPM2) software. The fMRI task required participants to provide yes/no responses to adjectives in three separate descriptor-referential conditions: self-evaluation, other evaluation, and non-referential semantic positivity-evaluation. Single sample group t-tests were performed for each condition in both groups, followed by second level between-group analyses. The threshold p value was set to <0.005 and a voxel threshold = 50. Results: The EPS group showed a significant decrease in activation of the posterior left STS (FDR corrected $P < .049$) and a trendworthy decrease in activation of the right middle frontal gyrus (FDR corrected $P < .073$) during MEs of others compared to HCs. There were no significant group differences in areas of activation during self-evaluative processes. Conclusion: To our knowledge, this is the first study of the neural correlates of MEs regarding the self and others in EPS. Hypoactivity of the left STS may provide the neural basis for disturbances in MEs of others associated with failures of source monitoring and theory of mind (ToM) found in patients with EPS. Deficits in MEs regarding others may mediate key symptoms of psychosis (eg, delusions and auditory hallucinations) and lead to misattributions regarding others' intentions that contribute to the functional disability of schizophrenia. Larger, prospective follow up studies are required to further assess the relationships between decreased activation of neural circuits associated with awareness of others, specific forms of metacognition (eg, ToM and source monitoring), and the clinical/functional course of schizophrenia.
ID: 551685

DEVELOPMENTAL CHANGES IN FUNCTIONAL ACTIVATION DURING WORKING MEMORY IN ULTRA-HIGH RISK SUBJECTS AND HEALTHY CONTROLS

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Across adolescence and young adulthood ongoing neurodevelopmental changes occur, including processes such as synaptic pruning and myelination, as the brain begins to settle into an adult-like architecture. Functional and structural imaging studies indicate that there are observable changes in both functional activation and grey matter density throughout adolescence. This period of change represents a time of special vulnerability for patients with schizophrenia; onset of the disorder occurs during this period and is thought to be associated with either a disruption in this developmental process or the exertion of a normal developmental process on an already compromised system. Further, this period is of particular interest in subjects at ultra-high risk for schizophrenia, as understanding any dynamic developmental differences may offer a unique opportunity

to identify points of intervention. Previous studies of brain development indicate that patients with schizophrenia and controls may have different trajectories of grey matter change over time, but this has not yet been assessed using functional imaging. To assess these issues of neurodevelopmental changes in the prodrome, we performed a cross-sectional analysis of ultra-high risk (UHR) and healthy control subjects ranging in age from 12 to 26 years. A verbal Sternberg-style working memory task was used as a functional probe of the working memory circuitry, which is known to be compromised in schizophrenia. Subjects performed this task while undergoing functional magnetic resonance imaging (fMRI) scans. Using polynomial regression we assessed the differences between the relationship of functional activation in the working memory circuitry and age in UHR and control groups. The function defining the relationship between age and neural activation in the UHR group differed from that in controls, and may indicate a different developmental trajectory in these subjects. This finding may have implications for our understanding of functional neuroanatomic changes that occur leading up to the onset of psychosis.
ID: 551652

SPECIFIC DEFICITS DURING MEMORY FORMATION AS A MARKER OF SHORT-TERM CLINICAL OUTCOME IN FIRST EPISODE PSYCHOSIS: BEHAVIOURAL FMRI RESULTS

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Background: Memory is one of the cognitive functions most affected in schizophrenia with deficits observed from the first episode of psychosis (FEP). Both short-term and long-term outcome have been related to various memory deficits. However, no previous study has examined specific aspects of memory formation in relation to short-term clinical outcome in FEP patients. Methods: To examine specific memory processes in FEP in relation to clinical outcome. Behavioural fMRI data were collected in 55 FEP patients (32 poor outcome and 23 good outcome—based on six-month clinical outcome) and in 32 matched healthy controls. Participants completed 2 fMRI encoding sessions each comprised of 56 different pairs—28 semantically unrelated items and 28 semantically related items. They were cued to use one of two specific encoding strategies—associative (ie, to compare the 2 images and answer which of the two would be bigger in real life) or deep item-oriented (ie, to judge whether one of the images represented a living entity). Recognition, not accompanied by a fMRI session, was a yes/no answer for identifying a previous pair with 112 pairs presented in each of two sessions. Results: In general, compared to healthy controls, the FEP patients show a poorer recognition performance for arbitrary pairs relative to the semantically related pairs; supporting our previous finding with a smaller sized sample. More particular to the patients, there was a significant triple interaction (encoding strategy x semantic relatedness x group; $F = 13.18$, $P = .001$). More specifically, the poor outcome group performed worse than the good outcome group when using the associative encoding strategy for semantically related pairs only. Conclusions: This selective deficit that affects memory performance in FEP may confer greater vulnerability to not only psychotic disorders but also to a poorer outcome after six months of treatment. These findings may have therapeutic implications.
ID: 551642

MATERNAL RESPONSIVENESS IN NEW MOTHERS WITH SCHIZOPHRENIA: AN FMRI STUDY

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Bowlby suggested that parenting behaviour is likely to have biological roots which produce unique, powerful emotions experienced by mothers with new infants. We and others have previously reported that, when healthy new mothers see their infants, an extensive brain circuit is activated, which integrates affective and cognitive information to direct maternal behaviour. We have also described a range of deficits in the capacity of new mothers with schizophrenia to respond to infants. This study begins to explore the relationship between maternal brain responses and behaviour in schizophrenia. In this study we aimed to use fMRI to examine the neural correlates of maternal responsiveness in new healthy mothers and compare them to new mothers with schizophrenia and present preliminary findings. 11 healthy and 7 new mothers with schizophrenia (matched on age, education and infant age) undertook an 8min fMRI task. Participants viewed alternating 30sec blocks of prerecorded video showing their own infant, an unfamiliar (age matched) infant interspersed with neutral video (moving traffic). Whole brain images were acquired on a 1.5T Philips Intera scanner using a TR of 2.55s. Data were analysed using SPM5. We replicated our findings in healthy mothers: compared to neutral stimuli, new mothers showed widespread visual activation (eg, BA19) when viewing infants. Ill mothers viewing own baby vs neutral show decreases in orbitofrontal cortex (OFC) (BA47) and frontal pole (BA10) activation relative to controls. Viewing other baby vs neutral, ill mothers had a decrease in activation in anterior cingulate (AC) and an increase in middle temporal gyrus (BA21) relative to controls. Finally, when viewing just their own babies, healthy mothers showed increased activity in AC (BA32), left amygdala, right frontal pole (BA10), right putamen and hippocampus compared to ill mothers. These findings suggest a blunted response to emotionally salient stimuli in ill mothers which may be related to their poor parenting outcomes. Further studies aim to relate these effects to behavioural deficits in maternal responsiveness observed in mothers with schizophrenia.
ID: 551604

IMPACT OF PHARMACOTHERAPY ON HIPPOCAMPAL VOLUME AND FUNCTION IN SCHZIOPHRENIA

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Neuroimaging studies have reported deficits in hippocampal volume and function in schizophrenia patients. Structural analyses, such as region of interest (ROI), and functional imaging paradigms, such as novelty detection (ND), have been employed frequently to assess hippocampal volume and function, respectively. However, too few studies have investigated relationship between hippocampal volume and function. We have hypothesized that ND-induced hippocampal activation with novel stimuli will correlate with hippocampal volume. This is an ongoing study to examine correlation between hippocampal volume and function in schizophrenia subjects with (on-meds) and without (off-meds) antipsychotic medications. These preliminary data are based on a partial sample in 14 right-handed schizophrenia subjects with DSM-IV TR diagnosed schizophrenia or

schizoaffective disorder and seven right-handed normal controls (NC; average age = 34.7 ± 12.6; M/F = 2/5). Seven out of 14 schizophrenia subjects are off-meds (average age = 36.7 ± 10.1; M/F = 5/2) and seven are on-meds (average age = 39.7 ± 8.5; M/F = 6/1). Psychopathology is assessed with Positive and Negative Syndrome Scale (PANSS) and cognitive function with the Repeatable Battery to Assess Neuropsychological Status (RBANS). Structural and functional MRI scans are obtained on a 1.5 T GE system. Morphometric measurements are conducted on BRAINS 2 by a trained rater blind to clinical information and all hippocampal volumes are adjusted for total brain volume (TBV). Our preliminary findings show a larger right ($t = 4.36$; $df = 12$; $P = .0009$) and left hippocampal volume ($t = 2.40$; $df = 12$; $P = .03$) in NC as compared to off-meds schizophrenia subjects. However, only the right hippocampal is larger in NC as compared to on-meds schizophrenia subjects ($t = 3.22$; $df = 15$; $P = .005$). No significant differences in right or left hippocampal volumes are found between on- and off-meds schizophrenia subjects. Likewise no significant associations are found between any TBV-adjusted hippocampal volumes and PANSS or RBANS scores. Caution is required in the interpretation of these preliminary findings as they are based on a small sample. Findings from a larger sample will be reported later along with the analysis of relationship between hippocampal volume and function.
ID: 551603

THE ACUTE EFFECT OF THETA BURST STIMULATION IN SCHIZOPHRENIA MEASURED WITH A VERBAL FLUENCY FMRI PARADIGM

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Decreased prefrontal, but increased cerebellar activity has been associated with cognitive deficits and negative symptoms in patients with schizophrenia. Here, we tested our hypothesis that theta burst stimulation (TBS) to the left dorsolateral prefrontal cortex (DLPFC) or to the medial cerebellum would produce a cognitive enhancing effect in patients. In a factorial, between-group design, 36 patients with chronic schizophrenia were assigned to receive either 600 TBS pulses of left DLPFC facilitation (intermittent TBS), cerebellar suppression (continuous TBS) or sham TBS at an intensity of 80% resting motor threshold. Patients were scanned twice using the identical letter fluency task (which has been associated with prefrontal and cerebellar activation), immediately before and after TBS. Functional data were acquired using a 3T system, and were analysed using SPM2 (random-effects, $P < .001$, uncorrected). Patients' verbal responses during scanning were recorded and scored off-line to produce total numbers of correct responses, omission errors, clustering and switching. Following left DLPFC TBS facilitation, there was significant increase of activation in right DLPFC (BA 46), along with caudate nucleus, left medial prefrontal cortex (BA 10) and left premotor area (BA 6). The increased right DLPFC activation was associated with decreased number of omission errors ($r = -.76$, $P = .005$) and increased total number of clustering ($r = .77$, $P = .004$). In the cerebellar TBS suppression group, areas activated more following TBS included left inferior frontal gyrus (Broca's area) and inferior parietal lobule (BA 40), bilateral superior temporal gyri (BA 22), pulvinar of the thalamus, and anterior cerebellum (lobule III). The increased anterior cerebellum activation following TBS was positively correlated with increased number of switching ($r = .78$, $P = .003$). The sham group activated right DLPFC (BA 46), but this activation was not related to performance measures. In this study, we investigated the acute effect of TBS protocols on DLPFC and cerebellar activity during fMRI. The results support evidence that high frequency TMS produced increases activation in task-specific

brain areas in healthy volunteer studies. Hence, this study provides a scientific justification for the design of further TBS experiments and clinical evaluation in patients with schizophrenia.
ID: 551565

BRAIN ACTIVATION CHANGES ON FMRI FOLLOWING COMPUTERIZED COGNITIVE TRAINING

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Cognitive remediation in schizophrenia can be achieved through neural "restoration"– restoring normal activity in brain regions that are active during a task in healthy subjects, but are under- or over-active in patients prior to treatment. It can also be achieved through neural "compensation"– changes in activity in brain regions in patients that increase (rather than decrease) the differences between patients and healthy subjects. In this ongoing study, we asses the relative contribution of these two processes by performing fMRI scans before and after 100 hours of computerized cognitive remediation exercises. There are three subject groups: schizophrenia patients receiving cognitive remediation, and patient and healthy subject control groups. During both fMRI sessions, subjects perform three different cognitive activation tasks: N-back with letter stimuli, color-word Stroop, and Go-No go response inhibition. The use of three different tasks allows further assessment of the nature of the underlying neuropathology as well as its response to treatment. In our work to date, at baseline, patients and healthy subjects show highly similar general patterns of activation during all three tasks, indicating that the patients were successfully engaged in the tasks. There are also significant differences between patients and controls on all three tasks, the location of which differ among the tasks. These data suggest that schizophrenia is characterized by impaired recruitment of task-specific neural systems. Patients show changes after treatment ($P < .05$) on all tasks, and these changes are in areas that do not show significant change on re-testing in healthy controls. Nearly all changes are in areas in which patients differ from healthy subjects pre-treatment, and serve to decrease these differences, thus suggesting neural "restoration." The changes are primarily in different anatomic locations on the three tasks, providing preliminary evidence for system-level plasticity in the response to treatment. If borne out in larger samples, these data will provide light on mechanisms of cognitive remediation, and guide further development of this new and important treatment approach.
ID: 551530

DOES IV THC INCREASE THE AVAILABILITY OF DOPAMINE IN THE STRIATUM?

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Background: For centuries people have used cannabis to produce altered state of consciousness. A wealth of evidence suggests that, in some individuals, cannabis can induce an acute schizophrenia-like psychosis. Of the 66 individual cannabinoid molecules found in herbal cannabis, Δ9-tetrahydrocannabinol (THC) has been identified as the component underlying the psychotomimetic effects. Despite the indirect evidence that psychotic symptoms are attributed to alterations in the levels of the neurotransmitter dopamine (DA), to date there is little evidence that administration of THC in humans leads to an increase in DA levels. Furthermore it is unknown if excess striatal dopamine underlies the psychotomimetic properties of THC. Method: Under randomised, double-blind, placebo-controlled conditions we used IBZM-single photon emission tomography (SPET) to measure

striatal dopamine D2/D3 receptor availability, prior to, and following a challenge with intravenous THC (2.5mg). Ten male healthy volunteer completed two IBZM-SPET scanning sessions. Receptor availability was calculated using a region-of-interest approach, using a reference region to control for non-specific binding. Psychotic symptoms were rated using the PANSS scale. Results: Administration of THC increased positive psychotic symptoms ($z = -2.5$, $P = .01$). Differences in striatal dopamine release under placebo versus THC sessions were compared. Initial analysis suggests that THC increases DA release in the striatum. Conclusion: The administration of THC does lead to the experiencing of psychotic symptoms in otherwise healthy males and preliminary analysis suggests it also increases DA release in the striatum. The relationship between THC-psychosis and THC-DA release will be discussed further.
ID: 551525

MODAFINIL EFFECTS ON PREFRONTAL CORTEX DURING COGNITIVE CONTROL IN SCHIZOPHRENIA: A PHARMACO-FMRI STUDY

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Background: Schizophrenia is characterized by dysfunction of prefrontal-dependent cognition. This prominently includes impairments in cognitive control and its basis in a cortical network centered on the dorsolateral PFC (DLPFC) and anterior cingulate cortex (ACC). These PFC areas are also strongly modulated by catecholamines, and there is evidence that pro-catecholaminergic agents improve PFC-dependent cognitive performance in animal models and in humans. We sought to test whether the novel agent modafinil exerts a remediating effect on PFC-dependent cognitive dysfunction in schizophrenia. Methods: To date, 12 adults with clinically-stable chronic schizophrenia participated in a double-blind, placebo-controlled crossover study of a single oral dose of modafinil 200 mg. Subjects were scanned 3–4 hours after dosing, and performed the Preparing to Overcome Prepotency (POP) task during slow event-related fMRI with GLM-based analysis of BOLD contrast. In the POP task, color cues are presented which signal congruent (Green Cues) versus incongruent (Red Cues) stimulus-response mappings to subsequent targets (left or right-pointing arrows). Cue-Target delay period activity is elicited in DLPFC as a measure of context processing, whereas Post-Target period activity is elicited as a measure of conflict monitoring in the ACC. Both regional BOLD responses are stronger after Red Cues. Results: To date, the patients show higher delay-period DLPFC and ACC activity on modafinil compared to placebo, particularly for Red Cue-related activity, with improved performance. Conclusions: A single dose of modafinil is associated with improved DLPFC activity during context processing. Additional studies are underway to evaluate the relative effects of single-dose versus sustained modafinil treatment.
ID: 551503

ANHEDONIA AND SUBJECTIVE EMOTIONAL EXPERIENCE IN SCHIZOPHRENIA: AN FMRI STUDY

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Emotional disturbances such as anhedonia and flat affect are well-known clinical features of schizophrenia (SCZ), but self-report data suggests that emotional experience is intact in SCZ. We explored this disconnect among different components of emotion in SCZ by using fMRI to examine brain activity in response to affect-eliciting stimuli and its relationship to clinical measures of anhedonia. 40 SCZ and 32 demographically matched controls

(CON) made arousal and valence ratings to pictures, words, and faces that varied in both arousal and valence. Behaviorally, the pattern by which the ratings were modulated by the emotional content of the stimulus was the same in SCZ and CON. fMRI analysis revealed that the pattern of functional activity varied with the valence and arousal characteristics of the stimuli in largely the same way in SCZ and CON. Contrast analyses sensitive to the valence and arousal characteristics of the stimuli revealed no differences between groups in a whole-brain analysis, or in an ROI analysis of the amygdala. An ROI analysis of the basal ganglia, however, revealed a group difference in which SCZ showed reduced activity to positive stimuli as compared with controls. This suggests a possible role of abnormal basal ganglia activity in anhedonia in SCZ. To examine the relationship between emotional experience and individual differences in clinical measures of anhedonia, we correlated the behavioral ratings and the fMRI data with SANS global anhedonia and Chapman physical and social anhedonia scores. While SCZ showed greater anhedonia overall, greater anhedonia was associated with less-valenced (ie, more neutral) ratings of the emotional stimuli in both groups. Furthermore, in both groups, greater anhedonia was associated with reduced amygdala activity to positive stimuli as compared to negative and neutral stimuli. The basal ganglia, however, showed opposite patterns between the two groups. In CON, greater anhedonia was associated with less activation to positive versus neutral and negative stimuli. In contrast, SCZ showed greater anhedonia in association with greater activation to positive versus neutral and negative stimuli. Together, these results suggest that subjective emotional experience and its associated brain activity are largely intact in SCZ, with the exception of activity in the basal ganglia, which shows blunted responses to positive stimuli and an abnormal association with symptoms of anhedonia.
ID: 551493

PREFRONTAL BRAIN SYSTEMS IN SCHIZOPHRENIA AND PUTATIVE INTERACTING DOPAMINERGIC GENE MECHANISMS

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Schizophrenia has complex genetic heritability. It is also likely to be genetically heterogeneous. To the extent that genes are associated with symptom constellations of schizophrenia, they do so by affecting the development and function of brain cells and neural systems that mediate the expression of such diverse behavioral, cognitive and perceptual phenomena. While precise mechanisms of human brain dysfunction remain to be well understood, dopaminergic brain processes have been well implicated in the cognitive dysfunction and symptomatic treatment response in schizophrenia, and is an important foothold to elucidate disease mechanisms. Here, we will review recent findings of aberrant neural correlates of prefrontal brain systems engaged by disease-associated working memory processes, particularly executive processes tapping rapid updating of information in working memory (Tan et al. Am J Psychiat 2006). We will extend observations of dysfunctional brain network physiology to explore its underlying dopaminergic gene mechanisms using 'imaging genetics', an emerging field that attempts to integrate the basic biology of putative genetic mechanisms of disease with intermediate brain-based neuroimaging phenotypes from the live functioning human brain. In this regard, we will review recent imaging genetics findings of prefrontal-striatal working memory updating and executive processes mediated by dopamine-associated signal-to-noise processing (Tan et al. J Neurosci 2007). Further, we will examine genetic variation in pathways of interacting dopaminergic and glutamatergic systems implicated in schizophrenia (eg COMT and GRM3), and their modulation of prefrontal brain physiology (Tan et al. PNAS 2007); we will also examine recent suggestions that downstream dopamine-associated intra-cellular signaling molecules (eg AKT1)

are implicated (Tan et al. J Clin Invest 2008). In conclusion, these findings suggest that emerging developments in imaging genetics to examine multi-gene pathways could potentially provide a viable platform to understand human genetic mechanisms of cognitive brain processes relevant to neuropsychiatric diseases such as schizophrenia.
ID: 551454

FUNCTIONAL NEUROIMAGING FOLLOWING COGNITIVE REMEDIATION IN SCHIZOPHRENIA

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Cognition has become a focus of treatment development in schizophrenia (SCZ), due to the adverse effect that cognitive dysfunction has on psychosocial outcome in the illness. However, despite promising preclinical data, pharmacological interventions have not yielded improvements in cognition. Therefore, it has been hypothesized that the implementation of pharmacological treatments may require a behavioral component in order to become manifest. Cognitive remediation (CR) is a behavioral intervention that appears increasingly promising in improving both cognitive function and psychosocial outcomes in individuals with SCZ. Moreover, it holds considerable face validity, given current knowledge of brain plasticity mechanisms and their reliance on repetition to change function. However, few studies have investigated the effect of CR on brain function. Cognitive deficits in SCZ have been correlated with changes in rCBF in multiple brain areas, and it is hypothesized that CR may normalize these deficits. We developed a four-cell intervention designed to test two treatments (atomoxetine and cognitive remediation) alone and together in people with stable SCZ and demonstrable cognitive dysfunction. We have carried out an interim analysis with an $N = 6$ in each of four groups (atomoxetine[A]+control[Con]; A+cognitive remediation[CR]; placebo[P]+ Con; P+CR) , to look both at symptom and cognition outcomes and at potential biomarker outcomes represented by changes in functional imaging characteristics. Here we report the outcomes of CR vs Con in individuals with SCZ who have participated in CR three times weekly (60–90 min) for 12 weeks using CACR-developed software. These volunteers participated in MR imaging before and after the intervention, while performing the N-Back task with fMRI BOLD assessment. Voxel-wise analysis using SPM software allowed us to contrast the group of individuals with active cognitive remediation vs similarly treated computer control individuals. In the CR minus Con contast (1-back minus 0-back), there was a significant increase in fMRI BOLD signal following CR in the regions corresponding to the tertiary visual cortex; whereas, in the Con minus CR contrast(1-back minus 0-back), the regions where CR diminished activations was in the prefrontal cortex, particularly in the middle frontal gyrus. These results suggest that CR increases the use of sensory regions of the brain while enhancing processing efficiency of association areas.
ID: 551421

SCHIZOTYPAL PERSONALITY TRAITS ARE ASSOCIATED WITH ATTENUATED LATERAL TEMPORAL BRAIN ACTIVATION DURING IRONY COMPREHENSION

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A failure to decode ironic meanings during language comprehension in schizophrenia has been documented by a number of recent studies. Recent work assumed a similar deficit in subjects with schizotypal personality traits (Langdon and Coultheart, 2004). Most authors suggested a theory of mind deficit is crucial for irony comprehension deficits in schizophrenia, however the underlying pathophysiology and neurobiology is unknown and recent research accents a possible role of language comprehension abnormalities. The aim of this work was to detect fMRI brain activation changes associated with schizotypal personality traits during irony comprehension. We hypothesised that either a frontomedial (theory of mind) or lateral temporal (language abnormalities) activation deficit is associated with schizotypy. 15 female right-handed subjects (age 20–53 years) completed personality testing as well as functional magnetic resonance imaging and neuropsychology. Subjects were recruited from the general population. No subject had lifetime history of relevant psychiatric disorder or treatment, however subjects differed in their score on the German version of the Schizotypal Personality Questionaire (SPQ). During the fMRI-scans, subjects silently read 44 short text vignettes which ended in either an ironic or literal statement. Imaging was performed using a 3 T Siemens scanner. The influence of schizotypy on brain activation was investigated by using a SPM5 regression analysis with the SPQ total score and SPQ cognitive-perceptual factor as regressors. There was no effect of schizotypy on behavioral data. However, during reading of ironic sentences, brain activation in the temporal lobe of both hemispheres showed a significant negative association with the SPQ total score and SPQ cognitive perceptual factor. Significant positive correlation with the SPQ total score was present in the left inferior frontal gyrus. We conclude attenuated temporal lobe activation is associated with brain activation during pragmatic language comprehension in schizotypy. Structural and functional abnormalities in the middle temporal gyrus, a key region of language comprehension, have been shown in previous research in both schizophrenia and schizotypy. Recently, Sievers (Sievers and Davis, 2004) suggested a temporal deficit is compensated in the lateral prefrontal cortex in schizotypy, but not schizophrenia. The brain activation pattern in our study could support this model.
ID: 551408

THE EFFECTS OF HALOPERIDOL AND ARIPIPRAZOLE ON AUDIO-VISUAL MATCHING IN HEALTHY VOLUNTEERS: AN FMRI STUDY

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Deficits in the integration of information from different sensory modalities are present in excess in patients with schizophrenia. The contribution of antipsychotic medication to such deficits, independent of the pathophysiology of the disorder, remains poorly understood. This study investigates the functional impact of antipsychotics in healthy volunteers. Haloperidol (3mg) and Aripiprazole (10mg) were administered to 10 healthy Caucasian, right handed males (age: 21, SD:3) in a repeated measures, counterbalanced placebo controlled design. Volunteers had no past psychiatric history and abstained from smoking and recreational drug use for at least 3 months prior to the study. Images were acquired on a 1.5T scanner whilst a computerised version of the audio-visual integration sub-test of the Neurological Evaluation Scale (Buchanan and Heinrichs, 1989) was administered. In this task volunteers listened to an auditory paced tone sequence (varying in length), then selected either the visual representation of the auditory sequence from three different options, or selected the 'forced choice'. Random effects analysis was performed in SPM5. Haloperidol significantly reduced overall activation in the left superior and right middle temporal gyri and left cerebellum compared with placebo, and in the right superior temporal gyrus and left cerebellum compared with Aripiprazole. In the experimental relative to control condition, activation was greater after Aripiprazole in the right insula compared with Haloperidol and in the cerebellum bilaterally, compared with placebo. Reduced activation in the right inferior frontal gyrus was observed in the experimental relative

to rest condition, in the Haloperidol group compared with placebo. In accordance with the literature in individuals with psychosis, compared with placebo and Aripiprazole, Haloperidol was associated with reduced activation in regions known to be involved in audio-visual matching (frontal, temporal, cerebellar, insula). Although structural abnormalities in these areas have been identified in patients, evidence for the contribution of antipsychotics to sensory integration deficits are mixed. These findings indicate that sensory integration functioning is altered by even a single dose of antipsychotic medication. This implicates a role for antipsychotics in sensory integration deficits observed in treated patients with Schizophrenia.
ID: 551396

HIGH-FREQUENCY OSCILLATIONS DURING PERCEPTUAL ORGANISATION IN CHRONIC AND FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Recent evidence suggests that patients with schizophrenia are characterized by reduced synchronous, oscillatory activity in the beta- and gamma-band range that may index a core dysfunction in the coordination of distributed neural activity. However, it is currently unclear to what extent high-frequency oscillations (>60Hz) contribute to impaired neural synchronization as research has so far focussed on gamma-band oscillations between 30–60 Hz. Secondly, it is not known whether deficits in high-frequency oscillations are already present at the onset of the disorder and to what extent reductions may be related to the confounding influence of medication.
To address these issues, we employed magnetoencephalography (MEG), a method particular suited for the examination of low-amplitude, high-frequency oscillations, during perceptual organisation in a sample of chronic patients with schizophrenia ($N = 13$), a sample of first-episode, never-medicated patients ($N = 10$), and in a group of healthy controls ($N = 25$). Perceptual organisation was examined with Mooney Faces. MEG signals were analysed for spectral changes in oscillatory activity in the frequency range of 25–200Hz. Compared to healthy controls, both groups of schizophrenia patients showed a highly significant reduction in high-frequency gamma-band activity (60–120Hz) over parieto-occipital sensors. Furthermore, we observed a relative increase of gamma-band power in the lower frequency range (25–45Hz) on fronto-temporal channels in schizophrenia patients compared to controls. Chronic patients were characterized by a pronounced deficit in gamma-band activity and perceptual organisation relative to first-episode patients. To identify the neural generators of gamma-band activity, we used a beamforming technique and performed source localization in the frequency range of maximum power in the gamma band. The analysis of high-frequency gamma-band activity in source space revealed reduced power in the lateral occipital complex (LOC) in chronic schizophrenia patients compared to controls, suggesting that dysfunctional processing in LOC might underlie the observed deficits in perceptual organisation. These results suggest that schizophrenia is associated with a widespread reduction in high-frequency oscillations that indicate local network abnormalities. These dysfunctions are independent of medication status and already present at onset, suggesting a possible progressive deficit during the course of the disorder.
ID: 551387

BRAIN ACTIVITY RELATE TO EMOTIONAL WORDS IN SCHIZOPHRENIA

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Auditory hallucinations are a core feature in schizophrenia. Affective processing deficits have been implicated in the pathogenesis of this symptom. Nowadays, functional neuroimaging techniques are used to study the neurobiological mechanisms of the emotional response in such patients. We apply an emotional auditory paradigm to evaluate cerebral activation using fMRI in 26 healthy volunteers and 32 psychotic patients (20 with chronic hallucinations and 12 without hallucinations). The aim is compare differences in brain activation with listening to emotional words between three groups of study. A different and more extensive pattern of brain activation in patients compared to healthy control subjects was discovered. In particular, a differential activation due to emotional words processing was observed in patients in the frontal areas, globus pallidus, precentral, hipocampus/parahipocampus and cerebellum. Differences in activation were found between hallucinators and non-hallucinators, particularly in middle temporal sulcus, hippocampus and parahipocampus and vermis.
ID: 551376

CATECHOL-O-METHYLTRANSFERASE (COMT) GENE MODULATES THE NEURAL BASIS FOR THE ACUTE EFFECTS OF CANNABIS ON LEARNING AND PSYCHOSIS

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Recent evidence suggests that variation in the Catechol-o-methyltransferase (COMT) gene modulates the effects of cannabis use on memory(1) and long-term risk of developing schizophrenia(2). However, whether the acute effects of cannabis on brain function and behaviour in man depend on their COMT status has not been formally investigated. We investigated this by combining functional MRI and pharmacological challenge with delta-9-tetrahydrocannabinol (delta-9-THC), the main psychoactive ingredient of cannabis, in individuals with known COMT genotype as part of an ongoing study. 20 healthy males (10 Val homozygotes and 10 Met carriers) were studied twice, following oral administration of 10mg of delta-9-THC or placebo 1 hour prior to scanning, in a double-blind design. MR images were acquired while subjects performed a verbal learning task. During the encoding condition, relative to placebo, delta-9-THC augmented activation in the parahippocampal gyrus such that the normal linear decrement in activation across successive encoding blocks was no longer evident. During the recall condition, relative to placebo, delta-9-THC attenuated activation in the ventral striatum which was directly correlated with the severity of psychotic symptoms it induced. In both regions, the effect of delta-9-THC on activation was greater in Val homozygotes than in Met carriers. There was also a trend for Val homozygotes to experience more severe psychotic symptoms following delta-9-THC than Met carriers. Evidence that delta-9-THC influences function in these regions provides a plausible mechanism for the increased risk of schizophrenia in regular cannabis users, as the medial temporal cortex and striatum are critically implicated in the pathophysiology of the disorder. The influence of COMT genotype on the neural

response to delta-9-THC in these regions is consistent with the modulatory effect of COMT genotype on the risk of developing schizophrenia following regular cannabis use and provides preliminary evidence for the biological plausibility of this hypothesis. Funding: This study was funded by the Psychiatry Research Trust, UK and a Joint MRC/Priory Clinical Research Fellowship to Sagnik Bhattacharyya.

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DOES COMPUTERIZED COGNITIVE REMEDIATION CHANGE BRAIN ACTIVATION PATTERNS IN SCHIZOPHRENIA

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Abstract: Cognitive abnormalities, particularly of working memory (WM), are important features of schizophrenia. WM functions appear to be mediated by neural networks involving the dorsolateral prefrontal cortex (DLPFC) and have shown hypoactivity in schizophrenia. The aim of this study is to determine brain activation changes in the DLPFC during stimulation with a neurocognitive task before and after computerized cognitive remediation therapy (CRT). Methods: Patients with DSM IV diagnosis of schizophrenia are randomized to a 12 week trial of CRT using COGPACK software or to a 12-week control condition. Patients in the CRT group complete a total of 36 one-hour sessions. Patients receive at baseline and endpoint an fMRI scan while performing a WM task (N-back test); a neuropsychological test battery (MATRICS); and functional and symptom assessments. Results: We present preliminary results of this ongoing study. Patients in the CRT group showed significantly more improvement in WM than patients in the control group. All patients in the CRT group who received an fMRI scan showed improvement in accuracy on the verbal letter 2-back task after CRT. The signal difference between 2-back and 0-back in DLPFC was significantly higher in the post-CRT scans as compared to the pre-CRT scans. Conclusion: Results indicate an increase in activity in WM related brain areas after 12 weeks of CRT supporting an adaptive cortical effect of CRT. This study offers an opportunity to examine the underlying neurophysiological effects of neurocognitve treatments of WM deficits.
ID: 551369

AUDITORY CORTEX HYPER-RESPONSIVITY DURING AUDITORY STREAMING IN SCHIZOPHRENIA: CORRELATED INCREASES IN FMRI ACTIVITY AND EVOKED GAMMA OSCILLATIONS

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Fundamental physiological abnormalities in sensory cortical processing may contribute to reality distortion and cognitive impairment in schizophrenia (SZ). To probe sensory processing abnormalities, we examined fMRI activity and related it to EEG gamma oscillations as SZ patients and healthy controls (HC) performed an auditory perceptual integration task. Subjects performed identical tasks in separate EEG and fMRI sessions. Subjects passively attended to 42-sec blocks of tones separated by18-sec blocks of white noise (fMRI baseline). Tone blocks consisted of 50msec pure tone stimuli of different pitches, organized in triplets (ABA_ABA…), with tones separated by 50msec and triplets separated by 100 msec. Tone A was always 1000Hz; tone B varied across blocks (500, 950, 1100, or 2000 Hz). In blocks where B and A are close together (small pitch step), a single 'galloping' rhythm is heard; in blocks with a large pitch step, a perceptual shift (streaming) occurs where the initial galloping rhythm separates after several seconds into two distinct rhythms (A..A.. and B…B…). 3T fMRI BOLD data were preprocessed and analyzed with standard techniques. BOLD responses in auditory cortex (Superior Temporal Gyrus, STG) to streaming and galloping blocks were evaluated for differences between conditions and groups. An across-subject correlation analysis examined the relationship of BOLD amplitude to EEG gamma oscillatory power (see companion abstract by Leitman et al. for EEG methods and results). Both groups showed fMRI activation of bilateral auditory temporal cortex extending throughout the STG, which was greater for streaming than galloping blocks. Consistent with EEG results, SZ showed greater STG BOLD activation than HC in both streaming and galloping conditions, as well as a greater difference between conditions. Both groups showed a positive correlation between gamma power and auditory cortex BOLD activation. To our knowledge, this is the first study using fMRI to examine auditory streaming in SZ, as well as the first study to directly relate evoked gamma oscillations to fMRI BOLD activation in a cohort of patients with SZ. We suggest that that the observed enhancement of both BOLD signal and gamma oscillations reflect the same basic underlying abnormality in neuronal processing, perhaps a deficit in inhibition or habituation mechanisms thought to underlie streaming phenomena. Supported by NIMH P50 MH64045.
ID: 551356

BRAIN-PERFORMANCE CORRELATES OF MEMORY RETRIEVAL IN SCHIZOPHRENIA

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Studies correlating cognitive performance with brain activity have found atypical patterns of brain-behavior organization among individuals with schizophrenia. Most studies, however, have used composite performance measures to correlate with brain activity. We used a probability model of a Serial Item Recognition Paradigm (SIRP) to identify cognitive components of memory retrieval to correlate with brain function. Eighty-nine patients with schizophrenia or schizoaffective disorder and 93 healthy individuals received a SIRP task during a multisite functional magnetic resonance imaging (fMRI) study. The SIRP included an encode period, when participants learned a memory set composed of one, three, or five digits, and a recognition probe period. Four stochastic models fit to SIRP response times were compared. Voxel-wise regression models that included group, site, and probability model parameters were used to test for group

differences in correlation patterns. The best fitting probability model assumed exhaustive serial memory scanning followed by self-terminating familiarity matching with one intercept parameter to represent SIRP encoding and response processes. Patients displayed significantly longer response times with increasing memory load and differed on the memory scanning, familiarity matching, and intercept parameters of the best fitting probability model. Group differences in the correlation of the memory scanning parameter with linear brain response to increasing memory load during the probe period were found in the left inferior frontal gyrus, left middle frontal gyrus and in the left, dorsal, anterior cingulate gyrus. The pattern of findings indicated that greater scanning capacity was associated with greater neural capacity among healthy subjects, but that greater scanning capacity required a larger brain response to increasing memory load among schizophrenia patients. Group differences in the correlation of the model's familiarity matching parameter with BOLD response to memory load were found in multiple dorsal mid-sagittal regions. Group differences in the model's intercept parameter were observed in the superior left frontal gyrus and left angular gyrus during the encoding phase and in mid-line cerebellum, mid-brain, and inferior medial frontal cortex in the probe period. Poorer performing schizophrenia patients experienced either inefficient or deficient neural activation depending on which component of item recognition was assessed.
ID: 551327

EFFECTS OF GROUP PRESSURE ON DECISION MAKING IN PATIENTS WITH SCHIZOPHRENIA IN DAY HOSPITAL PROGRAMS: A FMRI STUDY

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Social cognition has been proposed to mediate the influence of cognitive impairment to social functioning in patients with schizophrenia. Despite impairment in social cognition, patients with schizophrenia show behavioral improvements required for social adjustment through group environment and group therapy provided by day hospital programs. In this study we examined how therapeutic factors of group milieu, such as group cohesion and group pressure affect the brain function of patients with schizophrenia in decision making process. Thirteen patients with schizophrenia attending day hospital programs in two university hospitals, one general hospital, one community mental health center and one psychiatric clinic, and 15 healthy controls from the same group in work places or graduate schools participated in this study. Participants were shown 3 photographs of their group members or strangers along with each of their response to a prior survey and then immediately asked to decide on the more frequently used meaning of 50 homographs while being scanned by a 3T MRI scanner. Patients with schizophrenia showed significantly lower Working Alliance Inventory scores, but no significant difference in the conformity rates to group opinion in the homograph meaning decision task than healthy participants. While healthy participants did not show significant difference in the response time between strangers and group condition, patients with schizophrenia responded significantly faster to group opinion than strangers' opinion. Greater activity to group condition as compared to stranger condition was observed in the parahippocampal gyrus in healthy participants. In addition to the parahippocampal gyrus, patient with schizophrenia showed greater activities to group condition in the insular gyrus, fusiform gyrus, precuneus, and the superior frontal gyrus. These findings demonstrate that patients with schizophrenia being treated in group milieu

are more influenced by their own group in their decision making and that this process may involve the recruitment of neural networks related to emotional processing and mentalizing. This study also suggests possible neural mechanism behind group therapy in patients with schizophrenia.
ID: 551317

FUNCTIONAL IMAGING OF MOTOR FUNCTION IN SCHIZOPHRENIA: DISSOCIATIONS BETWEEN PERFORMANCE AND LEARNING

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Performance of motor tasks is known to be impaired in schizophrenia but learning of motor skills has often found to be preserved; this study examined functional imaging correlates of this dissociation. Forty-three chronic schizophrenic patients and 34 normal controls underwent fMRI while performing easy and hard versions of a motor sequence skill acquisition task. Activation associated with performance of the task was measured in comparison to a baseline non-motor task. We also measured changes in activation as a function of repetition of the task and consequent improvement in performance. Normal subjects showed significant activation in a number of motor-related brain regions associated with performance of the task, including the cerebellum, basal ganglia, bilateral precentral gyrus and supplementary motor area. The schizophrenic patients showed reduced activation in these and other areas activated during task performance. These differences were not a function of neuroleptic dosage or presence of extrapyramidal side-effects. In the normal subjects repetition of the task was associated with progressive de-activation in the precentral gyrus and supramarginal gyrus, plus, in the hard version of the task, the basal ganglia and extensive areas of the prefrontal cortex. The schizophrenic patients showed few areas of differences from the controls associated with repeated performance of the task (although in the hard version of the task they showed significantly less de-activation in the right dorsolateral PFC). These findings support previous findings that patients with schizophrenia show reduced brain activation during motor task performance. The lack of differences between patients and controls associated with improved performance over time may reflect the finding of preserved procedural learning in the disorder. Supported by the Instituto de Salud Carlos III (FI05/00322, PI05/2693, CP07/00048), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), and Marie Curie European Reintegration Grant (MERG-CT-2004-511069).
ID: 551315

MODULATION OF FUNCTIONAL CONNECTIVITY OF THE DEFAULT MODE NETWORK BY ANTIPSYCHOTIC DRUGS

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Hallucinations and delusions have been conceptualised as errors in social cognition. Neural substrates for these functions are suggested to lie in the medial frontal regions, the posterior parietal cortex (PCC) and lateral parietal cortices. These regions comprise the so called "default mode" (DM) of the brain, which is active at rest but deactivates during cognitive tasks. Abnormalities in this network are implicated in the pathogenesis of schizophrenia. The aim was to analyse the effects of antipsychotic drugs on the DM network in healthy volunteers to understand their mechanism of action

without confounding effects of disease state on the DM network. 36 male subjects were randomised to receive a single oral dose of 5 mg aripiprazole (ARI), 1mg risperidone (RSP) or placebo (PBO) before having a 5 min resting state scan. Group independent component analysis was carried out on the resting state data using the fMRI toolbox GIFT. The DM component was identified as that which correlated most significantly with a predefined mask of the DM network. The DM components from all 36 subjects were analysed for group effects in SPM5. A preliminary functional connectivity analysis was carried out for 20 subjects. Time series were extracted from the medial frontal gyrus (MdFG) and PCC as identified from the DM component and used as linear regressors in SPM to give functional connectivity maps of the DM network. MdFG and PCC were less active after ARI and RSP treatment compared to PBO. Reductions in anterior MdFG were significantly more pronounced after ARI than RSP whereas RSP reduced activity in the left inferior temporal gyrus compared to ARI. Both drugs reduced the connectivity of the DM compared to placebo. In the connectivity maps seeded from the MdFG, connections to the PCC and angular gyrus were attenuated by both drugs whereas only RSP attenuated connections seeded from the PCC. Despite their contrasting pharmacological mechanisms (partial D2 agonism vs antagonism) both drugs reduced activation and functional connectivity of key areas of the DM network. This supports the idea that aberrant social cognition in schizophrenia is reflected in altered DM processing, which can be targeted by antipsychotic drugs. Their different pharmacologies may be reflected in the different emphasis on the DM network. However, modulating connections from the prefrontal cortex may be a primary antipsychotic action as both drugs attenuated anterior to posterior connections.
ID: 551306

DECREASED CONNECTIVITY IN THE AUDITORY SYSTEM OF SCHIZOPHRENIA PATIENTS WITH AUDITORY VERBAL HALLUCINATIONS

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It has been suggested that auditory hallucinations (AVH's) may be caused by increased connectivity between auditory and language areas (Hofmann e.a., 2007). In contrast, other authors have hypothesized that AVH's may originate from disconnectivity of these areas (Silbersweig e.a., 1998). Resting state connectivity is a suitable way to test both hypotheses. Right-handed, male patients with schizophrenia with AVH's (VH; $n = 9$), without AVH's (NVH; $n = 7$) and healthy controls (HC; $n = 10$) participated in a resting state fMRI study. Independent Component Analysis (ICA) was used to extract so-called independent components, which are brain regions that have a similar temporal pattern. Components of the thalamus, superior temporal gyrus (STG) and Broca's area were selected, and correlations of the time courses were calculated between each two brain regions for all groups. Correlation coefficients were converted to Z-scores and statistically compared between groups with the Kruskal-Wallis test. A Mann Whitney U test was used for post-hoc comparisons. Results are listed in the table below. There was a significant difference in correlations of STG and thalamus time courses. The difference between NVH and HC time courses was significant, and nearly significant for VH vs HC. The Kruskal-Wallis of STG—Broca and thalamus—Broca almost reached significance. For both connections, differences between VH and HC, and VH and NVH were almost significant. According to the these results, connectivity between thalamus and STG was larger in healthy controls than in patients with and without AVH's. On the other hand, in contrast to healthy controls and non-hallucinating subjects, hallucinating patients might be characterized by an absence of connectivity between these areas. Thus, our results suggest that changes in connectivity may underlie some aspects of AVH's.

Table.

Connection	VH	NVH	Kruskal Wallis	VH vs HC	VH vs NVH	NVH vs HC
STG—thalamus	0.36	0.40	0.74	$P < .046^*$	$P < .079$	$P < .962$	$P < .012^*$
STG—Broca	-0.051	0.21	0.17	$P < .084$	$P < .053$	$P < .088$	$P < .758$
thalamus—Broca	0.068	0.19	0.21	$P < .068$	$P < .065$	$P < .043$	$P = 1.00$

ID: 551262

AN fMRI STUDY OF THE EFFECTS OF PSYCHOTIC SYMPTOMS ON SALIENT STIMULI PROCESSING IN PATIENTS WITH SCHIZOPHRENIA

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The ability to accurately perceive affective facial expressions is a crucial component of interpersonal communication. Schizophrenia is associated with difficulties in the recognition of facial affect, which contribute to social dysfunction of the patients and these difficulties are more pronounced for threat-related, emotionally salient expressions such as fear. "Positive symptoms" of schizophrenia (ie, hallucinations and delusions) are thought to be associated with aberrant assignment of salience to external objects and internal representations. The aim of the present study was to identify brain regions associated with amelioration of hallucinations and delusions in a group of patients with schizophrenia during processing of emotionally salient stimuli. Factor analytic studies of schizophrenia symptoms have shown that hallucinations and delusions, irrespective of content, comprise a distinct syndrome of schizophrenia symptoms, the reality distortion syndrome, which may suggest a common underlying pathological process involving a shared network of brain regions. We used functional Magnetic Resonance Imaging to measure cerebral blood oxygenation changes during an implicit emotional task in 11 patients with schizophrenia, who were scanned at two different stages of their illness 6–8 weeks apart. We found that reality distortion syndrome reduction in the patients was associated with increases in activation of the affective division of anterior cingulate cortex and bilateral middle frontal gyri. Our findings may indicate that changes in the activation of the affective division of anterior cingulate and lateral prefrontal cortices may represent neural markers of psychotic symptoms' improvement.
ID: 551232

REDUCED FUNCTIONAL CONNECTIVITY IN AN FMRI IMPLICIT SEQUENCE LEARNING TASK: FURTHER EVIDENCE FOR FRONTOSTRIATAL DYSFUNCTION IN SCHIZOPHRENIA

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Several studies have reported impaired implicit sequence learning indicative of a frontostriatal dysfunction in schizophrenia patients. Using 3 Tesla

functional MRI we examined functional connectivity of neural correlates associated with implicit learning on a serial reaction-time task (SRT) in nineteen schizophrenia patients and twenty-one matched healthy control participants. In the SRT paradigm the degree of implicit learning depends on participants' profiting from a hidden stimulus sequence measured as a faster responding on sequential compared to random blocks. Whole-brain analyses as well as time series analyses for predefined regions of interest were performed. Schizophrenia patients revealed significantly decreased functional connectivity between bilateral putamen and prefrontal regions (Brodmann areas 46 and 9) compared to controls for sequential blocks and to a lesser extent for random blocks. In controls, but not in patients, activation in bilateral putamen, left insula, and right frontal middle gyrus was significantly correlated with the degree of implicit sequence learning. Our results provide further evidence of frontostriatal dysfunction in schizophrenia patients.
ID: 551220

PROBABILISTIC REASONING IN PSYCHOSIS: FIRST RESULTS OF A GERMAN MULTI-CENTER PROJECT ON THE NEURAL CORRELATES OF A COGNITIVE BEHAVIORAL THERAPY

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Under conditions of uncertainty patients with psychosis frequently make a decision or form a conclusion based on comparatively few evidence ('jumping to conclusion'). The corresponding neural correlates and even more so potential effects of psychotherapy have only been investigated for very small sample sizes. In the German Psychosis Psychotherapy Network, 80 patients with psychosis and 80 matched healthy subjects will be investigated in the fMRI scanner using a decision making paradigm—before and after 9 month of Cognitive Behavioral Therapy or Supportive Therapy. The fMRI data of 40 patients with chronic psychosis and 40 healthy subjects have been collected at six University Hospitals in this ongoing study, so far. During scanning, participants were asked to perform a "balls in the bottle" decision task investigating the potential "jumping to conclusions" phenomenon. Red and blue beads were presented in a block design. Subjects had to decide by button press from which of two jars they had been drawn (with either 60 red and 40 blue balls in one jar or vice versa in the other jar). Measurements took place before and after 9 months of either Cognitive Behavioral Therapy or Supportive Therapy. SPM5 analyses investigated differences in brain activation between patients and healthy subjects as well as brain activation changes after psychotherapy. We found a widespread activation pattern of ventromedial, ventrolateral and dorsolateral prefrontal areas, the anterior cingulate and the parietal cortex in healthy subjects. Decreased brain activation in patients with positive symptoms was mainly found in dorsolateral prefrontal areas and the inferior parietal cortex. Preliminary results of patients who completed psychotherapy yielded an increase in brain activation in a small medial prefrontal cluster as well as a substantial brain activation increase in the precuneus and other parietal areas. Therefore, decision making under uncertainty resulted in decreased brain activation in psychotic patients in key areas of the decision making process. An increase of activation in parietal areas (mainly the precuneus) and the medial prefrontal cortex after 9 month of psychotherapy might reflect the correlates of newly learnt coping strategies in patients with psychosis. So far, our data suggest that—in contrast to older beliefs—Cognitive Behavioral Therapy could be a valuable element of the common routine care of patients with psychotic disorders.
ID: 551219

HYPOFRONTALITY IS A FEATURE OF CHRONIC, BUT NOT FIRST-EPISODE SCHIZOPHRENIA

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Reduced activation in the dorsolateral prefrontal cortex (DLPFC) and other frontal regions has been found in many, but not all, functional imaging studies of schizophrenia. We used fMRI to image groups of schizophrenic patients: chronic schizophrenic patients and first episode patients with non-affective functional psychosis during performance of the n-back task. Both groups were matched with age- and sex-matched controls. The chronic schizophrenic patients showed reduced activation in a network of cortical regions similar to those identified in a meta-analsysis of studies using the n-back task1: bilateral rostral frontal cortex, bilateral DLPFC, bilateral mid-ventrolateral PFC, bilateral and medial posterior parietal cortex, bilateral motor cortex, and dorsal cingulate/medial premotor cortex including the supplementary motor area (BA 32,6). In contrast the first-episode patients showed no areas of reduced activation compared to age- and sex-matched controls. The results suggest that reduced task-related prefrontal activation or hypofrontality is a function of chronic schizophrenia but not acute schizophrenia, in accordance with the findings of a recent meta-analysis2. Supported by the Instituto de Salud Carlos III (PI05/2693, FI05/00322, CP07/00048), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), and Marie Curie European Reintegration Grant (MERGCT-2004-511069).

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ID: 551192

THE DYSEXECUTIVE HYPOTHESIS OF THOUGHT DISORDER: A NEUROPSYCHOLOGICAL AND FMRI STUDY

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This study examined whether the symptom of formal thought disorder (FTD) in schizophrenia is associated with underlying frontal/executive

dysfunction, as assessed neuropsychologically and by functional imaging. Thirty-two intellectually preserved schizophrenic patients with FTD, 36 without FTD and 23 matched normal controls were examined on a battery of tests assessing executive function, memory, language and visual/visuo-spatial function. 14 patients with FTD, 19 without FTD and 22 controls also underwent fMRI during performance of a working memory task (the n-back task). The patients with FTD differed from patients without FTD on a composite measure of executive function, the Behavioural Assessment of the Dysexecutive Syndrome (BADS, $P = .02$), but not on a working memory task, letter-number sequencing. The patients with and without FTD also differed significantly from those without FTD on one of four long-term memory measures (verbal recall), the Token Test but none of 7 visual/visuospatial tests. As a group, the schizophrenic patients showed significantly reduced activation in prefrontal and other regions compared to controls during performance of the n-back task. However, there were no differences between patients with and without FTD in any prefrontal subregions, but significant differences were found in the left temporal cortex and fusiform gyrus. The results provide qualified support for the hypothesis of a neuropsychological deficit in executive function associated with the symptom of FTD. However, prefrontal cortical functional brain abnormality does not differ between patients with and without FTD, at least when a working memory task is used. Supported by the Instituto de Salud Carlos III (CM07/00016, PI05/2693, CA06/0129, CP07/00048), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM).
ID: 551185

FUNCTIONAL MAPPING OF EFFECTS IN BRAIN OF SUSCEPTIBILITY GENES SHARED BY SCHIZO-PHRENIA AND BIPOLAR DISORDER

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While risk for schizophrenia and bipolar disorder show overlap in families and several recent genetic associations are common to both diagnoses, the molecular basis of the clinical differences is unknown. We have explored with functional and structural neuroimaging associations with several candidate susceptibility genes common to both disorders to identify pathways to the clinical phenomenology. fMRI during N back working memory and during emotional face matching and VBM have been explored in a large sample of normal subjects genotyped for SNPs genes that have been associated both with schizophrenia and bipolar disorder, including DISC1, NRG1, ErbB4, COMT, AKT1, GRM3, GRM7, all of which have been implicated in both schizophrenia and bipolar disorder, but with variable consistency. Conjunction analyses also were performed looking for common effects. Our results show that risk alleles in each of these genes converge on a pattern of inefficient prefrontal function during executive cognition, but show less consistent effects on amygdale/hippocampal processing of negative emotion. DAOA, GRM3, NRG1 and COMT show strong effects on hippocampal/amygdala processing. Our results suggest overlapping but dissociable effects of genetic variation in genes related to schizophrenia and bipolar disorder that may clarify the figurative Ven Diagram of overlapping risk factors associated with these disorders.
ID: 551184

THE NEURAL CORRELATES OF SEVERE COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

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This study aimed to identify structural and/or functional brain correlates of severe cognitive impairment in schizophrenia ('schizophrenic dementia'). We carried out structural MRI and voxel-based morphometry in 25 cognitively impaired and 22 cognitively preserved schizophrenic patients plus 37 healthy controls. Presence of cognitive impairment was defined on the basis of performance below the 1st percentile on either the Rivermead Behavioural Memory Test (RBMT) or the Behavioural Assessment of Dysexecutive Syndrome (BADS), or below the 5th percentile on both. A subset of 15 cognitively impaired patients, 15 cognitively preserved patients, and 29 controls, also underwent fMRI during performance of a working memory (n-back) task. No differences were found between cognitively intact and cognitively impaired patients in lateral ventricular volume or whole brain volume. Voxel-based morphometry revealed no clusters of significant difference in grey matter volume. However, during performance of the n-back task, cognitively impaired patients showed hypoactivation compared to cognitively intact patients in the anterior cingulate, superior ventromedial frontal cortex, dorsolateral prefontral cortex, bilateral insula, thalami, and left basal ganglia. Other areas of activation included L > R precentral and parietal cortex and precuneus. These findings replicate and extend those of an earlier, small scale study1 and indicate that cognitively impaired schizophrenic patients show no more structural brain abnormality than in the disorder as a whole, but that their brain function is more compromised. Supported by the Instituto de Salud Carlos III (CA06/0129, PI05/2693, CM07/00016, FI05/00322, CP07/00048), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), and Marie Curie European Reintegration Grant (MERG-CT-2004-511069).

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ID: 551143

DEFAULT MODE NETWORK DYSFUNCTION: A POTENTIALLY SIGNIFICANT ABNORMALITY IN SCHIZOPHRENIA

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Recent studies have implicated the default mode network—medial cortical and other brain regions which are active at rest but which de-activate during performance of a wide range of cognitive tasks—in schizophrenia. We carried out fMRI during performance of the n-back working memory task in 32 chronic schizophrenic patients, 18 manic patients and 16 bipolar depressed patients, plus normal controls. The schizophrenic patients showed apparent hyperfrontality in the medial prefrontal/anterior cingulate cortex, similar to that found in other studies using working memory tasks(1). However, further analysis revealed that, rather than being due to intrinsic hyperactivation, this represented failure of de-activation, in an area corresponding to the anterior midline node of the default mode network. The manic and depressed patients showed smaller and less robust clusters of

failure to de-activate in the same area. Our findings suggest that some of the 'hyperfrontality' found in recent fMRI studies of schizophrenia is artefactual and in reality reflects failure of de-activation in the default mode network. This failure is marked in schizophrenia but is evident to a lesser extent in bipolar manic and depressed patients. Failure to de-activate the default mode network during performance of cognitive tasks could provide a novel way of accounting for cognitive impairment in schizophrenia. Additionally, the default mode network is currently believed to play an important role in maintaining one's sense of self and so offers intriguing new ways for relating symptoms to brain dysfunction.

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ID: 551061

SCHIZOPHRENIA AS A HEREDITARY 'DISCONNECTION' SYNDROME: EVIDENCE FROM DIFFUSION TENSOR IMAGING (DTI), AND DYNAMIC CAUSAL MODELLING OF FMRI DATA

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A single observed cortical abnormality, which is both sufficient and necessary, for the development of schizophrenia has not been identified, leading to proposals that schizophrenia is a disorder of connectivity (eg, Friston and Frith, Clin Neurosci, 1995). Schizophrenia appears highly heritable, and changes in connectivity may represent an endophenotype. We sought to test this hypothesis by combining measures of structural and functional connectivity, in families multiply affected by psychosis. 20 patients with DSM-IV schizophrenia, 20 of their unaffected first degree relatives and 20 healthy controls, underwent DTI and fMRI scans. Measures of structural connectivity from DTI (Fractional Anisotropy- FA) were compared in a voxel based analysis. In addition an fMRI scan of the n-back (0-,1-,2-,3-back) working memory paradigm, facilitated group level comparisons of BOLD activation, as well as effective connectivity measurements using Dynamic Causal Modeling (DCM) in SPM-5. Subjects were generally well matched for demographic variables, with no differences identified in comparison to the control group. DTI: Reductions in FA were identified in probands, within the genu, left sup. longitudinal fasciculus, and posterior regions of the inf. longitudinal fasciculus bilaterally. Relatives showed trend level FA reductions within these clusters (P = .079). fMRI: Reduced cortical activation was identified in schizophrenia probands and their unaffected relatives in bilateral inferior frontal gyri, left frontal pole, left dorsolateral prefrontal cortex (DLPFC) and bilateral inferior parietal lobule, that was not related to impaired task performance (at 2-, 3-back) in probands. DCM: Intrinsic connectivity values were assessed between DLPFC, inferior prefrontal cortex (VLPFC), and posterior parietal lobe (PPL), in a fully connected model. Impaired intrinsic connectivity was identified in schizophrenia probands between prefrontal and PPL regions, both within and between hemispheres. A significant positive correlation was observed between a summary measure of the intrinsic connec-

tivity paths and FA values extracted from clusters showing FA reductions in the proband vs control comparison (r = 0.331, P = .014). In summary, correlated structural and functional connectivity impairments are apparent in schizophrenia probands, and also (at trend level) in their unaffected relatives, suggesting that genetic mediation of connectivity abnormalities may underlie psychosis.
ID: 551033

A LANGUAGE INDEPENDENT N-BACK TASK FOR NEUROIMAGING STUDIES IN SCHIZOPHRENIA IN A MULTI-LINGUAL SETTING—A VALIDATION STUDY

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The N-back task is widely used in neuroimaging investigations to study the neurocognitive processes involved in working memory and executive functions. Variants of this task have been used to explore frontal lobe dysfunction in schizophrenia. The promise of gaining better insights into the etiopathology of schizophrenia by linking specific genotypes to prefrontal functions has renewed interest in paradigms like the N-back task suited for imaging executive functions. N-Back tasks adapted for neuroimaging have generally used monitoring the identity or location of letters, numbers or abstract shapes. The letter and number based tasks presume the ability to read and are often difficult to administer in schizophrenia patients from varied educational backgrounds as encountered in developing countries. Moreover the letter based tasks are language specific and pose difficulties in settings involving subjects who are linguistically heterogeneous. In view of these methodological issues, we aimed to develop and validate a N-back task for fMRI which would be independent of language and suitable for use in a schizophrenia imaging-genomics project in a multi-linguistic population such as that in South India. Simple characters chosen from the CJK Ideographs subset of the Arial Unicode MS font type were used as stimuli in a block design 2-back task which included a zero-back baseline condition. An echo planar imaging sequence was used in a 3T Philips MR scanner to acquire the fMRI time series which were then processed and analysed using SPM5. The prefrontal cortical hemodynamic responses elicited by the above N-back task in a sample of 20 healthy subjects demonstrates the validity of the above task as a test of executive function which can be utilized in imaging genomics studies of schizophrenia in a multilingual setting.
ID: 551005

NEURAL CORRELATES OF WORKING MEMORY DYSFUNCTION IN EARLY ONSET SCHIZOPHRE-NIA: AN FMRI STUDY

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A dysfunctional prefrontal cortex is suggested to be a part of the neural underpinnings of working memory deficit in general as well as in individuals with schizophrenia. Several studies have shown prefrontal dysfunction in adult onset schizophrenia and the current study aimed to examine whether this region is dysfunctional in early onset schizophrenia as well. fMRI BOLD data were acquired at 1.5T (Siemens, Sonata). The working memory task consisted of 2-back and 0-back blocks. Twelve adolescents with schizophrenia symptoms and eleven healthy controls between 13–17 years were included. The two groups were matched on age and gender. Preliminary analysis showed stronger activations bilaterally in the dorsolateral prefrontal cortex (DLPFC) in the patient group compared to the healthy controls. The behavioral data yielded no significant difference in performance in working memory between the groups. These preliminary results indicate that neural dysfunction in DLPFC is present in adolescents with schizophrenia. The data suggests a hyperactive DLPFC in the patients performing at the same level as healthy controls. Thus, these findings on early onset schizophrenia are in line with recent studies on adult onset schizophrenia displaying a non-efficient activation pattern.
ID: 550986

FUNCTIONAL NEUROIMAGING OF LANGUAGE NETWORKS DURING DISCOURSE PROCESSING IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS

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Language processing abnormalities are a hallmark feature of schizophrenia. Yet, no study to date has investigated underlying neural networks associated with discourse processing in adolescents at ultra-high risk (UHR) for developing psychosis, in order to determine whether abnormalities in language systems may predate illness onset. Forty UHR youth and 24 demographically matched healthy controls underwent functional neuroimaging (fMRI) while performing a naturalistic discourse processing task. fMRI data were acquired on a Siemens 3T scanner. We assessed differences in blood oxygenation level-dependent (BOLD) activity between task conditions (Topic Maintenance vs. Reasoning) and between groups (ie, UHR vs. controls, UHR subjects who subsequently developed psychosis vs. those who did not). Furthermore, we examined the association of regional brain activity with symptom severity and social outcome at 12–24 month follow-up. Across groups, whole-brain analyses revealed activation in a large bilateral network of regions typically associated with language processing, including the left inferior temporal lobe, inferior frontal gyrus, and anterior cingulate, as well as their right hemisphere homologues (corrected cluster $P < .01$). Further, increased activity in the superior temporal gyrus (IT; BA38), caudate, left inferior frontal gyrus (LIFG; BA44/45and47) and anterior cingulate (BA24and32) distinguished those who subsequently developed psychosis. Within the UHR sample, the severity of positive formal thought disorder at follow-up was positively correlated with signal change in the LIFG, superior frontal gyrus, and IT, whereas social outcome was inversely correlated with signal change in these regions. Our results suggest that language networks may be disrupted in youth at ultra-high risk for developing psychosis. In particular, subsequent conversion to psychosis was associated with increased activity in brain regions involved in language

processing. These findings are consistent with a neural inefficiency hypothesis in those at greatest risk for psychosis, and additionally suggest that baseline activation differences are predictive of symptomatic and functional outcome. These results highlight the need to further investigate the neural systems involved in conversion to psychosis, and how language disruption changes over time in at-risk adolescents.
ID: 550960

THE RELATIONSHIP BETWEEN ANTICHOLINERGIC BURDEN AND FUNCTIONAL BRAIN RESPONSE DURING A LEARNING TASK IN SCHIZOPHRENIA

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The effects of anticholinergic (ACH) burden on cognition in schizophrenia are well established. It has been found that that high ACH burden is linked to impairment in verbal learning and memory in patients with schizophrenia (Tracy et al. 2001; Minzenberg et al. 2004). Functional abnormalities in the prefrontal cortex during learning and memory have repeatedly been reported in patients with schizophrenia. Eyler and colleagues (2008), for example, found that brain response was significantly lower among schizophrenia patients than healthy individuals in the inferior frontal gyrus (IFG) during a word pair learning task. The relationship between ACH burden and functional abnormalities during learning remains unexamined however. Our aim was to examine the relationship between ACH burden and brain response in a priori regions previously shown to respond abnormally during learning in schizophrenia. Specifically, we examined the relationship of anticholinergicity to functional brain response in three clusters within the IFG during a verbal learning task among 26 outpatients with schizophrenia/schizoaffective disorder. Brain response during novel word pair learning compared to fixation was measured with functional magnetic resonance imaging. Mean brain response was calculated for each individual across all voxels within three clusters in the IFG that had been identified as under-responsive in patients compared with healthy individuals. Subsequently, the mean brain response in each cluster was correlated with serum anticholinergicity (pmoles/ml of atropine equivalents) from a recent blood draw. We found a negative relationship between functional brain activation and anticholinergicity in one of the clusters in the left IFG ($r = -.45$; $P = .05$) and a negative, but non-significant, correlation in the right hemisphere cluster ($r = -.42$, $P = .07$). Patients with high ACH burden demonstrated the most abnormal brain response patterns (greater deactivation) illustrating the inability to engage the IFG to levels seen in healthy controls when performing the same verbal paired-associates task. Further studies are needed to replicate these findings and to investigate the specificity of these relationships to schizophrenia.
ID: 550951

NORMAL SENSORIMOTOR RESERVE IN SCHIZOPHRENIA: AN FMRI STUDY

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While there is a wealth of literature establishing abnormalities in schizophrenia (SCZ), little is known about the reserve of normal tissue or function in SCZ. To define normal sensorimotor reserve we investigated the activation of the primary motor and sensorimotor cortex in stable SCZ

patients and healthy controls (HC) during a unilateral finger-tapping task in response to a flashing checker board. A total of 86 HC and 85 SCZ patients aged 19–65 from eight different sites were enrolled. All contributing sites were part of a multi-site functional MRI (fMRI) study (Functional Imaging Biomedical Informatics Research Network—fBIRN). Voxel-wise fMRI analysis was carried out using the fBIRN Image Processing Stream (FIPS), an fBIRN multi-site fMRI analysis package based on FSL. Percent signal changes (PSC) in predefined regions of interest (ROI) and a weighted laterality quotient (WLQ) were calculated. Our voxel-based analysis showed similar activations and no significant differences between the HC and SCZ subjects. All results were thresholded at z > 2.23, with a cluster-wise significance of $P < .05$. In the ROI analyses, neither the effect of diagnosis nor the interaction of hemisphere and diagnosis were significant. As predicted based on the task unilaterality, the PS change in the motor cortex and the weighted laterality quotient were greater in the left hemisphere for both SCZ and HC; however, there were no significant between groups differences. Combined data from the 3T scanner sites showed stronger mean PS changes than the 1.5T sites. Power analyses indicate that based on these data, with 171 subjects, we were sufficiently powered to detect a difference in PS change of 0.12 between SCZ and HC. Our tapping task, contingent on the checkerboard flashing, rather than being fast rhythmic movements, was designed to be performable equivalently by schizophrenics and controls and to result in strong activation levels. The overall results of our multi-site fMRI study showed similar activation in primary motor and sensorimotor cortex activation in SCZ patients and HC during this task, providing a basis for tasks aimed to show equivalent function in SCZ and normal controls. Future studies can build on these results to further investigate motor system dysfunction in SCZ.
ID: 550897

FUNCTIONAL CONNECTIVITY ABNORMALITIES ASSOCIATED WITH ABNORMAL BEHAVIOR IN SCHIZOPHRENIA

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Functional connectivity abnormalities have been previously reported in schizophrenia (SZ) patients. These abnormalities may underlie behavioral problems associated with schizophrenia. The present study examines the relationship between functional connectivity abnormalities and behavior in schizophrenia. In order to investigate this, the relationship between intrinsic fluctuations of the default mode network (DMN) during rest and behavioral measures such as clinical symptoms and cognitive performance was examined. Twenty nine chronic SZ patients (11 females, age: M = 41.3, SD = 9.28) and 29 healthy participants (11 females, age: M = 41.1, SD = 10.6) were recruited. SZ patients were assessed with scales for the assessment of negative and positive symptoms (SANS and SAPS). All participants were assessed with D-KEFS Tower and Grooved pegboard tests. Participants underwent a 6 min rs-fMRI scan during which they were instructed to stay still with their eyes closed and remain awake. Independent components analysis was used to identify (1) the group DMN and (2) each individual's contributing time-course to the group DMN. Voxel-wise whole-brain multiple regressions with corresponding DMN time-courses were conducted for each individual. An unpaired t-test was conducted on resulting maps to look for differences in DMN connectivity between groups. In addition, voxel-wise correlations were conducted to investigate the relationship between individually identified DMN and behavioral measures. Between-group results revealed altered connectivity in medial frontal and anterior cingulate gyri within the DMN of SZ patients. In addition, DMN connectivity was significantly associated with both the negative and positive symptoms of SZ patients. SZ patients also showed positive correlations (1) between D-KEFS Tower test and activity in anterior cingulate, precuneus, cuneus, and dorsolateral prefrontal cortex and (2) between the Grooved pegboard

test scores and activity in right cerebellum, visual cortex, and left motor cortex ($P < .05$, corrected). Results suggest that schizophrenia is associated with functional connectivity abnormalities in the DMN. In addition, resting-state connectivity in schizophrenia was associated with clinical symptoms as well as cognitive performance. Results from this preliminary study provide support for the hypothesis that altered functional connectivity is associated with behavioral problems in schizophrenia. Supported in part by NIH MH-060662.
ID: 550896

BEHAVIORAL AND NEURAL CORRELATES OF POOR SACCADIC CONTROL IN UNDERGRADUATES

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Correct antisaccade (AS) performance requires inhibition of a reflexive glance to a newly appearing visual cue and generation of a saccade to its mirror image location. Patients with schizophrenia make an increased proportion of AS errors which are associated with dysfunction in prefrontal cortex (PFC) circuitry. It is uncertain whether this relationship is specific to schizophrenia, or if decreased PFC activity is associated with increased AS errors in non-clinical samples. Undergraduate students ($N = 350$) participated in an eye movement study involving AS and prosaccade (PS: requires a glance towards a peripheral cue) tasks. Good and poor performers (as identified by scores in the upper or lower 33% of the distribution on two different days of testing) performed AS and PS tasks while fMR images were acquired. Poor performers made significantly more errors on the AS task, but did not significantly differ in saccade latencies compared to their good performer counterparts. In both groups, saccade tasks were associated with activation in the well-defined circuitry: frontal and supplementary eye fields, posterior parietal cortex, thalamus and basal ganglia. Additionally, AS performance was associated with activation in bilateral PFC. Although region of interest analyses showed few between-group differences, the poor performing group showed evidence of decreased activation in PFC and supplementary eye fields that also was related to behavior. In the poor performing group there was an inverse relationship between antisaccades errors and PFC activity such that more errors were associated with lesser PFC activity. Despite an increased proportion of errors on the AS task, poor performers as a group seem to successfully activate the neural circuitry supporting saccades. There also was evidence, however, that as the demand for cognitive control increases, the poor performers were unable to recruit additional neural resources to offset increased task difficulty. Overall, these data suggest that healthy people who show compromised inhibitory control may be more likely to show evidence of disregulation of PFC circuitry under conditions of increased task demand.
ID: 550883

NEURAL BASIS OF REWARD PROCESSING IN SCHIZOPHRENIA

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Introduction: Anhedonia, amotivation, and apathy are core negative symptoms of schizophrenia. It has been speculated that these symptoms reflect abnormalities of brain reward systems. Several paradigms have recently emerged to probe these systems, which are quite distinct form regions involved in traditional cognitive functions. For example, ventral medial cortex is associated with processing rewards, but little data exist as to brain activation patterns in schizophrenia when processing reward. Method: To address this question, we examined reward processing with a monetary incentive paradigm in 12 (4 female; age = 36.3 ± 11.2) stable outpatients with schizophrenia and 11 (2 female; age = 36.5 ± 10.8) demographically matched healthy controls using event-related fMRI. Subjects were presented with cues indicating whether a correct response in a two-choice reaction time task (modified from an Erikson Flanker task) would result in a gain of money (10c or 50c gain trials), avoidance of a loss of money (10c or 50c loss trials), or no change in money (neutral trials). Responses were followed immediately by feedback. Loss and neutral trials followed by a correct response were later labelled as no-gain trials. Subjects underwent fMRI BOLD imaging, with standard pre-processing and statistical analysis with the general linear model. Results: Both schiz patients and controls showed high accuracy on the task (schiz: 93.6 ± 9.8%; control: 98.2 ± 2.0%, n.s.). There was no significant group difference in reaction time (schiz: 1011 ± 172ms; control: 933 ± 130 ms, n.s.). During the outcome phase of gain vs. no-gain trials, while controls showed activation in rostral anterior cingulate/ventral medial prefrontal cortex (rACC/vmPFC) (−3, 24, −3; Z = 4.14, k = 8), no significant signal was observed in schiz patients. Two-sample t-test showed that schiz patients demonstrated lower activity than controls on gain vs. no-gain trials in rACC/vmPFC (−9, 33, 33; Z = 4.61; k = 9) (9, 27, 21; Z = 4.55, k = 10). Discussion: Patients with schizophrenia failed to show expected activation in rACC and vmPFC, brain regions associated with the outcome phase of reward processing. While this pilot study is limited by small sample size and the use of medicated patients, further investigation of these regions in schizophrenia during reward processing is warranted.
ID: 550882

GENE DISCOVERY THROUGH IMAGING GENETICS: IDENTIFICATION OF TWO NOVEL GENES ASSOCIATED WITH SCHIZOPHRENIA

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Background: Genome-wide association scans (GWAS) allow the identification of genes whose relationship with the disease phenotype has not even been hypothesized. GWAS offer enormous promise in identifying genetic variation involved with illness and its response to treatment by allowing all areas of the genome to be considered. Methods: We combined a genome-wide screening strategy with neuroimaging measures as the quantitative phenotype and identified the Single Nucleotide Polymorphisms (SNPs) related to these genes as consistently associated with the phenotypic variation. Genotyping was performed with the Illumina Infinium Human1 chip and HumanCNV370 Duo Bead Chip yielding 105,950 autosomic SNPs. Samples successfully genotyped in less than 90% of markers on either array were excluded from analysis. The quantitative phenotype was BOLD activation in the left dorsal lateral prefrontal cortex measured during a working memory task. We determined the impact of genetic variation on the DLPFC activation using permutation testing to control for false positives. The discovery sample consisted of 28 chronic schizophrenic patients. The differential distribution of SNPs associated with these two genes in cases and controls was then corroborated in a larger, independent sample of patients with schizophrenia (n = 82) and healthy controls (n = 91) matched for gender and age. This was part of a larger cohort collected by the Functional Imaging

Biomedical Informatics Research consortium (FBIRN). Results: Twenty-seven SNPs in one gene on chromosome 3 and 19 on chromosome 6 were significantly associated with activation in the DLPFC by permutation testing. Thirteen of the 17 chromosome 3 SNPs tested and 6 of the 18 chromosome 6 SNPs tested were significantly associated with a diagnosis of schizophrenia in the Corroborative sample, substantiating a role of these two genes in schizophrenia. Conclusions: We introduce the use of fMRI activation as a quantitative phenotype in conjunction with genome-wide association as a gene discovery tool. With this tool, we have both discovered and verified the association of two genes with schizophrenia. Up until now these genes have not been linked to any neuropsychiatric illness, although both genes have a role in prenatal brain development and functioning of the prefrontal system relevant to schizophrenia deficits.
ID: 550876

ALLELIC VARIATION IN KCNH2 IS ASSOCIATED WITH DORSOLATERAL PREFRONTAL CORTEX ACTIVATION DURING WORKING MEMORY

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The coordination of cortical microcircuits for organized neuronal firing is essential for higher order information processing in human beings and may be disrupted in schizophrenia. Recently, single nucleotide polymorphisms (SNPs) in KCNH2, a voltage-gated potassium channel that regulates neuronal firing and is highly expressed in human prefrontal cortex, have shown association to schizophrenia across 5 independent samples (Huffaker et al., in submission). Here we explore the effects of a SNP identified as showing association with schizophrenia and with hippocampal function. Using the N-back paradigm, we used fMRI to assay BOLD activity in 150 right-handed Caucasian healthy volunteers across genotype (M33; N = 62 GG, N = 65 GA, N = 23 AA) Performance and demographic measures did not differ across genotype groups. Using SPM2, we conducted a correlation of KCNH2 genotype with task-dependent activation at 2-back. We found that subjects with the risk allele at M33 (A) exhibited increased activation of the left dorsolateral prefrontal cortex (DLPFC) (-30 30 41; P < .05 small volume correction) relative to subjects with the non-risk major allele, in spite of equivalent accuracy and response time. This inefficient DLPFC response in healthy subjects at 2-back suggests that individuals with the A allele at M33 required increased cortical resources for WM processing relative to individuals with the non-risk allele. These results in healthy individuals map faithfully onto the intermediate phenotype of prefrontal inefficiency observed in unaffected relatives of schizophrenic probands (Callicott et al., 2003) and a PFC region reported to show moderate heritability for this task in twins (Blokland et al., in press). Additional analyses revealed that this activation difference was independent of the DLPFC efficiency effects of COMT Val158Met (Egan et al. 2001). Whether an interaction exists between KCNH2 allelic variation and other genes associated with this phenotype and schizophrenia awaits further study.
ID: 551934

INVESTIGATING DIFFERENTIAL CORRELATIONS BETWEEN FMRI AND LANGUAGE-ASSOCIATED GENES USING PARALLEL ICA, IN HEALTHY CONTROLS AND SCHIZOPHRENIA PATIENTS

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We utilized task-related imaging findings from an fMRI auditory oddball (AOD) task as a potential intermediate phenotype (endophenotype) to investigate genomic factors derived from multiple single nucleotide polymorphisms (SNP's) from risk genes for language between groups of SZ patients and controls. We studied 33 controls and 20 SZ patients (matched on age, ethnicity and sex). All subjects performed an AOD task, which consists of detecting an infrequent sound within a series of frequent sounds. Each subject was characterized on 22 different SNP markers spanning different risk genes previously associated with various language disorders. We used a recently developed technique named parallel independent component analysis (paraICA) to identify simultaneously independent components of each modality and the relationships between them. Data were preprocessed using SPM2, which involved realignment, normalization and smoothing with a 12 mm3 kernel. First-level statistics were run to derive contrast images for subjects responding to AOD that were then carried over as input to the paraICA algorithm. Six independent fMRI and genetic components (each) were estimated using the minimum description length criteria. We found 4 fMRI components significantly correlated with four distinct gene components. The fMRI components, along with their significant genetic profile (dominant SNP) correlations were as follows: 1) Cuneus- SFG-R STG-Post-central gyrus-Thalamus and rs2304503 (ROBO1), rs1087266 (DCDC2) $[r = -.47; P = .0004]$, 2) STG-MTG-MFG-Precentral gyrus and rs1087266 (DCDC2) $[r = -.42; P = .001]$, 3) SFG-Posterior Cingulate and rs807724 (DCDC2), 4) Default Mode Network-Cingulate-STG-IFG-IPL and rs6795556 (ROBO1), rs6935076 (KIAA0319). Many of the above regions (including DLPFC, cingulate, STG, IPL, IFG) are identified as abnormal in SZ. The above described fMRI regions are all spatially independent; eg, STG regions appearing in component 1 and component 4 are different sub-regions that cytoarchitecturally fall within the same Brodmann area. Importantly, gene-fMRI combination 4 ($t = 2.80; P = .007$) listed above showed a significant difference between controls and patients, based on their correlated loading coefficients. Our findings suggest that genomic SNP factors can be investigated by using endophenotypic imaging findings in a multivariate format and that language-related genes may play a role in SZ.
ID: 555108

NEURAL CORRELATES OF VERBAL FLUENCY TASKS IN KETAMINE-INDUCED MODEL PSYCHOSES: A FMRI STUDY

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The glutamatergic N-methyl-D-aspartate (NMDA) receptor has been implicated in the pathophysiology of schizophrenia. In healthy individuals, a subanaesthetic dose of the non-competitive NMDA antagonist ketamine reproduces positive, negative and disorganized symptoms of schizophrenia, including speech disturbances and thought disorder. 19 healthy, right-handed, native German-speaking male individuals performed an overt verbal fluency task while brain activation was measured with functional magnetic resonance imaging (fMRI). A within-subject, placebo controlled,

counterbalanced design was assessed for all subjects. Overall performance was impaired under the ketamine condition. In contrast to the placebo condition increased brain activation was found in frontal regions (Brodmann area 9/10) and in the right anterior pole of the temporal lobe (Brodmann area 38). The increased activation in frontal and temporal regions can be linked to the cognitive impairments observed in schizophrenia as these regions show differential activation when compared to healthy individuals. The regions that were found to be differentially activated are key regions in speech production and working memory. These results offer further support for a role of glutamatergic dysfunction in the symptoms of schizophrenia.
ID: 554802

NEURONAL RESPONSE TO VIRTUAL NAVIGATION IN SCHIZOPHRENICS AND CONTROLS

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The ability to complete complex tasks including learning and memory is known to be impaired in individuals with schizophrenia. Both anatomic and functional deficits have been identified using a variety of techniques. In this study we compare brain functioning and behavioral processing in 13 schizophrenic patients and 15 controls using a virtual water maze adapted from classic animal studies. Patients performed as well as the controls when the virtual platform was visible, but more poorly during the hidden trials ($P < .001$). Imaging studies were performed using a GE 3.0 T MR scanner. fMRI data was acquired using EPI T2* BOLD (Blood Oxygen Level Dependent) contrast technique. BOLD echo-planar data (TR = 2000,TE = 30, 642 matrix, 240 mm2 FOV, 28 axial slices angled parallel to the planum sphenoidale, 4mm thick, 0 mm gap) were motion corrected, normalized to standard space, spatially smoothed with an 8 FWHM kernel and evaluated using the GLM in a random effects analysis in SPM2 (Wellcome Department of Imaging Neuroscience, London). A network of brain regions were involved in completing the test. The most active areas in controls were the cerebellum, R parietal areas, frontal eye fields, the anterior insula and inferior frontal gyrus, the DLPFC, and the basal ganglia and striatum (FDR = 0.001). In some regions, schizophrenics demonstrated significantly less activation than controls, including the cerebellum, the occipital and parietal visual areas, the medial thalamus, the left DLPFC (FDR = 0.01). A region of interest analysis of the hippocampus also demonstrated significantly less activation in schizophrenics, particularly in the very posterior part of the hippocampus. This area is of special interest since it has been shown to demonstrate the greatest growth potential following intensive training in normal controls (Maguire et al. 2000), suggesting that it may be a focus for cognitive training.

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ID: 554640

FUNCTIONAL FONNECTIVITY FOLLOWS THE ANATOMICAL CONNECTIVITY MORE CLOSELY IN SCHIZOPHRENIA PATIENTS

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Introduction: A novel method of combining functional and anatomical connectivity estimates has been recently described [1], to quantify the relationship between two distinct features of brain connectivity. Anatomical Connectivity is measured using DTI analysis of the integrity of white matter tracts, while Functional Connectivity represents the strength of correlations in the resting fMRI fluctuation. These two measures are related in healthy subjects. In this study we analyzed the relationship between anatomical and functional connectivity in schizophrenia patients. Data Analysis: 19 healthy control and 19 age matched schizophrenia subjects were scanned on a 3T Allegra Siemens scanner. Resting state time courses of gray matter voxels were correlated to create a resting state connectivity matrix. After standard deterministic fiber tracking the connectivity between each two white matter voxels was estimated by integrating multifiber paths and propagated into grey matter. Results: While overall measures of anatomical and resting correlation did not differ significantly between the control and schizophrenia populations, we found a strong and significant ($P < .02$) difference in the correlation between functional and anatomical connectivity maps when comparing schizophrenia patients and healthy controls. In the schizophrenia patients the maps agreed less, ie, their functional connectivity measures were less in agreement with the anatomical connectivity map than in healthy controls. Between- group differences were most prominent for connections originating in the Anterior Cingulate, Cuneus, and Precuneus. The differences between control and schizophrenia group were further confirmed by the correlation between the coherence score in schizophrenia subjects and the Thought Disorder Index. Conclusion: Significant differences exist in the brain connectivity of schizophrenia patients. The multimodal approach in which a functional and anatomical measure of connectivity are combined together provides a more powerful measure of connectivity deficit than each measure taken alone.

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ID: 554629

BRAIN SYSTEM CHANGES UNDERLYING THE DEVELOPMENT OF WORKING MEMORY THROUGH ADOLESCENCE: NEUROIMAGING STUDIES

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The ability to have voluntary executive/cognitive control of behavior continues to develop through adolescence as important brain maturational processes are still taking place. Core to cognitive control of behavior is working memory (WM), the ability to retain information on-line in order to guide goal directed behavior in a planned manner. The purpose of the following studies was to characterize the developmental trajectory of working memory through adolescence to adulthood with behavioral studies and neuroimaging studies using functional Magnetic Resonance Imaging (fMRI). Studies were performed using the oculomotor delayed response task (ODR) (memory-guided saccade task) where subjects are instructed to make a planned eye movement directed to the location retained in working memory of a cue presented previous to a delay period. This is a well-characterized method that has been widely used in single cell non-human primate studies to delineate the neural circuitry underlying WM. Behavioral results indicated that working memory accuracy as well as reaction time continued to improve through adolescence indicating protracted development of WM. Subjects also performed event related fMRI studies

while performing WM tasks. The first study presented short and long delay period to assess developmental differences in WM maintenance. With age fronto-caudal areas were recruited which supported saccade precision while posterior parietal cortex was recruited to support extended delay periods. The second study manipulated both encoding and maintenance durations. We found the prefrontal cortex became better specialized into adulthood supporting both encoding and maintenance aspects of working memory. Diffusion Tensor Imaging (DTI) studies, were also performed to assess indirect measures of myelination that may underlie improvements in working memory. Results indicated that white matter regions adjacent to prefrontal cortex (BA9) as well as orbitofrontal and striatal regions continue to mature through adolescence. Together these studies indicate a protracted development of working memory through adolescence that is subserved by continued specialization of a widely-distributed brain circuitry that supports optimal encoding and precision of WM, which may reflect a stage of particular vulnerabilities to developmental abnormalities including schizophrenia. Supported by MH067924.
ID: 554368

PROFOUND SOMATOSENSORY SYSTEM DEFICITS IN SCHIZOPHRENIA REVEALED BY MEG DURING A MEDIAN-NERVE ODDBALL TASK

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Cognitive impairments related to somatosensory functions are common in people with schizophrenia, including reduced speed and/or accuracy of somatosensory information-processing. However, the somatosensory system has been largely ignored in functional imaging research of schizophrenia. The present study used magnetoencephalography (MEG) to identify the neural networks that support selective-attention to somatosensory stimuli in healthy adults and abnormalities in these networks in schizophrenia. A median-nerve oddball task was used to probe for selective-attention to somatosensory stimuli during MEG recordings, and an advanced high-resolution MEG source-imaging method was used to analyze the MEG data. In healthy subjects, selective-attention-related activations were seen in a sensorimotor network involving primary somatosensory area (S1), secondary somatosensory area (S2), primary motor area (M1), pre-motor area (PrM), and paracentral lobule (PCL). In addition, the frontal-parietal-temporal "attention network" which contains dorsal- and ventral-lateral prefrontal cortex (DLPFC and VLPFC), orbitofrontal cortex, anterior cingulate cortex (ACC), superior parietal lobule (SPL), inferior parietal lobule (IPL)/supramarginal gyrus (SMG), and the temporal lobe areas, was also activated. Individuals with schizophrenia showed early hyper-activations related to selective-attention in S1 and M1, but hypo-activation in S1, S2, M1, PrM, and SPL at later latency in the sensorimotor network. Within the attention-network, hypo-activations were found in DLPFC, medial aspect of orbitofrontal cortex, and dorsal aspect of ACC at a variety of latencies, but hyper-activations were seen in SMG/IPL, frontal pole, and ventral aspect of ACC in individuals with schizophrenia. These findings link attention-related somatosensory deficits to dysfunction in both the sensorimotor and the frontal-parietal-temporal networks in schizophrenia.
ID: 554268

REWARD AND SUBJECTIVE WELL-BEING IN SCHIZOPHRENIA: AN FMRI STUDY

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Patient subjective well-being is a major determinant of treatment compliance. Comparisons of conventional and atypical medication, as well as neuroimaging studies have suggested that the subjective experience of patients may be related to the mesolimbic dopamine system crucial in processing reward information. Negative subjective changes have been shown to be related to altered reward processing, and striatal dopamine function. As dopamine may be associated with subjective experience and is the major neurochemical component in reward; and reward systems have been shown to be impaired following dopaminergic medication, negative subjective experience may be due to impairment of the reward system. The primary aim of the study was to examine whether the relationship between dopamine and subjective well-being is attributable to dysfunctional reward processing. It was hypothesised that patients low in subjective well-being will have decreased activation in anticipation of reward in the ventral reward system. Twenty patients with schizophrenia were administered a Monetary Incentive Delay task, previously used by Knutson et al. (2001), while undergoing fMRI brain imaging on a 3T scanner. Positive, neutral and negative stimuli predicted valence of subsequent reward on each trial, while reaction time to hit a target determined trial outcome. Reward was obtained in reward trials, and loss avoided on losing trials on 66% of trials irrespective of subject performance abilities as determined by an automated adaptive timing algorithm which adjusted target speed. Functional images were preprocessed and modeled with SPM5. Analysis contrasted brain activation during anticipation of reward in positive trials (financial gain) with anticipation of outcome on neutral trials (zero gain). BOLD activation was significantly greater in the left inferior frontal lobe and caudate nuclei in response to positive reward. It was also of interest to establish whether there were differences in activation between subsets of patients with low and high subjective well-being. Preliminary analyses suggest that patients with high subjective well-being ($N = 5$) have greater activation in ventral medial temporal and inferior frontal structures compared to patients low subjective well-being ($N = 5$) during anticipation of rewarding outcomes. Activation in ventral structures may directly be associated with subjective well-being or alternatively via inhibition of primary reward areas such as the striatum.
ID: 552306

HYPER-RESPONSIVITY TO STRESS IN THE HPA AXIS DURING EARLY PSYCHOSIS

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A series of studies have been conducted in Melbourne, Australia investigating hypothalamic-pituitary-adrenal (HPA) axis function in young people at ultra high risk (UHR) of psychosis, young people experiencing a first psychotic episode (FEP) and healthy controls. Our findings suggest the acute phase of psychosis is associated with hyperactivity of the HPA axis, indicated by enlarged pituitary volume and impaired glucocorticoid receptor functioning. Recent preliminary findings suggest a subset of FEP patients with a history of childhood trauma exhibit enhanced negative feedback of the HPA axis, similar to the biological abnormalities seen in PTSD. The hippocampus is highly sensitive to the neurotoxic effects of gluococorticoids. We have conducted a longitudinal study in drug-naïve FEP patients investigating the relationship between HPA axis function and metabolic changes in hippocampal and prefrontal brain regions during the initial three months of treatment. These studies will be described in detail and future directions for research will be suggested.
ID: 552032

DELUSIONAL IDEATION MAY BE ASSOCIATED WITH ABERRATIONS IN CONFLICT PROCESSING

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Introduction: To better understand delusional ideation we must identify which core processes are malfunctioning to allow the formation and maintenance of delusions. Dual-stream decision-making models propose two interacting processes; a fast, intuitive system (Stream 1) and a slower, more logical process (Stream 2). When the two streams diverge, healthy individuals may experience conflict, which we suggest biases decision-making towards Stream 2 and increases the likelihood of a judgment in keeping with the available evidence. In schizophrenia, a failure in this conflict-modulation system may allow erroneous intuitive interpretations to endure unchallenged. Study 1: Patients with schizophrenia and healthy controls judged the logical validity of two-part conditional statements that were either congruent or incongruent with respect to agreement between their logical validity (Stream 2) and the believability of their concluding sentences (an automatic, Stream 1 judgment). Performance deficits in the patient group were significantly worse for the incongruent condition, which was designed to generate conflict between the two streams. Study 2: A simplified version of our conditional reasoning paradigm was performed by subjects while undergoing functional magnetic resonance imaging. For the incongruent condition, healthy controls exhibited significantly greater activation in the dorsal anterior cingulate cortex (BA32) and dorsolateral prefrontal cortex (BA46) than for the congruent condition. This significant pattern of activation was absent in patients with schizophrenia. Conclusions: The behavioural data provides support for our suggestion that dual-stream conflict may pose a particular difficulty for patients with schizophrenia. The fMRI results indicate that, in schizophrenia, attenuated activation of regions associated with conflict detection and logical reasoning may underlie the increased likelihood to make erroneous decisions when there is a conflict between intuition and reason.
ID: 552016

THE EFFECT OF CANNABIDIOL (CBD), A CANNABIS SATIVA CONSTITUENT, ON NEURAL CORRELATES OF ANXIETY: A REGIONAL CEREBRAL BLOOD FLOW STUDY

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Cannabis use is common in patients with psychiatric disorders such as schizophrenia, bipolar and anxiety disorders. Anecdotal reports suggest that some patients take this drug to alleviate both anxiety and psychotic symptoms. Animal and human studies have shown that cannabidiol (CBD), a major compound of the cannabis plant, may possess anxiolytic and antipsychotic properties, but how these effects are mediated centrally is not fully understood. Regional cerebral blood flow (rCBF) was measured at rest using 99mTc-ECD SPECT in ten subjects with high levels of trait anxiety, randomly divided in two groups of 5 individuals. Each subject was studied on two occasions, one week apart. In the first session, subjects were given an oral dose of CBD (400mg) or placebo, in a double-blind procedure. SPECT images were acquired 90 minutes after drug ingestion. The VAMS scale was applied to assess subjective states. In the second session, the same procedure was performed using the drug that had not been administered in the previous session. Within-subject between-condition rCBF comparisons were performed using SPM. CBD significantly decreased subjective anxiety without increasing sedation, while placebo did not induce significant changes. Assessment of brain regions where anxiolytic effects of CBD were predicted a priori revealed decreases in ECD uptake in the CBD relative to placebo condition: revealed one voxel cluster of significance ($P < .001$, uncorrected) located in the left parahippocampal gyrus and hippocampus, extending to the inferior temporal gyrus (BA20). Significantly increased ($P < .001$, uncorrected), ECD uptake in the CBD relative to the placebo condition was also evident in one region located in the right posterior cingulate gyrus (BA23/31). Considering the CBD condition, the SPM showing negative correlations with Anxiety VAMS factor revealed two clusters (>20 voxels) which achieved statistical significance level ($P < .001$, uncorrected for multiple comparisons): one located in the left whereas the other was located in the right amygdala. These results suggest that CBD has anxiolytic properties and that these effects are mediated by an action on limbic and paralimbic brain areas and may help to reconcile apparently conflicting findings obtained with cannabis sativa in relation to its use in patients with anxiety and other psychiatric disorders such as schizophrenia.
ID: 551942

NEUROFUNCTIONAL EFFECTS OF DELTA-9-THC AND CANNABIDIOL ON EMOTIONAL FUNCTIONING

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Context: Cannabis use can both increase and reduce anxiety in humans. The neurophysiological substrates of these effects are unknown. Objective: To investigate the effects of two main psychoactive constituents of Cannabis Sativa, (delta-9-tetrahydrocannabinol [delta-9 THC] and cannabidiol [CBD]) on regional brain function during emotional processing. Design: Subjects were studied on three separate occasions using an event-related fMRI paradigm while viewing faces that implicitly elicited different levels of anxiety. Each scanning session was preceded by the ingestion of either 10mg of delta-9-THC, 600mg of CBD, or a placebo, in a double-blind, randomised, placebo controlled design. Patients and other participants: Fifteen healthy English-native right-handed men who had used cannabis fifteen times or less in their life. Main outcome measures: Regional brain activation (BOLD response), electrodermal activity (Skin Conductance Response, SCR) and objective and subjective ratings of anxiety. Results: delta-9THC increased anxiety, as well as levels of intoxication, sedation and psychotic symptoms, whereas there was a trend for a reduction in anxiety following administration of CBD. The number of SCR fluctuations during the processing of intensely fearful faces increased following administration of delta-9THC but decreased following administration of CBD. CBD attenuated the BOLD signal in the amygdala and the anterior and posterior cingulate cortex while subjects were processing intensely fearful faces, and its suppression of the amygdalar and posterior cingulate responses was correlated with the concurrent reduction in SCR fluctuations. Delta-9-THC mainly modulated activation in frontal and parietal areas. Conclusions: delta-9-THC and CBD had clearly distinct effects on the neural, eclectrodermal and symptomatic response to fearful faces. The effects of CBD on activation in limbic and paralimbic regions may contribute to its ability to reduce autonomic arousal and subjective anxiety, whereas the anxiogenic effects of delta-9-THC may be related to effects in other brain regions.
ID: 551935

15. 15. Neuroimaging, Structural

WHITE MATTER MARKERS FOR PSYCHOSIS IN A PROSPECTIVE ULTRA HIGH RISK COHORT.

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First episode schizophrenia patients have regionally reduced fractional anisotropy (FA), however, to a lesser extent than chronic patients[1]. Subjects at Ultra High Risk (UHR) for developing psychosis have volumetric white matter reductions, although to a lesser extent than first episode schizophrenia patients[2]. No one has yet investigated FA in UHR subjects. Hence we investigated a prospective cohort of UHR subjects and compared whole brain FA of those who would later develop psychosis (UHR-P) to those who would not (UHR-NP). We recruited 37 subjects who fulfilled UHR criteria[3]. 3 Tesla MRI scans and PANSS ratings were obtained at baseline. Subjects were assessed at 9, 18 and 24 months for development of frank psychosis. Subsequently UHR-P and UHR-NP FA and white matter densities were compared and FA was correlated to PANSS ratings. UHR-P subjects had significantly lower FA than UHR-NP subjects lateral to the right putamen and of left superior temporal lobe. FA in the right superior temporal lobe negatively correlated with positive symptoms at baseline. Further, UHR-P had higher FA in the right medial temporal lobe. UHR-P had a corresponding white matter density reduction lateral of the right putamen, but this did not survive correction for multiple comparisons. Concluding, UHR subjects that develop psychosis have differences at baseline in white matter integrity compared to UHR subjects who do not develop psychosis. These differences implicate the striatal and superior temporal regions, areas known to be involved in schizophrenia. Further, FA in the superior temporal region negatively correlates with positive symptom severity at baseline. This study was funded by grant QLGU-CT-2001-01081 of the European Commission.

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ID: 542646

GRAY AND WHITE MATTER VOLUMETRIC INTERMEDIATE PHENOTYPES ACROSS THE PSYCHOSIS SPECTRUM

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In this study we attempted to contrast gray matter (GM) and white matter (WM) intermediate phenotypes across the psychosis spectrum to characterize effects of psychosis on brain structure. 62 subjects: 19 schizophrenic patients (SZP), 16 schizoaffective patients (SADP), 17 patients with psychotic bipolar I disorder (BDP) and 10 healthy controls (HC) were included. MRI was performed on a 3T Magnetom Trio scanner following the ADNI protocol. T-1-weighted MPRAGE sequences were used for standardized VBM analysis (MATLAB7.0, SPM5). Socio-demographic characteristics were comparable between the study groups. Although GAF and total BPRS scores did not differ between the groups, SZP had higher psychosis BPRS scores ($d = 0.8$) and BDP had higher affective BPRS scores ($d = 1$). SZP and SADP performed worse on the Social Functioning Scale compared to BDP and HC. SZP and SADP showed diffuse loss of GM with similar regions in superior temporal and middle frontal gyri, caudate and thalamus; BDP showed decreased GM volumes in caudate bilaterally, compared to HC. WM comparisons showed that SZP and SADP had lower volumes in anterior cerebellum, brain stem and postcentral gyrus; while BDP showed diffusely reduced WM in left (L) anterior cerebellum, superior temporal and middle frontal gyri; in the right (R) cerebellar tonsil, superior frontal and subcallosal gyri; and bilaterally in posterior cerebellum, compared to HC. The psychosis groups (SZP, SADP and BDP) did not differ significantly in either GM or WM volumes. BPRS psychosis scores directly correlated with GM volumes in L inferior temporal lobe and R medial frontal gyrus in SZP; in R superior frontal gyrus in SADP, and in middle and superior frontal, middle occipital and superior temporal gyrus in BDP. Patients treated with atypical and typical antypsychotics (AP) ($n = 8$) had higher GM volume in medial frontal gyrus compared to AP-free individuals ($n = 11$). In this preliminary analysis, the greatest volumetric GM and WM differences were found between HC and psychosis groups across the SZ/BD boundary. SZ and SAD cases were structurally similar and showed diffuse decrease in GM, while BDP showed no significant GM loss but diffuse WM reduction. Across the psychosis spectrum the groups did not significantly differ in either GM or WM volumes. This may suggest gross effect of psychosis on brain structure independent of categorical diagnosis. Severity of psychosis and AP treatment showed effect on GM volume in all psychosis groups.
ID: 550805

RELATIONSHIP OF THOUGHT DISORDER IN SCHIZOPHRENIA WITH BRAIN STRUCTURE AND WITH WHITE MATTER INTEGRITY: ANALYSIS OF DATA COLLECTED BY THE MIND RESEARCH NETWORK (MRN) JOINT STUDY OF FIRST EPISODE AND CHRONIC SCHIZOPHRENIA

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The purpose of this study is to explore the relationship between the severity of thought disorder (TD) in schizophrenia and brain structure and connectivity. TD has been not been studied as extensively as negative symptoms and psychotic symptoms in relation to longitudinal course, psychosocial outcome and underlying neuroanatomical abnormalities. The persistence thought disorder after the resolution of the first psychotic episode(s) is a strong predictor of poor response to behavioral and pharmacological treatment and of poor psychosocial outcome, and is related to poor performance on tests of visual perceptual organization (Uhlhaas and Silverstein 2005). A better understanding of thought disorder in precise neuroanatomical terms will enhance our knowledge of the basic neuroscience of schizophrenia and will generate ideas for the development of new treatments. This study is based on data collected by the MIND Research Network (MRN) Joint Study of First Episode and Chronic Schizophrenia that included investigative teams from four imaging centers and collected brain MRI data on 153 subjects with schizophrenia and 160 healthy controls. TD was studied with The Scale for the Assessment of Positive Symptoms (Andreasen 1984). Anatomical and diffusion tensor imaging MRI scans

were collected using either a 1.5T Siemens Scanner (University of Iowa, University of New Mexico, Harvard University-MGH) or a 3.0T Siemens Trio scanner (University of Minnesota). Structural data were analyzed using FreeSurfer, an automated set of software tools for study of cortical and sub-cortical anatomy (Fischl and Dale, 2000) and by voxel-based morphometry with SPM5 (Wellcome Department of Cognitive Neurology). DTI data were processed using GTRACT software (Cheng et al., 2006). DTI data and the anatomical data were co-registered to allow identification of the white matter compartment. Results will be presented examining: 1) the relationship between severity of TD with poor psychosocial functioning and with poor performance on cognitive tests of visual perceptual organization; 2) the relationship between severity of TD and brain anatomy, particularly, with gray matter volume in brain regions involved in visual perceptual organization: striate cortex, lateral occipital complex, fusiform gyrus, posterior parietal regions; 3) the correlation between severity of TD and DTI measures of white matter structural connectivity.

ID: 550752

MULTIMODAL IMAGING STUDY OF THE THALAMUS IN FIRST-EPISODE PSYCHOSIS

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The thalamus (Th) is a central node of pathophysiology in schizophrenia. Structural and neurochemical abnormalities are seen using different imaging techniques such as morphometric assessment, tissue segmentation, and 1H MRS. However, no integration of these imaging methods into a single sample set has been attempted to date. To investigate structural abnormalities in first-episode psychosis (FEP) patients we conducted a longitudinal multimodal structural magnetic resonance (MR) assessment of the Th in FEP at two time points. Preliminary baseline findings from structural MRI and MRS scans are reported here. Methods: 29 FEP (mean age 20.7 years; 15 male) and 18 age and gender-matched volunteers (mean age 20.8; 13 male) were recruited as part of larger longitudinal study. FEP patients with less than 8 weeks of total lifetime exposure to antipsychotic treatment were included. 1.5mm thick axial SPGR images were obtained on a GE 1.5 T MRI scanner. Manual tracing of thalamus was performed, and thalamus mask was used to apply a geometric subdivision of the thalamus so that thalami would be parceled out along the coronal plane into 40:40:20 subdivisions, and along the sagittal plane by 50% subdivisions. Single-voxel (1HMRS) was used to measure concentrations of NAA in the left Th. Spectra from 3.24mL voxels, centered in the left thalamus, were acquired using a PRESS sequence. NAA peaks determined from LCModel were corrected for T1 and T2 relaxations, and CSF content. Statistical analyses were performed using SPSS 11.0. and Superanova. Results: At baseline, ANCOVA (ICV covariate) analysis showed no significant differences in total right or left thalamic volume ($F_{1,44} = 0.031$, $P = .86$; $F_{1,44} = 0.094$, $P = .76$). ANCOVA (ICV covariate) for Anterior, Mediodorsal, and Pulvinar nuclei on both sides did not show any statistical significant difference. Finally, ANCOVA (age covariate) for the left thalamus 1H MRS voxel, showed a statistically significant reduction in Th absolute NAA in SCZ ($F_{1,43} = 5.14$, $P = .028$). Additionally, there was a statistically significant diagnostic x age interaction ($F_{1,43} = 4.04$, $P = .05$). Conclusions: Although there were no differences in total thalamic volumes or particular nuclei, there was a reduced NAA content in left Th at baseline. Current results highlight the relevance to integrate different imaging modalities, and point towards a different effect on structure vs. biochemical content in early stages of schizophrenia.

ID: 550686

MULTIPLE-STRUCTURE ANALYSIS OF LONGITUDINAL SHAPE CHANGE IN SCHIZOPHRENIA

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Objective: Progressive decreases in cortical gray matter volume have been reported in individuals with schizophrenia. However, recent longitudinal neuroimaging studies of progressive change in subcortical structures have not yielded consistent findings. In a previous study of individual structures, we reported that brain structures that receive direct, excitatory connections from the cortex may be more likely to show progressive changes, as compared to brain structures that receive indirect, inhibitory connections from the cortex. In this study, we combined shape information from the above individual structures to examine the longitudinal change in the network of subcortical structures. Methods: Two high-resolution, T1-weighted magnetic resonance images were collected two years apart in 55 schizophrenia and 62 control subjects. Large-deformation high-dimensional brain mapping was used to generate surfaces for the thalamus, caudate nucleus, nucleus accumbens, globus pallidus, putamen, hippocampus and amygdala at baseline and follow-up. Deformation maps were computed for each structure with respect to the population mean to form vector fields at the structural boundary. These vector fields were combined across all structures in each hemisphere. Baseline shape was computed as eigenvectors from principal components analysis on these vector fields, which have support across all structures. Follow-up shape was expressed in terms of the baseline eigenvectors. Repeated-measures ANOVA on the first ten eigenvectors was used to test for longitudinal changes in shape. Results: The schizophrenia subjects exhibited a longitudinal shape change that was significantly different from the controls (shape-by-group interaction: Wilks' Lambda $F = 3.1$, $df = 10,106$, $P = .0017$). Visual inspection of the pattern of progressive changes confirmed the previously-reported variable patterns of between-group differences, and these differences spanned across the thalamus, caudate nucleus, nucleus accumbens and hippocampus. The other structures either showed similar changes in both groups (amygdala and putamen) or no progressive changes (globus pallidus). Conclusions: These results suggest that there is ongoing volume loss in subcortical brain structures in schizophrenia, and that this volume loss may be accentuated in structures that have more direct connections with the cortex. Further research is underway to investigate long-term changes in neural networks in schizophrenia.

ID: 550685

ABNORMAL FRONTAL CORTICAL ASYMMETRY PREDICTS NONRESPONSE TO ANTIPSYCHOTICS IN FIRST-EPISODE SCHIZOPHRENIA

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The identification of predictors of response to antipsychotic medications in patients with schizophrenia is an important goal for imaging research. The lack of controlled treatment trials from which to recruit patients for

imaging studies to investigate relationships with treatment response/outcome has limited studies in this area. In this study we tested the hypothesis that abnormalities in the normal, healthy pattern of cortical asymmetry would be associated with nonresponse to antipsychotic medication in patients experiencing a first-episode of schizophrenia. Magnetic resonance (MR) imaging exams consisted of 124 coronal images (slice thickness = 1.5 mm) acquired using a 3D Fast SPGR with IR Prep at 1.5T. Thirty-nine (30M/9F) patients experiencing a first-episode of schizophrenia who were enrolled in a treatment trial comparing the efficacy of risperidone (dosage range = 1 to 6mg) versus olanzapine (dosage range = 2.5 to 20mg) received MR imaging exams either prior to or close to the onset of treatment and had a median of 0 days (range = 0 to 14 days) cumulative lifetime exposure to antipsychotics. Twenty-five patients were classified as responders and 14 patients were classified as nonresponders. Cortical pattern matching methods were used to spatially associate homologous cortical locations across the two hemispheres. Regional hemispheric shape asymmetries were mapped by computing radial distances from the origin (the anterior commissure point at midline) to thousands of spatially equivalent points on the left and right hemispheric surface. An asymmetry index was then computed at each hemispheric location within subjects and compared across responders and non-responders at high spatial resolution. Statistical maps, obtained by comparing asymmetry measures at thousands of homologous locations across the hemispheric surface, showed significantly ($P < .05$; uncorrected) greater asymmetry in the frontal lobes among the responders, but not nonresponders. In addition, significant differences ($P < .05$; uncorrected) in cortical asymmetry were observed when responders were compared directly to non-responders. These preliminary findings suggest that a pattern of abnormal cortical asymmetry may be useful in identifying a subgroup of patients with first-episode schizophrenia who are nonresponsive to atypical antipsychotics at standard dosages.
ID: 550399

NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA—STATE-RELATED OR A TRAIT?

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Although minor motor and sensory deficits, or neurological soft signs (NSS), are among the best established neurobiological findings in schizophrenia, the question whether NSS are rather state or trait related is not yet resolved. We therefore investigated NSS (i) in the clinical course of first episode schizophrenia, (ii) in subjects with an increased genetic liability of disease, and (iii) by using magnetic resonance imaging (MRI) with respect to their potential cerebral correlates. NSS in first episode patients were significantly elevated relative to healthy subjects and subjects with an increased genetic liability at both examinations performed one year apart. Whereas NSS remained stable in healthy subjects (time 1: mean = 4.8, SD = 3.3; time 2: mean = 4.6, SD = 3.9), they significantly decreased in patients (time 1: mean = 15.7, SD = 7.1; time 2: mean = 10.1, SD = 7.9). This effect was more pronounced in patients with a favourable versus a chronic course and mainly accounted for by motor signs. Interestingly, NSS scores obtained in the former were in the same range as those of high-risk subjects. Follow-up NSS scores were predicted by NSS levels at t1 and treatment compliance. Voxel based morphometry of MRI scans obtained in 103 first episode patients yielded significant associations of NSS-total-scores with reduced gray matter densities in the pre- and postcentral gyrus, middle and inferior frontal gyrus, lingual gyrus, caudate nucleus, thalamus and cerebellum. Preliminary analyses of follow-up MRI scans taken in a subsample after 1 year confirmed a progression of the respective changes in the frontal and temporal cortices but not in the thalamus or the cerebellum. Our findings demonstrate that NSS refer to both, state and trait characteristics of schizophrenia. The variation of NSS in the clinical course is clearly state dependent, while their association with genetic liability and non-progressive cerebral changes refers to a trait. From a clinical perspective, NSS may serve as a marker of both, the disease process and genetic liability.
ID: 550354

CANNABIS SMOKING AND WHITE MATTER IN HEALTHY VOLUNTEERS

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Introduction: Cannabis smoking has been implicated in the aetiology of psychosis, a condition that is associated with alterations of white matter connectivity. We used Diffusion Tensor Imaging (DTI) to examine associations between cannabis and white matter in healthy volunteers. Methods: DTI data were acquired in 45 healthy volunteers, at mean age 18.5 years (SD 0.97), using a 1.5T GE MRI scanner. 30 individuals had used cannabis at some point during their lives; 15 had been lifelong abstainers. There were no significant group differences in age, socioeconomic status or gender distribution. We used group-mapping techniques implemented by locally-written software (XBAM) to compare those with and without a history of cannabis use. Results: The cannabis-using group had 2 clusters of reduced fractional anisotropy relative to the abstinent group ($P = .005$). Coordinates of the centres of mass of these clusters were: $-34, -48, 10$ (left occipito-frontal and superior longitudinal fasciculi); and $20, -46, 36$ (right posterior corona radiata) respectively. Conclusions: Cannabis use is associated with reduced white matter integrity in healthy volunteers. Alterations of white matter connectivity may underlie the propensity of cannabis to cause psychosis.
ID: 550262

DIAGNOSTIC SPECIFICITY AND VALIDITY OF BRAIN MORPHOLOGICAL ABNORMALITIES IN SCHIZOPHRENIA SPECTRUM DISORDERS

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We aimed to investigate the specificity and validity of the brain structural abnormalities found in a putative broad sample of first episode patients with non affective psychosis. 142 first episode patients with schizophrenia spectrum disorders (schizophrenia:82, schizophreniform disorder:36, other psychosis-schizoaffective and brief psychotic disorder-:24) and 83 healthy volunteers were included in the study. MR images were acquired on a 1.5-T GE Signa scanner and processed using the software BRAINS2. Sociodemographic and clinical variables were also assessed. We examined the volumes of whole brain, whole brain gray matter cortical CSF and lateral ventricles, gray matter volumes of cortical and volumes of subcortical regions. Repeated-measure analyses of covariance were used with group (schizophrenia, schizophreniform, other psychosis, control) as the between-subjects factor, hemisphere as the within-subjects factor, and age as a covariate. Post-hoc comparisons were performed using the Bonferroni adjustment for multiple comparisons. Relative volume was used in the analyses. There were significant differences between groups in relative brain tissue ($F = 4.62$, $P = .004$), relative external CSF ($F = 4.27$, $P = .006$), relative thalamus ($F = 2.84$, $P = .039$), and relative lateral ventricle volumes ($F = 3.54$, $P = .015$).

Post-hoc analyses revealed that total tissue volume was smaller in patients with schizophrenia and shizophreniform disorder compared with controls (P = .006, P = .36 respectively). External CSF volume was bigger in patients with schizophrenia and schizophreniform disorder compared with controls (P = .017 and P = .23 respectively). Thalamus volume was smaller in patients with schizophrenia compared with controls (P = .039). Compare with controls, schizophrenia patients showed greater ventricular volume (P = .026) and schizophreniform disorder patients showed a trend level increase (P = .073). In conclusion, 1.- brain structural abnormalities are already present at early phases of the psychotic illness; 2.- these brain abnormalities seem to be specifically associated with the diagnoses of schizophrenia and schizophreniform disorder. Thus, structural brain anomalies might demarcate boundaries between nonaffective psychoses and provide valid quantitative phenotypes for genetic research. Funding: Instituto de Salud Carlos III, FIS 00/3095, 01/3129, PI020499, PI060507, SENY Fundació CI 2005-0308007, Fundación Marqués de Valdecilla API07/011.
ID: 550251

OLANZAPINE AND HALOPERIDOL EFFECTS ON HIPPOCAMPUS STRUCTURE IN FIRST-EPISODE PSYCHOSIS

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Structural brain abnormalities occurring early in the development of schizophrenia have been extensively described. In a previous longitudinal study of first-episode psychosis (Lieberman et al. 2005, Arch Gen Psychiatry), patients treated with the 'typical' antipsychotic haloperidol showed significant decreases in temporal lobe gray matter after 24 and 52 weeks, which were not observed in patients treated with the 'atypical' antipsychotic olanzapine. This implied possible haloperidol-associated toxicity or greater therapeutic effect of olanzapine. In a follow-up study of the majority of these patients, we tested the hypothesis that similar structural changes will be present in the hippocampus (which is located within the temporal lobe) as were found in temporal lobe gray matter. MRI scans of 145 patients with first-episode psychosis (predominantly from schizophrenia) and 50 healthy controls were obtained from 14 academic medical centers (United States 11, Canada 1, Netherlands 1, and England 1). Patients had been randomly allocated to treatment with either olanzapine (5-20 mg/d; n = 73) or haloperidol (2–20 mg/d; n = 72). Large-deformation high-dimensional brain mapping (HDBM-LD) was used to evaluate both volume and shape of the hippocampus at baseline and periodically for up to 104 weeks. At baseline, gender-adjusted mean hippocampal volumes of patients with first-episode psychosis were significantly smaller than that of controls (left: 2767 mm3 vs. 2986 mm3, P = .016; right: 3419 mm3 vs. 3684 mm3, P = .018). Hippocampal shape analysis using MANOVA of reduced measures of surface variability (ie, principal components) resulted in even more significant differences between probands and controls (left: Wilks lambda = 0.92, P < .0001; right Wilks lambda = 0.70, P < .0001). At baseline, there were no differences in either hippocampal volume or shape between subjects allocated to the two treatment groups, consistent with the prior study of the temporal cortex. We are currently analyzing longitudinal changes in hippocampal volume and shape at weeks 12, 24, 52 and 104, to determine if there is differential structural change across diagnosis and treatment.
ID: 550107

EFFECTS OF ANTIPSYCHOTICS ON BRAIN STRUCTURE AT THE FIRST PSYCHOTIC EPISODE AND 6 YEARS LATER

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The mechanisms underlying the different actions of antipsychotics on brain remain poorly understood. We aimed to establish whether antipsychotics affect brain anatomy, after short and long term treatment. We investigated global brain volumes of 84 patients at their first psychotic episode (32 female; mean age 27.1 ± 9 years; 47 with DSM IV Schizophrenia, 37 with Other psychoses) and followed them up 6 years later. Dual echo MRI data were acquired at 1.5T. Differences in grey matter between groups were estimated at each intracerebral voxel after registration of images in standard space. At the time of the first psychotic episode, 32 patients were taking typical antipsychotics, 30 were taking atypicals, and 22 were drug-free. There were no differences in global grey and white matter, and CSF volumes, between patients exposed to either typical or atypical antipsychotics and the drug-free patients. Over the 6 years follow up, the average time spent on treatment, mostly with atypicals, was 3 years. 47 patients had a second MRI scan at follow up. Length of time spent on atypicals was negatively correlated with white matter volume at follow up (0.049), and positively correlated with follow up CSF volume (0.08), but only in patients with schizophrenia or schizoaffective disorders. Long term exposure to atypical antipsychotic drugs may affect white matter and CSF volumes.
ID: 550003

CAN WHOLE BRAIN VOXEL-BASED MORPHOMETRY STUDIES APPLIED TO DTI DATA LOCALIZE WHITE MATTER CHANGES IN SCHIZOPHRENIA?

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Voxel-Based Morphometry (VBM) is a whole brain, voxel-wise analysis method that attempts to compare Diffusion Tensor Imaging (DTI) data across subjects and between populations. A number of schizophrenia studies have utilized this method to localize differences in Fractional Anisotropy (FA), a measure of white matter integrity, between patients and normal controls. Using this method, FA differences are seen over the entire brain at once and, using a statistical threshold, local differences in white matter integrity are documented, thus providing a hypothesis-free route for studying schizophrenia. The number of publications using this method has grown, although it is unclear how reproducible this method is since there have been no meta-analysis of VBM studies in schizophrenia to date. Here, we analyze and combine results from 20 studies published to date in order to evaluate the reproducibility of this method in DTI analysis. Using 3D Slicer, we plotted coordinates of each region reported in every VBM DTI study published thus far in schizophrenia onto a Montreal Neurological Institute (MNI) atlas (points listed in Talairach atlas space were converted into MNI space beforehand). Only statistically significant coordinates representing reduced FA in schizophrenic patients were plotted. For the papers with no points listed, coordinates were approximated by comparing the images in the papers to the Talairach atlas using the Talairach Applet and Sleuth v.1.1. These points were subsequently

converted into MNI space. The coordinates representing reduced FA in patients with schizophrenia were scattered across the brain. The genu of corpus callosum, the splenium of corpus callosum, the right anterior corona radiata, and the right posterior thalamic radiation (including the optic radiation) were the most consistently reported regions; each was reported in 30% of the papers we studied. Other instances of reduced FA were replicated at an even lower rate. When compared on the same atlas, findings from different papers were shown to be scattered across the brain and largely inconsistent, with only a small number of regions being reported individually in 30% of the papers reviewed. Differences in registration and segmentation methods, followed by other factors such as statistical threshold, subject age, medication, and/or other factors all likely contribute to the inconsistent findings across studies. Such factors need further consideration in future studies.

ID: 549968

CAUDATE AND HIPPOCAMPAL VOLUME REDUCTIONS IN ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIC PATIENTS: LIFETIME ABUSE SIDE-DIAGNOSIS MATTERS

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Two recent meta-analyses indicate only hippocampal volume reduction and ventricular enlargement to be consistently present in first episode schizophrenia, Vita et al. Schizophr.Res (2006), Steen et al. Br.J.Psychiatry (2006). Studies in antipsychotic-naïve first episode schizophrenia patients have generally focused on the basal ganglia. These studies tend to find reduced absolute volume caudate nucleus volumes, however, only few studies reach significance, likely due to small sample sizes. This study aimed to confirm the presence of reduced hippocampal volumes and enlarged ventricles in 38 antipsychotic-naïve first episode schizophrenic patients as compared to 43 matched healthy controls by means of VBM using a high-dimensional non-linear inter-subject warping. Moreover, reduction in the caudate nucleus was hypothesized. The possible effect of lifetime abuse was examined by categorizing patients into two subgroups; without ($n = 29$) and with ($n = 9$) lifetime (but not current) substance abuse side-diagnosis. Patients were diagnosed with SCAN interviews (DSM-IV). Clinical measures included PANSS and Duration of Untreated Illness (DUI). Subjects underwent a high-resolution 3D T1-weighted MRI-scan on a 3 Tesla scanner. Images were analysed using SPM5 and spatial normalized with DARTEL. Small volume correction was performed for hippocampus, caudate nucleus and the lateral ventricles, using FDR (0.05) to control for multiple comparisons. As hypothesized, patients as compared to healthy controls had significant bilateral reduced hippocampal and caudate volumes. The hippocampal reductions, however, were solely driven by the subgroup of patients with lifetime substance abuse side-diagnosis, while the caudate reductions were most prominent in the patients with no history of abuse. Ventricles were not enlarged. Differences in global gray or white matter or CSF were absent. Exploratory analyses revealed an association between left hippocampal volume reduction and longer DUI. Our results support the presence of hippocampal and caudate reductions in first episode antipsychotic-naïve schizophrenic patients. The hippocampal reductions, however, seem to be influenced by lifetime abuse and not specific to schizophrenia per se. The latter agrees with the fact that hippocampal changes are observed in various neuropsychiatric disorders, including substance abuse. Caudate volume reductions, on the other hand, might be specific for schizophrenia at the onset of the disorder.

ID: 549948

BRODMANN AREA ANALYSIS OF WHITE MATTER ANISOTROPY AND AGE IN SCHIZOPHRENIA

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Background: In Diffusion Tensor Imaging (DTI) healthy organized myelinated axon bundles have high anisotropy. Bundles where the fibers are crossing, oriented in different directions, or in which the myelin or axons are unhealthy have low anisotropy. This study investigates the changes in white matter anisotropy by Brodmann Area in schizophrenia and between first break and chronic disease states. Methods:97 adults with schizophrenia and 93 normal adults were scanned on a 3T MRI system. Each subject received a structural (MP-RAGE) sequence and a diffusion tensor sequence. Average Fractional Anisotropy (FA) values determined for white matter in each Brodmann Area in each hemisphere and T-tests were performed between groups. To determine the effect of duration of illness analysis of covarience were performed on the anisotropy values controlled for age for the white matter in each Brodmann region between the acute and chronic subgroups Results: Fractional anisotropy (FA) in white matter was decreased in patients with schizophrenia broadly across the entire brain, but to a greater extent in white matter underneath frontal, temporal and cingulate cortical areas. Both normals and patients with schizophrenia showed a decrease in anisotropy with age but patients with schizophrenia showed a significantly greater rate of decrease in FA in Brodmann area 10 bilaterally, 11 in the left hemisphere and 34 in the right hemisphere. When the effect of age was removed, patients ill more than three years showed lower anisotropy in frontal motor and cingulate white matter in comparison to acute patients ill three years or less. Conclusions: In schizophrenia deficits in language, memory, auditory hallucinations, social behavior, decision making, emotional processing and motor functioning are associated with the regions in which differences in anisotropy was seen. White matter deficits in several regions of the brain change progressively between the first break and the chronic state of the disease.

ID: 549866

ABNORMALITIES IN TENSOR MORPHOLOGY IN PATIENTS WITH SCHIZOPHRENIA: A DTI STUDY OF THE CORPUS CALLOSUM

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This study uses diffusion tensor imaging (DTI) to provide a detailed characterization of the diffusion properties of the corpus callosum in young healthy adults, in order to better infer the microstructural features of the commisural fibers. Additionally, in keeping with the prevailing 'connectivity' models of psychosis, this study also investigates abnormalities in the diffusion properties of the corpus in patients with chronic schizophrenia. 19 patients with chronic schizophrenia and 19 healthy controls,

matched on age, handedness, and parental socioeconomic status, participated in this study. Diffusion-weighted images were acquired with 51 non-collinear gradients on a 3T GE magnet (1.7 x 1.7 x 1.7mm voxels), and converted into DT images. The DT images underwent whole-brain tractography, followed by an automatic clustering procedure, and clusters constituting the corpus fibers were parcellated into 6 segments (frontal, pre-motor, sensorimotor, parietal, visual and temporal) on the basis of the 3-dimensional fiber projections. The diffusion properties of the corpus were quantified via three scalar indices (fractional anisotropy (FA), trace and mode), which were calculated and compared both between segments and between clinical groups. FA and mode exhibited a similar and distinctive 'U-shaped' pattern of change from the genu to the splenium. The visual and temporal fibers exhibited the highest anisotropy and most cylindrical mode, while the premotor and sensorimotor fibers exhibited lower anisotropy and a comparatively 'disk-shaped' mode. Trace was relatively stable between corpus segments. Relative to the healthy controls, the schizophrenia patients exhibited reduced FA in the frontal and temporal corpus segments. It seems likely that the high FA and cylindrical mode exhibited in the visual and temporal segments indicate that these fibers are either: a) more myelinated, b) more densely packed, c) more structurally coherent, and/or d) experience less fiber crossings relative to other corpus fibers. The fact that schizophrenia patients exhibited FA abnormalities in frontal and temporal corpus suggests an anatomical basis for the aberrant inter-hemispheric communication that has consistently been reported in patients with the disease. Furthermore, to the extent that DTI abnormalities have been shown to influence axonal transmission velocities, these results provide support for theories which emphasize neural timing abnormalities in the etiology of the disease.
ID: 549641

ANATOMICAL ABNORMALITIES OF THE HIPPOCAMPUS IN PATIENTS WITH SCHIZOPHRENIA

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Although overall volumetric reductions of the hippocampus have been reported in schizophrenia, findings have been inconsistent, revealing either abnormalities in the head of the hippocampus or in its tail. The purpose of this study is to clarify the pattern of anatomical abnormalities in the hippocampus using surface analytic techniques in a larger sample. We studied 65 patients with schizophrenia and 60 healthy controls. Surface morphologies of the hippocampus were compared across diagnostic groups while covarying for age, age2 and gender. We computed the signed Euclidean distances from each point of the surface of the hippocampus of every subject to the corresponding point on the hippocampus of a reference subject. We first used a rigid body similarity transformation to register each participant's brain with a template brain. Subsequently, we used these estimated parameters to register the manually defined hippocampus into the template space. The transformed hippocampus of each subject was then rigidly coregistered to the reference hippocampus and then warped onto this reference structure using a non-rigid high-dimensional warping algorithm. After identifying corresponding points on the surface of the hippocampus of each subject and of the reference hippocampus, we unwarped each subject's hippocampus in order to compute the distances. We detected localized volumetric abnormalities in the right and, to a smaller extent, in the left hippocampus. In the right hippocampus, volumetric reductions were located in the lateral aspect of the head (anterior CA1) and in the tail. An area of volumetric increase was also seen in the ventral aspect of the head. In the left hippocampus, volumetric reductions were present in the tail only. The anterior hippocampus is implicated in emotional, defensive and autonomic responses by virtue of its connections with the

mOFC, the amygdala, the accumbens and the hypothalamus. The posterior hippocampus, functionally linked to sensory and parietal areas as well as to the PFC, is implicated in spatial learning, spatial memory and working memory. Our study extends findings from prior imaging research and it suggests that the involvement of both anterior and posterior hippocampus could be the structural correlate of the disruption of fronto-limbic and dorso-parietal circuitry in schizophrenia.
ID: 549494

EVIDENCE OF CEREBRAL WHITE MATTER CHANGES ON COMBINED STRUCTURAL MRI AND DIFFUSION TENSOR IMAGING IN FIRST EPISODE SCHIZOPHRENIA

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Previous studies have revealed volumetric abnormalities of white matter in patients with schizophrenia but the corresponding white matter dysconnectivities are less studied in tandem. The aim of this study is to examine white matter integrity in the region of white matter volume deficit in patients with first-episode schizophrenia (FES). A cross-sectional, case-control design was adopted and we used empirically-defined region of known white matter volume deficit to interrogate diffusion tensors. The participants included 103 subjects comprising of 39 patients with FES and 64 age-, sex-, and handedness-matched healthy controls. The neurocognitive domains assessed included intelligence, attention, executive functioning, verbal and spatial working memory. The main outcomes were gray and white-matter partial volumes, fractional anisotropy, trace and geometric diffusion indices. Structural voxel-wise analyses revealed that patients with first episode schizophrenia had lower gray matter volumes in bilateral hippocampi ($P < .01$) and lower white matter volume in the right temporal-occipital region ($P < .005$) corresponding to the inferior longitudinal fasciculus. Further analyses of diffusion anisotropy in the right temporal-occipital region revealed lower planar anisotropy, cp, and higher linear anisotropy, cl ($P = .012$) in patients with first episode schizophrenia. However, no differences were found for fractional anisotropy and trace in the implicated white matter region between the two groups. Patients performed poorer in digit span, spatial working memory and executive functioning, compared to healthy controls. To the best of our knowledge, this is the first study to employ geometric diffusion measures in interrogating the nature of diffusion tensor in schizophrenia. We confirmed previous findings of white matter volume deficit in the region of inferior longitudinal fasciculus. The presence of changes in geometric diffusion indices in the implicated white matter region suggests that pathophysiological processes which underlie cerebral white matter volume reduction may not be reflected by changes in fractional anisotropy. Further research is needed to better understand the nature of these white matter changes and its progression in schizophrenia over time.
ID: 549454

PROGRESSIVE WHITE MATTER ABNORMALITIES IN SCHIZOPHRENIA: A MULTI-SITE DIFFUSION TENSOR IMAGING STUDY

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Diffusion tensor imaging (DTI) is a magnetic resonance imaging method that measures the spatial profile of the self diffusion of water molecules in tissue. DTI is sensitive to disruptions in white matter microstructure and may reflect aberrant connectivity between brain regions. The existing DTI studies examining patients with schizophrenia tend to have relatively small numbers and have disparate patterns of white matter abnormalities. One approach to increasing the number of subjects in clinical studies is to use multiple acquisition sites. While dramatically increasing the number of subjects, multi-center studies have added methodological issues related to site differences in scanning equipment and subject demographics. This study presents DTI results from a large multicenter study that involved the Massachusetts General Hospital and the Universities of Iowa, Minnesota, and New Mexico. The participants included 114 patients with schizophrenia (31 first-episode (FE) and 83 chronic patients) and 138 controls (43 matched to the first-episode and 95 matched to the chronic patients). The mean ages for the chronic and FE patient groups were 36.4 (SD 11.0) and 25.2 (SD 6.7), respectively. The mean ages for the control groups were 34.0 (SD 11.3) and 25.6 (SD 6.6), respectively. Positive, negative, and disorganized symptom scores measured using the SANS and SAPS were similar between the patient and FE groups. There was a significant effect of site, and thus site was used as a covariate in the analyses. Patients with chronic schizophrenia had lower fractional anisotropy (FA) in the whole brain, and in the frontal, parietal, occipital, and temporal lobes, but did not have lower FA in the brainstem or the cerebellum. FA was not significantly different between the FE patients and in all brain measures. However, comparing the chronic and FE patients, only the frontal lobe had significantly lower FA There is a trend for the FE patients to show FA intermediate between the control and chronic groups. Our findings suggest progressive alterations in white matter microstructure in cortical regions in patients with schizophrenia.
ID: 549443

ABNORMALITIES IN HIPPOCAMPUS VOLUME AND SHAPE IN NONPSYCHOTIC, ADOLESCENT/ YOUNG ADULT BIOLOGICAL RELATIVES OF SCHIZOPHRENIA PROBANDS

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Biological relatives of schizophrenia probands are more likely to have similar but subtler neuroanatomic, electrophysiologic, neurocognitive and behavioral deficits as schizophrenia probands. Most family studies to-date have examined older relatives. Studying adolescent or young adult relatives who are still at-risk has the potential to increase our understanding of the neurodevelopmental etiology of schizophrenia, and to discover biomarkers that may aid in early identification of the disorder. In this study, we utilized an artificial neural network segmentation algorithm to automatically define and reliably measure MRI hippocampus volumes. We compared 46 nonpsychotic first- or second-degree relatives of schizophrenia probands

against 46 healthy volunteers (HNV) without family history of schizophrenia (Mean age = 20.4 years; Range = 13 to 28 years). Relatives had significantly smaller left hippocampus volumes than HNV ($F = 4.53$, $P = .04$). On examining hippocampus volume-age relationships, we found hippocampus volume normally decreases with age during late adolescence into early adulthood. In contrast, relatives did not show these age-expected changes which may be indicative of aberrant hippocampal neurodevelopment. We further assessed how obstetrics complications (a trigger for aberrant neurodevelopment in utero) may contribute to hippocampus volume deficits. Relatives with a history of obstetrics complications ($N = 28$) had significantly smaller left and right hippocampi than relatives without obstetrics complications ($F \geq 4.31$, $P \leq .04$). In both relatives sub-groups, hippocampus volume-age relationships again differed from the age-expected reductions in HNV (Left: Pearson partial correlations = -0.26, -0.07 and 0.16 for HNV, relatives with and without obstetrics complications respectively; Right: $r = -017$, 0.04 and 0.22 respectively). We further analyzed hippocampal shape using spherical harmonics functions. Relatives had deformities in the heads of bilateral hippocampi corresponding to inward displacements compared to HNV. Schizophrenia likely involves different aberrant neurodevelopmental processes. Some neurodevelopmental anomalies occur during early brain maturation while others may manifest closer to illness onset in adolescence/early adulthood.
ID: 549200

IS THERE ROOM FOR THE 'LITTLE BRAIN' IN PSYCHOSIS? AN MRI STUDY EXAMINING CEREBELLAR VOLUME AND NEUROLOGICAL FUNCTION IN FIRST EPISODE PSYCHOSIS

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The role of the cerebellum in psychosis has been suggested to be important in contemporary research. This study examined the relationship between cerebellar volume and neurological soft signs in first episode psychosis (FEP) patients compared to healthy controls. Cerebellar volume and neurological soft signs were also compared between schizophrenia and other psychoses. Data were collected from 80 FEP patients (male:female 49:31; mean age 27.7 years ± 8.1) and 43 healthy controls (male:female 21:22; mean age 31.0 years ± 9.3) from the London arm of the ÆSOP study. Scans were acquired with a General Electric Signa 1.5-T system and whole cerebellum volume was obtained using stereologically unbiased volume estimation. An expanded version of the Neurological Evaluation Scale was used, comprising the following subscales; Primary, Sensory Integration, Motor Coordination, and Motor Sequencing. All comparisons were adjusted for age, gender, and ethnicity. FEP patients had a significantly smaller cerebellum volume than healthy controls ($P = .02$). In addition, schizophrenia patients had a significantly smaller cerebellum volume than other psychoses patients ($P = .049$). FEP patients had a higher total NSS score than controls ($P = .001$), but there was no difference in NSS scores between diagnostic subgroups. There was no relationship between cerebellar volume and NSS global scores or classical motor cerebellar signs in either patients or controls. Similarly, there was no such relationship in either the schizophrenia or other psychoses subgroups. Inclusion of premorbid IQ as an additional covariate did not affect results. This study suggests that cerebellar volume is reduced in FEP patients compared to controls, and that this is more marked in schizophrenia compared to other

psychoses. In addition, NSS were greater in subjects compared to controls. However, despite the presumed importance of the cerebellum in neurological function, no functional link with global volume was found in this study. This may reflect the fact that global cerebellar volume is a very gross measure of cerebellar structure; thus a more detailed analysis into cerebellar sub-regions is necessary.

ID: 549029

VOXEL-BASED MORPHOMETRY OF PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR I DISORDER

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The issue of similarities and differences in neuroanatomical structure between schizophrenia (SZ) and bipolar I disorder (BP), and how each group differs from healthy individuals is a long-standing question in psychiatry. Recently, voxel-based morphometry (VBM) has been increasingly applied in elucidating structural brain changes associated with these functional psychotic disorders. However, VBM studies in SZ and BP have reported inconsistent results. Potential causes of these inconsistencies include differences in the samples studied, especially differences in age, gender, duration of illness, or subtypes of BP. The aim of the study was to compare gray matter volumes in a cross-sectional VBM design including subjects with chronic SZ, chronic BP and healthy control (HC) subjects matched for age, gender and duration of illness. Seventeen subjects with SZ, 15 subjects with BP, and 21 HC subjects without psychiatric illness were studied. Study inclusion criteria were 1) age: 25–70; 2) duration of illness: over 3 years; and 3) DSM-IV bipolar I disorder or schizophrenia. Groups were well matched on age, gender, and illness duration. Scans were performed with a 1.5-Tesla Siemens Magnetom Vision scanner using an MPRAGE protocol (TR = 24 ms, TE = 5 ms, 1.0 mm thickness, voxel size = 1.0 × 1.0 × 1.0 mm). Data preprocessing and statistical analysis were performed using the VBM5 toolbox, which utilizes the new unified segmentation approach to optimize VBM and is implemented in SPM5. Preprocessed images were compared between diagnostic groups using an ANCOVA model controlling for the possible effects of age and gender. Significance was set at a p value of $P < .001$, uncorrected, with a minimum cluster size of 200 voxels. Then, a cluster-level threshold of $P < .05$, corrected for multiple comparisons, was applied. Compared with HC group, SZ and BP groups showed evidence of reduced right middle frontal region and right superior and middle temporal regions. However, reductions in bilateral thalamic regions and right hippocampus, amygdala and putamen were specific to SZ group. The results suggest similarities and differences in affected gray matter volumes in patients with SZ and BP, even when the two groups are matched on age, gender, and illness duration. These similarities and differences of structural abnormalities may be important factors in the common and differential manifestations of these two functional psychotic disorders.

ID: 548907

PARACINGULATE ASYMMETRY IN SCHIZOPHRENIA

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Structural correlates of hemispheric dominance for language are found in medial frontal cortex and superior temporal lobe. The paracingulate sulcus, a shallow sulcus that courses dorsal to the cingulate sulcus is more frequent on the left (Ide et al., 1999; Paus et al., 1996) in normal adults but not in schizophrenia (Le Provost et al., 2003; Yucel et al., 2002). Interestingly, a dorsal paracingulate sulcus was not identified by Ono et al., 1990). Instead, a large "double parallel" sulcus originating inferior to the genu of the corpus callosum ran parallel to the cingulate in about 25% of both the left and right hemispheres. In the present study of 46 adults (37 M, 9 F) with chronic schizophrenia (S), 37 (34 M, 3 F) controls (C) matched on age and SES, and 200 normal young adults (YA) (100 M, 100 F), we replicated Ono's finding of symmetry for the double parallel sulcus. Raters, blind to hemisphere, sex, and diagnosis, then used Yucel's criteria to rate the size of the dorsal paracingulate sulcus. This sulcus was significantly larger on the left in all samples (S: $t_{45} = 2.4$, $P < .02$; C: $t_{38} = 3.0$, $P < .005$; YA: $t_{199} = 5.23$, $P < .0001$) and this asymmetry was not affected significantly by sex, writing hand, diagnosis, or cognitive status. As this sample of schizophrenics also has normal leftward planar asymmetry it appears there must be particular conditions associated with disrupted brain asymmetry in schizophrenia. Supported by a Veterans Administration Research Service Merit Review Grant (JK) and NIH DC 006957 (CC).

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Table. Percent of of each sample demonstrating rightward asymmetry, symmetry and leftward asymmetry of the paracingulate sulcus.

	L<R	L = R	L>R
S ($n = 46$)	20	30	50
C ($n = 39$)	13	37	50
YA ($n = 200$)	26	22	52

ID: 548866

CHANGES IN THREE MAJOR FRONTOTEMPORAL WHITE MATTER TRACTS IN SCHIZOPHRENIA ACROSS THE ADULT LIFESPAN: A DIFFUSION TENSOR TRACTOGRAPHY STUDY

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The progression of white matter deficits and their relationship with age in schizophrenia is not well understood. Fronto-temporal white matter tracts represent an important susceptibility network in schizophrenia. Diffusion tensor imaging (DTI) is a powerful tool that can measure white matter tract integrity. Moreover, diffusion tensor tractography allows such measurements to be carried out along white matter tracts. The present study examines three frontotemporal tracts in schizophrenia patients and healthy controls across the adult lifespan using diffusion tensor tractography. 30 individuals with schizophrenia or schizoaffective disorder and 22 healthy controls ranging from 25–78 years were matched on parental socioeconomic status, gender, and age, and all subjects were right-handed. Diffusion gradients were applied in 23 non collinear directions, with two $b = 0$ images, whole brain coverage, repeated three times, on a 1.5 T GE system. Following co-registration, whole brain seeding and tractography, the uncinate fasciculus (UF), inferior occipito-frontal fasciculus (IOFF), and cingulum bundle (CB) were segmented. Fractional anisotropy, trace, radial, and axial diffusivity were calculated. Using Pearson correlation coefficients, left side fronto-temporal tract FA for each of UF and IFOF and CB were significantly negatively correlated with age in schizophrenia ($r = -.376$, $P = .019$, $r = -.498$, $P = .006$ and $r = -.341$, $P = .05$ respectively) and in healthy controls ($r = -.428$, $P = .004$, $r = -.398$, $P = .012$, and $r = -.375$, $P = .04$ respectively). While there were no differences between the late life groups, the early adult life schizophrenia group showed decreased FA in left UF ($P = .035$), right CB ($P = .028$), decreased axial diffusivity in left CB ($P = .029$) and increased radial diffusivity in right IOFF ($P = .031$) when compared to the early adult life control group. There is growing evidence that abnormalities of white matter integrity are progressive in schizophrenia, rather than occurring entirely prior to the first episode of psychosis. Our DTI tractography study across the adult lifespan in schizophrenia presents evidence that there are differences in white matter integrity in schizophrenia compared to controls, and that these differences are primarily detectable in the first half of adult life. Damage to fronto-temporal white matter tracts may be progressive in the first half of adult life but not in late life in schizophrenia compared to controls.
ID: 548671

CHANGES IN NEUROLOGICAL SIGNS AND THEIR ANATOMICAL CORRELATES, OVER 6 YEARS AFTER THE FIRST PSYCHOTIC EPISODE

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Introduction: An excess of neurological signs is present in psychosis, particularly in primary and motor coordination signs. It remains unclear whether these signs progress over the course of the illness, and it has never been investigated whether any progression is associated with changes in brain structure. Methods: We evaluated 49 individuals (mean age 27 years ±8; 59% males; 45% DSM IV schizophrenia) at the time of the first psychotic episode and 6 years later. We investigated neurological function using the Neurological Evaluation Scale, and grey matter volume using Magnetic Resonance Imaging, with a 1.5 T GE scanner. We estimated grey matter volume with automated segmentation methods. Results: Rates of primary and motor coordination signs remained stable over the follow up period, as did motor sequencing signs. In contrast, sensory integration signs increased over the follow up period ($P = .007$). Higher rates of primary signs (at baseline) and higher rates of motor coordination signs (at follow up) were correlated with more grey matter loss over follow up ($P = .05$ and $P = .07$ respectively). Conclusions: Primary and motor coordination deficits may represent trait markers of psychosis and their presence may be predictive of a more progressive illness course. Further work will investigate whether these signs are also associated with regional brain changes.
ID: 548642

REGIONAL BRAIN CORTICAL THICKNESS DIFFERENTIATE SCHIZOPHRENIA FROM BIPOLAR DISORDER AND HEALTHY CONTROLS

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Schizophrenia and bipolar disorder are currently classified as separate illnesses. Clinical and genetic studies suggest similarities between the disorders, while neuroimaging studies of the cerebral cortex have not consistently shown structural similarities. Previous studies have shown regional alterations in prefrontal cortex areas in bipolar disorder (1) and prefrontal and temporal cortex areas in schizophrenia (2), as compared to healthy controls, suggesting overlapping but dissimilar patterns of regional cortical alterations. In the present study, we measured cortical thickness in subjects with schizophrenia and bipolar disorder and in healthy adults enrolled in the Thematic Organized Psychosis Research Study (TOP) and assessed for differences across the three groups. Subjects included patients with schizophrenia ($n = 112$), bipolar disorders ($n = 84$) and healthy subjects ($n = 101$) were included. Patients were diagnosed according to DSM-IV and all participants underwent MR scanning. The FreeSurfer software was used for all automated image processing and to obtain estimates of cortical thickness. All analyses were corrected for age. Results were presented as continuous surface maps depicting statistical significant differences in cortical thickness between the subject groups. To adjust for multiple comparisons the level of significance was set at a False Discovery Rate of 0.05. In schizophrenia thinner cortices were found in several localized frontal areas and the superior temporal area in both hemispheres, as compared to healthy controls. In bipolar disorder no significant differences were found compared to healthy controls. Thinner cortices were found in the left superior temporal gyrus in schizophrenia compared to bipolar disorder. In frontal brain areas, cortical thickness in bipolar disorder did not significantly deviate from either schizophrenia or healthy controls, which suggest morphological similarities with both groups. A thinner cortex in the left superior temporal gyrus may differentiate patients with schizophrenia from patients with bipolar disorder.

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ID: 548487

AN MRI REGIONAL BRAIN VOLUMETRIC ANALYSIS IN ANTIPSYCHOTIC-NAÏVE FIRST EPISODE PSYCHOSIS SUBJECTS BEFORE AND AFTER ATYPICAL ANTIPSYCHOTIC TREATMENT

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Fronto-striatal neural pathways represent a priority for research in first-episode psychosis (FEP), as altered regulation of cortical and sub-cortical dopamine pathways have been implicated in the etiology of psychosis. In the current study we examined total brain, frontal and basal ganglia white and grey matter volumes in a cohort of antipsychotic-naïve FEP subjects and healthy volunteers. Twenty-five FEP and 31 healthy subjects were recruited. A total of 23 FEP subjects and 28 healthy volunteers completed all follow-up assessments. Subjects were scanned on a Philips 3T Achieva MRI Scanner at baseline, 4 weeks and 8 weeks after start of low-dose atypical antipsychotics; MR segmentation was automated. Symptom severity was assessed at each time point using the Positive and Negative Symptoms Scale (PANSS). Follow-up comparisons were performed on baseline and 8-week follow-up measures. At 8-weeks 21 of 23 FEP subjects were being treated with atypical antipsychotics (19 received risperidone, 2 received quetiapine). Mean total baseline PANSS scores were 47.3, and 32.4 at 8-week follow-up. Baseline frontal white and grey matter volumes were not significantly different between FEP subjects and controls (all P-values > 0.050). At follow-up FEP subjects experienced significant increases bilaterally in frontal grey matter volume after treatment with atypical antipsychotics (Left: $P = 0.009$. Right: $P = 0.02$). No significant changes in white matter volume were observed. In basal ganglia, FEP subjects had significantly larger left nucleus accumbens volumes compared to healthy volunteers at baseline ($P = .0008$). No differences in left or right caudate, putamen or globus pallidus were observed between groups at baseline (all P-values > 0.40). Striatal volumes remained stable at follow-up and no changes were observed in FEP subjects or healthy volunteers. Antipsychotic-naïve FEP subjects displayed differences in regional brain grey and white matter volumes compared to healthy controls, with both left and right frontal grey volume increased after atypical antipsychotic treatment. In contrast, striatal volumes were unchanged by exposure to low-dose atypical antipsychotic exposure, despite baseline abnormalities of left nucleus accumbens in FEP subjects. The findings provide further evidence for the importance of fronto-striatal brain regions in early psychosis.
ID: 548448

CHARACTERISTICS OF FRONTAL AND TEMPORAL CORTEX IN RELATION TO COGNITIVE DYSFUNCTION IN PATIENTS WITH FIRST-EPISODE PSYCHOSIS

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We examined the relationship between cortical parameters (thickness, surface area and grey matter volume) and cognitive measures in a group of patients with first episode psychosis (FE) compared to healthy controls. 37 patients (25 males; mean age 26.76) and 38 controls (22 males; mean age 24.98) were imaged on a 1.5T GE Signa MRI scanner. Patients had received medication for less than 12 weeks. A T1-weighted axial dataset was obtained using an IR-SPGR echo sequence with a 24 cm field of view and 256 x 256 matrix size to provide a resolution of 1.2 x 1.2 x 1.2 mm3. A total of 124 contiguous slices were acquired (TR = 15ms; TE = 5.4ms; flip angle = 15o). Images were processed using FreeSurfer software (version 4.0.1) that allows the measurement of cortical parameters using automated segmentation and surface topographical analysis. Premorbid IQ, current IQ, executive functions (working memory span, set shifting, planning, working memory manipulation) and episodic recall memory were measured. Associations between cortical parameters and cognitive measures were examined using linear mixed models. There were no significant differences in age, gender or handedness between patients and controls, but patients performed worse on all cognitive tests and showed smaller temporal area. The association of frontal area with premorbid IQ ($z = 2.28$, $P = .023$), current IQ ($z = 3.11$, $P = .002$) and set-shifting ($z = -2.49$, $P = .013$) was different in patients and controls. In patients, but not in controls, frontal area was associated with current IQ ($z = 3.52$, $P < .001$) and set-shifting ($z = -3.03$, $P = .002$). Patients also had a different association of frontal volume with premorbid IQ ($z = 2.39$, $P = .017$) and current IQ ($z = 3.08$, $P = .002$) from controls, although there were no differences in regional associations by diagnostic group. No associations were present between temporal cortical parameters and cognition or between side and cortical or cognitive measures. The most salient findings of our study were the differences in cortical area between patients and controls and the association between area of frontal cortex, current IQ and set shifting in patients, suggesting that in FE better cognitive performance is accompanied by larger frontal cortical area. By contrast, cortical thickness was not related to cognition. This pattern of cortical abnormalities is different from that observed in progressive neurodegenerative disorders and points to a developmental abnormality.
ID: 548428

EFFECT OF COMT VAL158MET GENOTYPE ON HIPPOCAMPAL GRAY MATTER VOLUME IN SCHIZOPHRENIA

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Cathecol-O-Methyltransferase (COMT) Val158Met is thought to modulate dopamine regulated neuronal plasticity in prefrontal cortex and in hippocampus in healthy subjects, and to weakly increase risk for developing schizophrenia. Recently we have demonstrated an association of COMT Val158Met with the phenotype of hippocampal physiology during memory encoding in schizophrenia. Aim of the present study was to investigate if this polymorphism is also associated with hippocampal gray matter (GM) volume in schizophrenia. 28 controls and 26 patients with schizophrenia (DSM-IV criteria) matched by COMT Val158Met genotype and by a series of socio-demographic variables were recruited. All patients were on stable antipsychotic treatment. Structural images were acquired on a GE 3T scanner using a gradient echo fast SPGR sequence with 124 sagittal slices of 1.3 mm thickness. Voxel Based Morphometry analysis and second level

random effects analysis (Factorial ANCOVA) were performed within SPM5 (all $P < .005$). A region of interest approach centered on the HF (WFU PiclAtlas) was used. We found a main effect of genotype, with Met/Met subjects showing reduced GM volume in left HF compared to Val homozygote; a main effect of diagnosis, with healthy subjects showing greater GM volume than patients in left anterior HF; and a gene-by-diagnosis interaction, in that the effect of diagnosis on HF GM was evident only in Met/Met subjects. As suggested by the lack of correlation with chlorpromazine equivalents, these differences were not because of pharmacological treatment. Collectively, our data indicate that COMT genetic variation may differentially contribute to modulate the phenotype of hippocampal morphometry in patients with schizophrenia.
ID: 548367

WHITE MATTER DISRUPTION IN INDIVIDUALS WITH PSYCHOSIS AND THOSE AT HIGH FAMILIAL RISK DETERMIEND BY SPECIFIC GENETIC VARIANTS

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There is strong evidence of white matter abnormalities and altered connectivity in schizophrenia and bipolar disorder, but there is a lack of studies examining diagnostic specificity, disruptions in high risk groups or the relationship to specific susceptibility genes. In a series of linked experiments, we used MRI and diffusion tensor MRI to assess white matter integrity in patients with bipolar I disorder, schizophrenia, subjects at high risk of psychosis and healthy controls. We also examined white matter associations with risk-associated variants in Neuregulin I and ErbB4. Fractional anisotropy (FA) was compared between the groups using voxel-based morphometry, automated region of interest analysis and probabilistic tractography. Patients with both disorders showed reduced FA in fronto-thalamic and frontotemporal connections compared with controls and these deficits were related to risk associated genetic variants, including NRG1 and ErbB4. Reduced white matter density and integrity is common to both schizophrenia and BD and those at high risk for genetic reasons. The white matter disruptions appear to be determined by shared genetic risk factors.
ID: 546715

PRINCIPAL COMPONENTS ANALYSIS OF CORTICAL THICKNESS IN SCHIZOPHRENIA AND RELATIONSHIP WITH CLINICAL SYMPTOMS

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Background: Thinning of the neocortex has previously been demonstrated in individuals with schizophrenia. In this study, we used principal components analysis (PCA) to examine the pattern of cortical thinning in schizophrenia subjects compared to healthy individuals. We hypothesized that cortical thinning would be more prominent in fronto-temporal regions. Method: 42 healthy participants and 42 subjects with schizophrenia were recruited from a ongoing longitudinal study of psychopathology, cognition and brain structure. Groups were matched for age, gender, race, education, handedness, and parental SES. Positive, Negative, and Disorganized symptoms domains were assessed using the SAPS and SANS. Structural data were processed using FreeSurfer 3.0.5 with user supervision. Cortical parcellations were obtained. PCA with Varimax rotation on cortical thickness was conducted for each hemisphere. One-way ANOVAs were performed on the principal component scores for group

analysis. Pearson correlations were calculated between the PCA scores and clinical symptoms. Results: Across both groups of subjects, a left hemisphere PCA yielded 6 components that explained ~70% of variance. Based on variable loadings, the LH components are described as: Lateral-medial Parietal/Occipital, Superior Medial Frontal, Dorsal Medial Frontal, Lateral Temporal, Ventolateral Frontal, and Anterior Temporal. A RH PCA yielded 6 components that explained ~70% of variance. These are described as: Dorsolateral Parietal/Temporal, Dorsolateral-medial Prefrontal, Dorsomedial Parietal/Occipital, Cingulate Cortex, Ventral Temporal, and Ventromedial Occipital. The RH Dorsolateral Parietal/Temporal component revealed a trend-level difference ($F = 6.01$, $P = .016$), while other components did not show group differences. This factor was negatively correlated with negative symptoms in the schizophrenia group ($r = -.355$, $P = .021$). Conclusions: Individuals with schizophrenia in this study exhibit a pattern of cortical thinning in parietal/temporal regions. Thinning in this region was correlated with more severe negative symptoms in the schizophrenia subjects. These findings lend support to the hypothesis that temporal and parietal heteromodal cortices play an important role in the pathogenesis of schizophrenia, and perhaps, in particular, the expression of negative symptoms. Support: MH071616 and MH056584.
ID: 546540

CLINICAL CORRELATES OF ANATOMICAL FRONTO-TEMPORAL DISCONNECTIVITY REVEALED BY TRACTOGRAPHY IN FIRST-EPISODE PSYCHOSIS

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Background: Changes in fronto-temporal anatomical connectivity have been proposed to be a central feature of pathophysiology in schizophrenia, with early occurrence. However, it remains unclear whether these changes exist early in the disease process during a first-episode of psychosis (FEP). Our study investigated whether baseline measures of white matter integrity, as assessed by diffusion tensor imaging (DTI) are related to symptom severity. Methods: Fifty-one FEP patients and 30 healthy controls completed DTI scans at baseline. FEP patients completed clinical assessments evaluated with SAPS and SANS. White matter integrity was assessed using fractionation anisotropy (FA) and total volumes. A probabilistic DTI-based tractography algorithm was used to generate tracts connecting frontal and temporal regions. Analyses focused on the uncinate fasciculus (UNC), the superior longitudinal fasciculus (SLF) and the cingulum. For the cingulum two separate segments were defined: the upper part along the cingulate gyrus (CGC: cingulum cingulate gyrus part) and the lower segment along the ventral side of the hippocampus (CGH: cingulum hippocampal part). Relationships between symptoms severity and structural values in areas showing between-group differences were also examined. Results: Volumetric measurements indicated no significant between-group differences in the three tracts. In contrast, lower FA values in FEP were observed for the UNC and the SLF, but not for both parts of the cingulum, relative to controls. With respect to symptoms, FA values for the UNC were inversely correlated with negative symptoms and positively correlated with positive symptoms. For the SLF, significant correlations emerged between FA values and negative, but not positive, symptoms. Conclusion: The FA decrease, associated with preserved volumes, in the UNC and the SLF suggests anatomical abnormalities of fronto-temporal connectivity in FEP, possibly resulting from disordered fiber networks or decreased neuropil density. These results also provide evidence that these early anatomical abnormalities are highly predictive of negative symptoms, and may constitute a predominant pathophysiological marker of psychosis.
ID: 550824

NO DIFFERENCES IN THE PREVALENCE OF CAVUM SEPTUM PELLUCIDUM AND ADHESIO INTERTHALAMICA BETWEEN FIRST-EPISODE PSYCHOTIC PATIENTS AND HEALTHY CONTROLS: A POPULATION-BASED STUDY

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Early neurodevelopmental alterations are considered one of the possible etiologic hypotheses for psychosis. Two of these abnormalities are the cavum septum pellucidum (CSP) and the absence of adhesio interthalamica (AI). Several magnetic resonance imaging (MRI) studies have investigated CSP and AI in psychosis, with conflicting findings. Differences in the prevalence of large CSP were seen in eight of 16 researches; and five of ten studies related higher incidence of non-AI in patients. Such discrepancies could be partly explained by differences in imaging techniques, CSP/AI definition criteria among the reports, and heterogeneity in the selection of the sample. For minimizing these contradictory results, recent works have employed more quantitative methods to analyze CSP e AI. However, there is no study that has carefully selected the subjects, particularly using a population-based sample. The objective of the present research was to evaluate, by using MRI, the CSP and the non-AI in first-episode psychotic patients, including a population-based sample in order to examine these alterations. The sample was composed by 122 first-episode psychotic subjects, who established contact with mental health services in the city of São Paulo between 2002 and 2005. For obtaining a population-based sample of controls, 94 next-door neighbors of each patient were invited to participate, matched on socio-demographic characteristics of cases. We investigated prevalence of small and large CSP (ie, ≥ 6 mm in length) and the volume of the cavity, as well as the incidence of non-AI. No significant differences were found between patients and controls in any of the measures of CSP and AI. Likewise, there was no association between these structures and neuropsychological tests. However, the absence of AI was higher among men when all the subjects were pooled together. This increased prevalence of non-AI in men is in agreement with the literature, given that sexual dimorphism seems to be related to abnormalities in this structure. On the other hand, the lack of differences between patients and controls in both CSP and AI data suggests that these abnormalities may not be neurodevelopmental markers of psychosis and cast doubt over the notion that they play a major role in the neurobiology of such disorders. Further, it emphasizes the importance of the strict selection of the sample, since bias in subject's recruitment could interfere in the results of case-control studies.
ID: 551903

STRUCTURAL CORRELATION OF THALAMIC ZONES WITH PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Abnormalities of the functional and anatomical relationships between the thalamus and dorsolateral prefrontal cortex (DLPFC) may be an important aspect of the pathophysiology of schizophrenia. However, relatively little is known about the patterns of structural correlation between the thalamus and DLPFC, particularly in regards to their sub-regions. Using high-resolution magnetic resonance images, we examined the correlation of sub-regions (ie, "zones") of the thalamic surface with gray matter volume of the three major gyri of the DLPFC—the superior (SFG), middle (MFG), and inferior (IFG) prefrontal gyri—in a group of 36 individuals with schizophrenia and 44 control subjects. Thalamic zones corresponding to the anterior, dorsal medial, pulvinar, and "remainder" portions of the thalamic surface were defined on a template thalamus, and automatically mapped onto the corresponding surface nodes of the thalamus of each subject using high-dimensional brain mapping. The product of the surface area of a zone with the average surface deformation of that zone (relative to a template) yielded a measure of volume change associated with each zone. The IFG, MFG, and SFG were delineated manually on the white matter surface of each subject, and gray matter volumes obtained for each gyrus by labeled cortical depth mapping. Left and right values for each thalamic zone and prefrontal gyrus were summed. MFG volume was positively correlated with the dorsal medial and remainder thalamic zones in the schizophrenia subjects (both Pearson's $r > 0.49$, $P < .003$), but not the control subjects ($|r| < 0.09$), such that the strength of these correlations differed significantly between the schizophrenia and control groups ($P < .03$ in a comparison of correlations using Fisher's z transformation). SFG volume was correlated with the anterior thalamic zone, but to a similar degree in both the schizophrenia and control subjects ($r = .46$ and 0.36, respectively). IFG volume was not correlated with any of the thalamic zones for either subject group. Notably, the correlation of the dorsal medial zone with MFG in schizophrenia subjects was stronger than with either of the other two prefrontal gyri ($P < .05$, using a one-tailed test for comparing correlated correlation coefficients). These results suggest that in schizophrenia, disease-related processes may affect the dorsal medial thalamus and middle prefrontal cortex in tandem, perhaps due to shared genetic and/or environmental influences.
ID: 551900

SEX DIFFERENCES IN CORPUS CALLOSUM FRACTIONAL ANISOTROPY IN SCHIZOPHRENIA PATIENTS: A PILOT TRACTOGRAPHY STUDY USING DIFFUSION TENSOR IMAGING

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The relative size of the corpus callosum (CC) is 5% larger in normal women compared to men. Studies in schizophrenia have shown that specifically the middle section of the corpus callosum (MCC) is larger in women compared to men. Very few studies attempted to investigate if volumetric findings are substantiated with intact white matter integrity. The aim of this study is to investigate white matter tract integrity in the MCC in patients with schizophrenia compared to healthy controls using fiber tracking and fractional anisotropy (FA) analyses. We scanned 17 men and 13 women with schizophrenia and controls matched for age and sex using Diffusion Tensor Imaging (DTI). Here we present the results in 2 women and 2 men with schizophrenia compared to healthy controls (2 women and 2 men). DTI analyses were performed using MedINRIA software (http://www.sop.

inria.fr/asclepios/software/MedINRIA/) to perform fiber-of-interest analyses using the "DTI Track module" of MedINRIA. White matter fiber tracts of MCC was created in 3D based on similarities between neighboring voxels in shape (quantitative diffusion anisotropy measures) and orientation (principal eigenvector map) of the diffusion ellipsoid. Our findings show that patients in general had lower FA, lower number of fibers and lower bundle volume compared to controls (mean volume = 4098 m^3; mean number of fibers = 373.5; mean FA = .62). Men in both groups had higher scores on the 3 items analysed except for FA which was only higher in healthy men compare to healthy women. Our results in the schizophrenia group are in accordance with previous findings on reversed normal sexual dimorphism in these patients. Nevertheless, results for healthy controls are not in accordance with volumetric findings of the CC, and suggest that DTI approaches could lead to differential results compared to other structural methods. These results should be interpreted with caution considering the small sample size and until a complete analyses is performed on all scanned subjects.
ID: 551877

MAPPING OF CORTICAL AREA 46 LAMINAR BOUNDARIES IN MRI VOLUMES: A METHOD DEVELOPED TO STUDY THE PRENATALLY IRRADIATED MACAQUE

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We have previously developed a multistep registration process to transfer cytoarchitectonic boundaries from high resolution photographic images of histological sections to ante-mortem magnetic resonance (MR) subvolumes of the same brain. Here we extend this methodology to transfer laminar boundaries from area 46, as identified in the histological sections, to the MR subvolumes. This process capitalizes on the strengths of both techniques as postmortem analysis of Nissl-stained sections allows precise localization of layer boundaries while volumetric analysis in the MR subvolume permits determination of the layer volumes that are not shrunken or distorted by postmortem fixation and processing. The motivation of this work is to develop a methodology that can be used to specifically identify the laminar pattern of cortical pathology in prenatally irradiated monkeys. We acquired MR *in vivo* volumetric scans of nine adult macaque brains with a resolution of 0.625 x 0.7 x 0.625 mm/voxel. A series of celloidin-embedded, 40μm thick Nissl-stained sections (approximately stereotactic) through the frontal lobe was generated from these same animals postmortem. High resolution digital photographic images (0.005534x0.005534 mm2/pixel) were acquired without any external reference point for each histological section. In the registration process, the MR scans were first reoriented to AC-PC orientation. Then the histological sections were used to manually segment the boundaries of area 46 and the boundaries between layer I/II and IV/V. Each histological section and its proximal MR section were landmarked to reconstruct a 3D histological image based on low dimensional affine transformations of the landmarks. LDDMM (large deformation diffeomorphic metric mapping) landmark matching was used to further align the reconstructed 3D histological volume to the 3D MR image subvolume, to overcome the difference in brain slicing orientation. LDDMM image matching was used to complete the registration. Volumetric analysis of layers in the MR subvolumes will be undertaken to determine whether cortical pathology in area 46 is restricted to infragranular or supragranular layers in the prenatally irradiated monkey. The combined use of *in vivo* neuroimaging analysis and postmortem cytoarchitectonic delineation of layer boundaries may have a wider application to study of neuro-

psychiatric diseases such as schizophrenia and affective disorders. Grants: P50 MH071616, P41 RR15241, R01 MH59329.
ID: 551867

HERITABILITY OF CORTICAL THICKNESS CHANGE OVER TIME IN SCHIZOPHRENIA PATIENTS AND THEIR DISCORDANT CO-TWINS

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Introduction: Structural brain abnormalities have consistently been found in schizophrenia, with increased familial risk for schizophrenia having been related to these abnormalities.1 Some brain volume changes are progressive over the course of the illness.2 Here we demonstrate that genes involved in the etiology of schizophrenia contribute to progressive brain volume loss observed in the patients and in their co-twins.3 This study is currently being extended with cortical thickness measurements. Methods: Two 1.5 T MRI brain scans were obtained from monozygotic (MZ) and dizygotic (DZ) twins discordant for schizophrenia (23 MZ and 23 DZ subjects) and matched healthy comparison twin pairs (29 MZ and 27 DZ subjects) with a scan interval of 5 years. Brain volumes were measured of the whole brain, gray and white matter of the cerebrum, cortical lobes, and lateral and third ventricles. Cortical thickness is estimated based on the algorithm designed at the McConnell Brain Imaging Centre of the Montreal Neurological Institute. Brain structure changes and disease and familial related effects in schizophrenia were analyzed using repeated measures analysis of co-variance and structural equation modeling with Mx software. Results: Significant additive genetic influences were revealed on the correlations between schizophrenia liability and whole brain, frontal and temporal lobe volume change. First analyses of cortical thickness show a difference in the extent of cortical thickness change in the sensorimotor cortex bilaterally and left orbitofrontal cortex in the discordant twin-pairs as compared to the healthy comparison twin-pairs. This change may be attributable to familial (possibly genetic) factors. Moreover, additional areas of more extensive change were found in frontal cortex bilaterally, which could be attributed to disease-related factors. Conclusions: The progressive brain volume loss found in patients with schizophrenia and their unaffected co-twins is at least partly attributable to genetic factors related to the illness. Influence of disease-related factors on cortical thickness change in some areas is also suggested.This research was supported by Grant No. 908-02-123 (HEH) from the Netherlands Organization for Health Research and Development ZonMw.

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ID: 551814

LATERAL VENTRICLE VOLUMES AS A NEURAL MARKER OF SHORT-TERM CLINICAL OUTCOME IN FIRST EPISODE SCHIZOPHRENIA

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Background: Abnormalities in brain morphology have been consistently described in schizophrenia with increased ventricular volumes being related to poor long-term clinical outcome. Very few studies have focused on short-term clinical outcome. In this study, we explored whether or not baseline lateral ventricle volumes are related to short-term clinical outcome. Methods: Ventricle volumes were manually segmented in 50 first episode schizophrenia (FES) patients with baseline MRI images. The patients were separated into 37 poor outcome and 13 good outcome patients. Good outcome was defined as a rating of 2 or less (mild) on all global subscales of the SAPS and SANS, except "attention", using six month clinical data. Results: At baseline, there were no significant differences in ventricular volumes between outcome groups. See Table 1 for results. Conclusions: Despite a numerical difference between the groups, this non-significant result suggests that ventricle volumes measured at baseline may not be related to short-term clinical outcome.

Table. Lateral ventricle volumes in poor outcome and good outcome FES [mean (SD)].

	Poor Outcome	Good Outcome	p-value
Left Ventricle	11021 (5941)	9927 (3778)	0.54
Right Ventricle	10732 (7305)	9630 (3053)	0.60

ID: 551795

CORTICAL GYRATION INTERACTS WITH TIME AND GENDER IN OFFSPRING OF SCHIZOPHRENIA SUBJECTS

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Background: Genetic factors may contribute to the etiology of schizophrenia (SZ) by affecting the neurodevelopment. A systematic study of adolescent offspring of SZ subjects (HR) before they manifest the illness could clarify neurodevelopmental antecedents associated with increased genetic risk. The cortical gyration indices may be such antecedents. We examined cortical surface area, curvature and thickness at baseline and one year among HR and matched healthy subjects (HS). Methods: Structural magnetic resonance scans were acquired on a series of HR ($n = 31$) and HS ($n = 33$). Of these, 15 HS and 16 HR underwent follow up scans after one year. Images were processed using BRAINS2. Lobewise cortical surface areas, thickness and curvatures were obtained from all these scans. We used MANCOVA models by including age, total brain surface area and gender as covariates to examine the differences between the groups at baseline and one year follow up. Results: Total brain surface area did not differ significantly between the two groups. Separate MANCOVA models that included lobar surface area, curvatures and thickness at the gyri and sulci controlling for age, sex and total brain surface area were each significant. Bilateral parietal gyral surface was reduced and sulcal curvatures were increased in HR compared to HS. HR showed reduced right parietal cortical thickness relative to HS. We observed a significant gender by study group interaction at the bilateral frontal sulcal mean curvatures such that male HR showed reduced right and left frontal sulcal curvature compared to male HS, and female HR showed increased right and left frontal sulcal curvature and right occipital gyral curvature compared to female HS. Repeated measures MANCOVA models showed that the right frontal gyral surface increased among HS whereas it decreased among HR over one year follow up. Similar patterns were observed at the occipital and parietal regions. Discussion: The main finding is that the HR show systematic differences in the parieto-occipital regions before the onset of the illness. This heteromodal association area is implicated in the integration of multimodal sensory inputs. Gender and risk status interaction at the frontal and occipital regions suggest that gender may have a pathoplastic effect. Frontal, occipital and parietal regions appear to follow different neurodevelopmental trajectories among HR compared to HS. Correlation with psychopathology and soft signs are being examined.
ID: 551780

SYMPTOM INSIGHT AT THE FIRST ONSET OF PSYCHOSIS: NEUROCOGNITIVE CORRELATES AT BASELINE AND FOLLOW-UP

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The capacity to correctly identify and attribute psychotic symptoms as pathological (symptom relabelling) may be the component of insight most closely associated with neurocognition. We compared the neurocognitive profile of first onset psychosis patients with no symptom relabelling ability to those with at least some symptom relabelling ability in 204 patients (124 males; mean age 29 SD 10; 90 schizophrenia) recruited from London, Nottingham and Bristol as part of the AESOP first-onset psychosis study. Patients were rated on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, 2.0), David's insight schedule and a neuropsychological test battery rating IQ, working memory, attention and verbal fluency. Structural MRI scans were acquired from a sub-sample of the patients at baseline ($n = 82$) and six years later ($n = 41$) using a Dual Echo sequence acquired with a 1.5T scanner. Brain volumes were measured with a voxel-based automated analysis. ANCOVA showed that at baseline patients with no symptom relabelling scored significantly lower than patients with at least some relabelling ability on NART ($P < .01$), FSIQ ($P < .01$), verbal fluency ($P < .05$), Trails A ($P < .05$) and auditory working memory, ($P = .001$). Baseline MRI analysis showed total grey tissue volume in patients with no symptom relabelling ability group was 6.7% lower than in patients with at least symptom some relabelling ability ($P = .01$). Significant regional reductions in grey tissue volume were also identified in the no symptom relabelling ability group at: 1) left insula, 2) right putamen, 3) left superior temporal gyrus, 4) bilateral posterior cingulate gyrus and 5) right pre-cuneus ($P = .002$). ANCOVA at six years follow-up showed no significant differences between patients with no baseline symptom relabelling ability and those with some baseline symptom relabelling ability in 1) global grey and white matter volume changes over the follow-up period and 2) global grey matter and global white matter volumes at time of follow-up scan. Our findings suggest a neurocognitive contribution to poor symptom relabelling ability during the first episode of psychosis, and implicate brain regions (eg, cingulate gyrus) which may be part of a mid-line cortical system involved in the self-appraisal of psychotic symptoms. The study however, found no evidence to suggest symptom relabelling ability at the first onset of psychosis is predictive of global brain matter changes over a six-year period.
ID: 551738

ANATOMICAL CORRELATES OF THOUGHT DISORDER IN SCHIZOPHRENIA: A FREESURFER STUDY

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Background and Objectives: Neuroimaging has delineated differences between subjects with schizophrenia and healthy controls, but correlating symptoms to structural changes has been difficult. We sought to describe relationships between thought disorder and cortical measures using an automated brain parcellation technique. We hypothesized we would find decreased cortical gray matter in the left superior temporal gyrus, an area previously associated with thought disorder. Methods: T1-weighted magnetic resonance images were obtained from 52 subjects with schizophrenia and were parcellated automatically using FreeSurfer software. Thought disorder was measured using the Scales for Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS). 33 regions were examined bilaterally to test relationships between gray matter decreases and severity of thought disorder. Results: We did not find significant correlations between structural measures of the left superior temporal gyrus and thought disorder. We then examined other variables in an exploratory fashion. Regions clustered in the inferior frontal, temporal, and temporo-occipital areas showed inverse correlations at the $P < .05$ level between gray matter thickness and thought disorder severity. The right parahippocampal gyrus, left lateral occipital cortex, and the right isthmus of the cingulate correlated negatively with symptoms in more than one structural measure. We confirmed a previously reported association between thought disorder and the inferior frontal gyri. Conclusions: Despite failing to replicate previous findings associating the left superior temporal gyrus with thought disorder, we did observe a number of inverse relationships between reduced cortical gray matter and thought disorder. The large number of variables tested increased the chances that correlations would achieve numerical significance in the absence of true relationships. Nevertheless, unambiguous trends towards inverse correlations between severity of thought disorder and cortical thickness emerged. Many of the affected areas, while not reaching statistical significance individually, nevertheless clustered together, especially in the temporal lobes and around the cingulate cortex. It is especially intriguing that two of the regions that were found to be affected bilaterally in this study (the lingual gyrus and the isthmus of the cingulate) are contiguous structures. Further studies will need to confirm these findings.
ID: 551735

REGIONAL PREFRONTAL CORTICAL GRAY MATTER VOLUMES IN ADOLESCENTS AND YOUNG ADULTS AT FAMILIAL RISK FOR SCHIZOPHRENIA

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Regional prefrontal cortical (PFC) gray matter (GM) reductions have been identified in magnetic resonance imaging (MRI) and postmortem studies of schizophrenia, and likely reflect a combination of genetic risk and disease effects, as well as age-related changes in the disorder's lifelong neurodevelopmental course. This is the first region-of-interest MRI study of PFC GM subregions in young biological relatives of schizophrenia patients. We hypothesized that reduced dorsolateral and ventromedial PFC GM would mark genetic risk for schizophrenia in adolescence (using family history as a proxy for genetic risk), and that ventromedial PFC GM deficits would also be associated with subpsychotic symptoms. Twenty-seven "familial high-risk" (FHR) adolescent relatives of schizophrenia patients and forty-eight "familial low-risk" (FLR) adolescents without a family history of psychosis underwent MRI scanning at 1.5 Tesla. The PFC was parcellated into polar, dorsolateral, ventrolateral, ventromedial and orbital subregions. The Chapman scales measured subpsychotic symptoms. General linear models examined PFC volume associations with familial risk and subpsychotic symptoms. For subregions that differed between risk groups, exploratory age regressions tested differences in slope and intercept between groups. Statistical significance level was .05. FHR adolescents had significantly reduced GM volume compared with FLR adolescents in ventromedial and polar PFC. Ventromedial GM was significantly negatively correlated with psychosis proneness scores within the FHR group. The intercepts of the regressions of age on polar and ventromedial GM were significantly lower in FHR than FLR adolescents. The slopes of the age regressions on polar PFC were similar, such that GM declined similarly with age in the two groups. The slopes of the age regressions on ventromedial PFC were different between groups at a trend level, such that FHR subjects did not show the GM decline with age seen within the FLR group. Ventromedial and polar PFC GM volume deficits may be markers of genetic risk for schizophrenia in young biological relatives. Ventromedial GM reduction may also mark the presence of subpsychotic symptoms in these relatives. Our findings suggest future avenues of research into age-related changes in neuroanatomical markers for schizophrenia: those that mark genetic vulnerability and those that may differentiate young relatives who develop psychosis.
ID: 551680

CHANGES IN GRAY MATTER VOLUME IN ROSTRAL MIDDLE FRONTAL GYRUS OF CHRONIC SCHIZOPHRENIA SUBJECTS

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Background: In this study we used structural MRI to determine volume differences in the mid-rostral middle frontal gyrus (MR-MFG) among chronic schizophrenia subjects and normal control subjects. MR-MFG is thought to be anatomically related to the Dorsolateral-prefrontal cortex (DLPFC), a functional site of working memory, which is one of the domains of cognitive feature and dysfunctional in schizophrenia. fMRI studies have shown reduced activation in this brain region in schizophrenia subjects performing working memory tasks, but the exact localization remains to be defined. Methods: 20 patients with chronic schizophrenia and 20 healthy controls, matched on age, handedness, and parental socioeconomic status, participated in this study. The acquisition of structural MRI was done on a 3-Tesla whole body MRI Echospeed system GE scanner. The images were processed using FreeSurfer tools (http://surfer.nmr.mgh.harvard.edu) and automated parcellation of brain regions was generated. Rostral MFG was then further delineated anteriorly and posteriorly using objective neuroanatomical landmarks. Gray matter volumes of MR-MFG were then compared between the schizophrenia and the normal subjects group and correlated with working memory tests. Results: MR-MFG was reduced in gray matter volume in patients with schizophrenia as compared with controls. Additionally, in the schizophrenia group

MR-MFG volume reduction in the right hemisphere correlated with poorer performance on the Wisconsin Card Sorting test, a measure of working memory. Discussion: These results support the theory that working memory abnormalities observed in schizophrenia are related to volume changes in MR-MFG and that MR-MFG is the anatomical site of DLPFC.
ID: 551569

DIFFUSION TENSOR IMAGING STUDIES OF SCHIZOPHRENIA PATIENTS, FIRST-DEGREE RELATIVES AND HEALTHY MZ TWINS

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Diffusion tensor imaging (DTI) provides anatomical connectivity information by examining the directional organization of white matter microstructure. Previous studies have suggested that anatomical connectivity and its abnormalities may be heritable traits. To further examine this hypothesis, two studies were conducted in which anatomical connectivity was compared (a) between monozygotic (MZ) twin pairs and random pairs and (b) between schizophrenia patients, their first-degree relatives and a healthy control group. Analyses focused on anterior regions of the brain following previous findings of anatomical connectivity abnormalities associated with schizophrenia. For Study 1, eighteen MZ twin pairs (11 female pairs, age: M = 25.44, SD = 5.69) were recruited. For Study 2, fourteen schizophrenia patients (4 females, age: M = 41.86, SD = 10.43), 12 of their first-degree relatives (6 females, age: M = 50.25, SD = 5.64), and 16 healthy controls (7 females, age: M = 37.31, SD = 11.09) were recruited. The primary DTI variable was fractional anisotropy (FA), which reflects the degree of white matter directional organization. The regions of interest in the frontal lobe included cingulum bundle and genu of corpus callosum. For study 1, voxel-wise correlations in the whole brain as well as in the ROI were conducted between (1) members of a MZ twin pair and (2) randomly generated pairs. For study 2, voxel-wise analysis of variance within the ROI was conducted to examine regional group differences. In Study 1, FA values were more strongly correlated between MZ twin pairs than between randomly generated pairs both in the whole brain as well as in the ROI. In Study 2, analysis of variance revealed significant overall group differences in the ROI ($P < .05$, corrected). Post-hoc analysis revealed lowest FA values in schizophrenia patients, and intermediate FA values in the relative group when compared to the control group ($P < .05$, corrected). The present study suggested that medial prefrontal cortex anatomical connectivity was moderately heritable, an important criterion in the development of an endophenotype. In addition, parametric abnormalities in white matter directional organization in this region suggested that altered anatomical connectivity may correspond to the level of genetic risk for schizophrenia.
ID: 551520

AMYGDALA VOLUME IN POOR OUTCOME FIRST-EPISODE SCHIZOPHRENIA: A MAGNETIC RESONANCE IMAGING STUDY

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Outcome from schizophrenia is heterogeneous. Of those that experience a poor outcome following a first-episode, a sub-group of patients can be identified that display persistent negative symptoms. Emotional dysfunctions are thought to be central to negative symptoms which may suggest the involvement of the amygdala. We investigated the association between amygdala volume and persistent negative symptoms (PNS) in the context of poor-outcome first-episode schizophrenia (FES) patients. Twenty subjects with FES underwent structural magnetic resonance imaging. They were separated into good (7) and poor (13) outcome groups based on six month clinical data as proposed by Andreasen et al. (2005). The poor outcome group was further sub-divided into patients presenting PNS (8) and patients who did not (5) according to a recently proposed definition by Buchanan (2007). Amygdala volumes were obtained through manual segmentation. Good and poor outcome groups did not differ in amygdala volume on either the right or left side. However, within the poor outcome group, the PNS sub-group showed a trend for larger left and right amygdala volumes compared to the non-PNS sub-group (left amygdala: $t_{11} = 1.87$, $P = .088$; right amygdala: $t_{11} = 1.88$, $P = .087$). From this small sample of FES patients, amygdala volume does not appear to have good predictive value for 6 month clinical outcome. However, it appears the amygdala is better for characterizing a sub-group of patients that will experience PNS. These preliminary results encourage the exploration of the amygdala and its possible role in negative symptoms that fail to remit.
ID: 551435

DURATION OF UNTREATED PSYCHOSIS PREDICTS POOR OUTCOMES BUT THIS IS NOT CAUSED BY GLOBAL BRAIN VOLUME CHANGES

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Background: Despite good evidence that longer duration of untreated psychosis (DUP) is associated with poorer outcome, it is not known whether DUP causes poor outcome and, if so, how. One theory is that long periods of untreated psychosis cause a deleterious impact on function through a 'toxic' effect on the brain: if one assumes that brain structure and function are linked, this model predicts that brain structural measures will be associated with length of DUP. This theory was tested here. Methods: 44 (28 male:16 female; 26 schizophrenia:18 other psychosis) subjects from an original cohort of 89 first episode psychosis patients, were re-scanned using Magnetic Resonance Imaging. Changes in tissue volume between baseline and follow-up were calculated, correcting for baseline whole brain volume. Results: Mean follow-up interval was 6.8 ($\pm$ 1.2) years. Median values: DUP = 6 weeks; duration of untreated illness (DUI) = 24 weeks. Grey matter volume decreased ($t = 4.72$; $P = .001$) and cerebrospinal fluid volume increased ($t = -3.48$; $P = .001$) over the follow-up period. Both longer DUP and DUI were significantly associated with a range of poorer outcomes at follow-up: greater global disability; higher likelihood of being psychotic; and of having had a continuous illness course. DUP and DUI were not significantly related to any tissue volume change in the entire sample or in the schizophrenia only subgroup. Discussion: The finding that longer DUP/DUI is associated with poorer clinical and functional outcome was replicated; however there was no evidence that this relationship was caused by changes in brain volume over time. If a toxic effect of DUP/DUI exists, it is not detectable in change in global brain tissue volumes over time.
ID: 551362

NEUROANATOMICAL CHANGE DURING COGNITIVE REHABILITATION: RESULTS FROM A TWO-YEAR TRIAL OF COGNITIVE ENHANCEMENT THERAPY

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Background: Cognitive rehabilitation has proven to be a promising method for addressing the social and non-social cognitive deficits experienced by individuals with schizophrenia. While the beneficial effects on cognition documented by a variety of approaches has a presumed neurobiologic basis, few studies have examined changes in neurobiology as a result of cognitive rehabilitation. We conducted a preliminary examination of neuroanatomical changes in gray matter in a sample of early course outpatients participating in a two-year randomized-controlled trial of Cognitive Enhancement Therapy (CET; www.CognitiveEnhancementTherapy.com). Methods: Outpatients in the early course of schizophrenia or schizoaffective disorder were randomly assigned and treated in a two-year trial with CET ($n = 30$) or an active Enriched Supportive Therapy (EST) control ($n = 23$), and assessed annual using structural magnetic resonance imaging and a comprehensive cognitive battery. CET is an integrated approach to the remediation of social and non-social cognitive deficits in schizophrenia that utilizes computer-assisted cognitive training and group-based secondary socialization techniques. EST focuses on illness management and stress reduction through an individualized psychotherapeutic approach. Results: Initial voxel-based morphometry analyses of gray matter change during the two-year trial indicated significant differential patterns of density change between treatment groups in a left hemispheric social-cognitive network cluster including the amygdala, fusiform, and parahippocampal gyrus. Subsequent volumetric analyses revealed that while individuals receiving EST showed a loss of gray matter volume in this social-cognitive network over the two years of study, patients receiving CET exhibit a preservation, and at times, significant increases in gray matter volume in these regions. Mediator analyses revealed that CET effects on social cognition could be indirectly accounted for, in part, by differential gray matter changes in the left amygdala/fusiform/parahippocampal gyrus social cognition network. Conclusions: CET is an effective approach for the remediation of social and non-social cognitive deficits in schizophrenia that may achieve its efficacy through acting on social cognition brain networks.
ID: 551352

PROGRESSIVE GM AND WM ABNORMALITIES IN CHILDHOOD-ONSET SCHIZOPHRENIA(COS)

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Structural neuroimaging studies in COS show profound parieto-frontal cortical GM loss during adolescence, where the pattern appears exaggeration of the normal GM maturation. Long term follow up shows that the GM loss slows with age and gets circumscribed to prefrontal and superior temporal cortices ($n = 84,197$ scans vs controls $n = 86, 220$ scans; age range 8–28yrs), mimicking a pattern seen in adult onset schizophrenia. Longitudinal analyses on healthy COS siblings ($n = 85,170$ scans) also show prefrontal and temporal GM deficits in early ages which normalize by age. Similar patterns of 'early deficits followed by their relative normalization in COS, and complete normalization in siblings' could suggest that the GM trajectory itself could be a trait marker. Candidate gene analyses support

these observations. For example, preliminary analyses comparing GM development in 59 COS subjects (160 scans), 36 healthy siblings(80 scans) and 183 healthy controls (221 scans) showed that subjects with GAD1 risk allele had accelerated GM loss across the three groups over most cortex. However, Group*Risk*Age interaction showed COS and healthy siblings without risk allele had slower rate of GM loss compared to those with the risk allele (a difference not seen in controls) suggesting a role for epistatic factors. Sub regional cerebellar maps in 85 COS subjects (206 scans), 78 healthy siblings, and 95 matched healthy controls (225 scans) show significant 'sub regional' decline in volume with age, while the vermal regiosn showed fixed deficits. The volume loss is shared by healthy COS siblings in the posterior inferior cerebellar regions (compared to the same set of controls) suggesting the trait nature of these changes at sub regional level. Finally, it is important to understand the progressive nature GM changes in the context of underlying white matter (WM) development. Our recent 3-D maps of local WM growth rates in 12 COS patients and 12 healthy controls matched for age, gender and scan interval, over a 5-year period, show up to 2.2% slower WM growth per year in COS ($P = .02$, all P-values corrected). The deficits appear early in the frontal regions and later in the parietal regions suggesting a progressive abnormality that follows the normal front to back WM developmental pattern. In addition to highlighting significant WM growth deficits in COS, these findings also suggest that the cortical GM loss in schizophrenia is unlikely to be the result of WM encroachment.
ID: 551328

INTERNAL CAPSULE ANISOTROPY AND TRACTOGRAPHY IN THE SCHIZOPHRENIA SPECTRUM

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Volume reductions of the thalamus (esp. mediodorsal nucleus) and prefrontal cortex have been demonstrated, and more recently also the internal capsule. Here we used diffusion tensor imaging and tractography to assess the anterior limb of the internal capsule, which provides the connections between the two brain regions. We obtained structural 3T MP-RAGE anatomical and diffusion tensor MR images on 111 patients with schizophrenia (mean age = 36.8 years, 79 men, 32 women), 29 patients with schizotypal personality disorder (mean age = 36.6 years, 17 men, 12 women), and 222 healthy controls (mean age = 31.3 years, 114 men, 108 women). Placement of anatomical images in standard AC-PC position, coregistration of DT images to the anatomical images, computation of anisotropy and of tract angles was done with FSL. We manually traced the axial slice of the anterior limb of the internal capsule at the dorsoventral level of the dorsoventral midpoint of the thalamus on the structural MRI. We oriented the tracing of the 3D vectors from the internal capsule toward the prefrontal cortex. Beginning with the anterior limb of the internal capsule region of interest, we counted the number of tracts which arrived through a 20x20mm vertical frame positioned 25% of the distance between the anterior tip of the internal capsule and the anterior most point on the brain, a distance typically of 40–60mm and approximately centered on the anterior thalamic radiations. Significantly more tracts arrived through the frame on the left side of the brain than on the right in all groups. Patients with schizophrenia had the greatest asymmetry (17 fewer on the right), patients with schizotypal personality second greatest asymmetry (10 fewer on the right) and normal controls the least asymmetry (7 fewer on the right; hemisphere×group interaction) and this was most marked in female patients. When voxels over the 0.3 anisotropy threshold were counted, patients with schizophrenia had fewer voxels than healthy controls. Taken together, this data is consistent with a deficit in the fronto-thalamic circuit in schizophrenia.
ID: 551300

WHITE MATTER ABNORMALITIES IN FIRST EPISODE OF PSYCHOSIS: A DTI STUDY

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Schizophrenia has been presented as a disconnectivity disorder. There is some evidence in the literature of white matter (WM) abnormalities in chronic psychotic patients. We aimed in this study to see whether there are differences in white matter integrity between patients recently diagnosed with a First Episode of Psychosis (FEP) and healthy volunteers. In order to assess WM integrity fractional anisotropy (FA) was measured using Diffusion Tensor Imaging (DTI). FA is a measure of anisotropic diffusion of water molecules in tissue and reflects the directional coherence of the fiber tracts thus white matter organization. Sixty-two patients with a First Episode of Psychosis (FEP) (31 M, 30 .8 ± 9.5 yo) and fifty-six matched control subjects (34 M, 30.1 ± 8.1 yo) underwent a DWI-MRI study. Subjects were right-handed and not drug or alcohol dependent. Imaging acquisition was performed on a 1.5T GE: EPI (25 directions, b = 1000s/mm2). Image Analysis: Voxel-based analyses of fractional anisotropy were done using in-house software with group mapping utilizing SPM2, and non-parametric statistical analyses in XBAMv3.4 (voxel significance P = .025; cluster significance P = .0001). Reduced fractional anisotropy was found in FEP when compared with the healthy control group on the Corpus callosum (Genu bilaterally and left body but not splenium), left external and posterior limb of the internal capsule, left superior longitudinal fascicle and left inferior fronto-occipital fasciculus. FA was also reduced Forceps Minor. There was not found any region where FA was greater in FEP than the control group. Our results show that reduction in white matter organization is already present in the onset of the illness, mostly in the left hemisphere. Abnormal connectivity can play a role in the pathophysiology of schizophrenia.
ID: 551144

AUDITORY CORTICAL VOLUME AND LOUDNESS OF AUDITORY HALLUCINATIONS IN SCHIZOPHRENIA

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We aimed to investigate the relationship between anatomy of the auditory cortex and perceived loudness of auditory hallucinations in people with schizophrenia. Nineteen patients with schizophrenia (mean ± SD age = 40.7 ± 10.5 years) and marked auditory hallucinations participated (mean Scale for the Assessment of Positive Symptoms global hallucination severity rating = 3.7 ± 0.7). On the day of scanning, each completed a visual analogue scale to describe the loudness of their auditory hallucinations (ranging from 'absent' to 'as loud as the loudest shouting'). Structural images were acquired on a 1.5 T Eclipse system (T1-weighted RF-FAST sequence; 190 slices; 1 x 1 x 1 mm voxels). Temporal lobe volumes-of-interest were measured using stereology implemented in Analyze 8.1 (Mayo Foundation, Minnesota). We measured left and right Heschl's gyrus (HG) and planum temporale (PT) volumes. Between-hemisphere differences in volumes were assessed using paired t-tests. Within the group, we ran bivariate correlations between measured volumes-of-interest and loudness ratings. Heschl's gyrus was significantly larger on the left than the right (13.7 ± 3.5 ml versus 11.8 ± 2.8 ml; t = 3.6; P = .002). There was no significant difference between left and right PT volumes (13.6 ± 2.8 ml and 13.8 ± 2.8 ml, respectively; t = 0.4; P = .670). The volume of left HG was positively correlated with hallucination loudness (r = 0.5; P = 0.035). Previous work has shown auditory hallucinations to be associated with smaller auditory cortical structures, including the superior temporal gyrus (Barta et al., Am J Psychiatry 1990; 147: 1457–1462). Our data suggest that within a group with auditory hallucinations, some relative preservation of Heschl's gyrus is associated with louder hallucinations. This is compatible with the idea that auditory hallucinations are abnormal perceptions, experienced as perceptions because their mechanism implicates cortex involved in normal perception.
ID: 551106

RELATIONSHIP BETWEEN ANTIOXIDANT STATUS AND BRAIN VOLUMES IN CHILDREN AND ADOLESCENTS WITH FIRST EPISODE PSYCHOSIS

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Background: Brain volume abnormalities and oxidative cell damage have been reported to be pathological characteristics of schizophrenia patients. This study aims to assess a potential relationship between these two characteristics in child and adolescent patients with first-episode psychosis. Method: 26 child and adolescent patients with first-episode early-onset schizophrenia, 14 with first-episode early-onset psychotic bipolar disorder, and 78 age- and gender-matched healthy controls were assessed. Magnetic resonance imaging (MRI) scans were used for volumetric measurements of five cerebral regions: gray matter of the frontal, parietal, and temporal lobes, sulcal cerebrospinal fluid (CSF), and lateral ventricles. Oxidative cell damage was traced by means of a systemic increase in lipid hydroperoxides. (LOOH). Results:Lateral ventricle volumes were significantly higher in schizophrenia patients than in controls. LOOH was significantly higher in bipolar patients than in controls. Brain volumes and oxidative cell damage were not significantly different between schizophrenia and bipolar patients. In schizophrenia patients, a significant positive relationship was found between oxidative cell damage (LOOH levels) and the abnormal enlargement of the lateral ventricles, after controlling for total intracranial volume, age, gender, daily smoking status, intelligence quotient (IQ), psychopathology, and time since onset of psychotic symptoms. No association was found between brain volume and oxidative cell damage in bipolar patients or control subjects. Conclusions: Our results suggest that, in

patients with first-episode early-onset schizophrenia, enlargement of the lateral ventricles is associated with chronic oxidative cell damage.
ID: 551091

AGE-RELATED CHANGES IN CORTICAL THICKNESS IN PATIENTS WITH SCHIZOPHRENIA: A 5-YEAR LONGITUDINAL MRI STUDY ACROSS THE COURSE OF ILLNESS

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Schizophrenia is characterized by excessive reductions in cerebral gray matter volume. Also, patients with schizophrenia show decreases in cortical thickness (CortT) as compared to healthy subjects. However, it is unresolved whether these changes are static or progress over time. Moreover, In case of excessive change in patients with schizophrenia it is investigated whether these changes are influenced by age. Two Magnetic Resonance Imaging T1 brain scans were obtained with an interval of 5 years from 96 schizophrenia patients and 113 healthy controls (age 16–57 years). In-house software was used to segment cerebral gray (GM) and white matter (WM). These segments were used as input for an advanced neural net classifier. A surface deformation algorithm was applied that first fits the white matter surface and then expands outward to find the gray matter-cerebrospinal fluid intersection (software Montreal Neurological Institute: CLASP). For each subject, CortT change is calculated for every vertex. Group difference in CortT change is calculated by using regression analyses with age and gender as covariates. The statistics were corrected for multiple comparisons by applying a false discovery rate of alfa = 0.05. Regression analysis in the form of a locally-weighted running-line smoother will be used to obtain the dependence of volume changes on age. Software for these analyses has been developed in house. For each group fits with different degrees of freedom (df) will be calculated for each vertex to find the one that described the data best. Excessive decreases in CortT in patients relative to controls were found predominantly in the frontal and temporal cortices ranging from 0.08 to 0.16 mm at vertices with the highest F-values. Parietal and occipital cortices were relatively spared. Excessive cortical thinning seemed more pronounced in the left hemisphere, particularly in the left frontal cortical areas. These findings are in line with earlier longitudinal volumetric and voxelbased morphometry studies suggesting progressive changes in schizophrenia patients in particularly frontal and temporal areas in the brain. We expect to find differences in age-related cortical thickness change between patients with schizophrenia and comparison subjects which would be suggestive for abnormal maturation of the brain in adult schizophrenia.
ID: 551081

OBSTETRIC COMPLICATIONS, GENETIC VARIATION AND HIPPOCAMPAL VOLUMES IN SCHIZOPHRENIA

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We retrospectively studied the effect of severe obstetric complications (OCs) on hippocampal volumes in schizophrenia patients and healthy control subjects, and examined to what extent such effects depends on allele variation in hypoxia-related genes. Fifty-four adult subjects with schizophrenia and 54 healthy control subjects were MR scanned, genotyped and assessed for OCs. Hippocampal and intracranial volumes were quantified by automated processing of MR images with the FreeSurfer software. Genomic DNA was extracted from whole blood samples. Forty-nine single nucleotide polymorphisms (SNPs) spanning five hypoxia-regulated genes (GRM3, BDNF, DTNBP1, NRG1 and PRODH) were genotyped with the Illumina BeadStation 500GX and the 1536-plex Illumina Golden Gate assay. Presence of OCs was determined from birth records, and scored blindly according to the McNeil-Sjöström scale. Severe OCs was defined as presence of at least one grade 5 complication. The effects of intracranial volume, age and disease on hippocampal volume were accounted for in the statistical analysis. As previously demonstrated hippocampal volumes were smaller in affected individuals than in healthy controls (P = .003). Surprisingly, individuals who had experienced severe OCs had larger hippocampal volumes than individuals who had not (P = .04), and this effect was independent of disease status (pdisease*OC = 0.37). None of the examined SNPs was associated to hippocampal volumes. However we noted that enlarged volumes of the right hippocampus in individuals who had experienced severe OCs were strongly associated with two GRM3 SNPs located in intron 1 (pSNP*OC = 0.0002). In this group, the nine carriers of the minor alleles had a clearly larger volume of the right hippocampus than subjects without OCs, whereas the 17 non-carriers had volumes similar to subjects without OCs. The volume of the left hippocampus showed a similar, but weaker association (pSNP*OC = 0.04). As a result, a combination of severe OCs and these GRM3 alleles related to a significantly disturbed hippocampal laterality (P = .001). Although the interaction between GRM3 and severe OCs was highly significant, and withstands Bonferroni correction, the finding must be viewed as preliminary due to limited sample size. The present study suggests that there might be an interaction effect between severe OCs and genetic variation on hippocampal size, but findings need further replication.
ID: 551079

IS THE THALAMUS SMALLER IN PATIENTS WITH SCHIZOPHRENIA? A VOXEL—BASED MORPHOMETRY STUDY

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Background: Previous studies have suggested a reduction of the thalamus in patients with schizophrenia (1) This reduction could be related specifically with auditory hallucinations (2). The aim of the present work is to replicated this findings in a larger clinically homogenous sample. Methods and Materials: 33 patients with DSM-IV schizophrenia with auditory hallucinations and 38 healthy paired subjects (same age, ethnic group [Caucasian], educational level [secondary school] and handedness [all right handed]) entered the study. All underwent a clinical evaluation and Magnetic Resonance imaging (1.5T) examination. Images were acquired with a spoiled gradient-echo pulse sequence. Data were processed according to VBM optimized protocol and statistically analyzed with the Statistical Parametric Mapping software (SPM5). Results: No significant gray matter (GM) differences were found in the thalamus when comparing

schizophrenic patients with auditory hallucinations and control subjects ($P < .05$ with False Discovery Rate correction). Conclusions: We were unable to find thalamic morphometrical changes in patients with schizophrenia and auditory hallucinations compare with control subjects. So our results do not support previous findings

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ID: 551067

PROGRESSIVE GRAY MATTER REDUCTION OF THE SUPERIOR TEMPORAL GYRUS DURING TRANSITION TO PSYCHOSIS

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Longitudinal magnetic resonance imaging studies have shown progressive gray matter reduction in superior temporal gyrus (STG) during the earliest phases of schizophrenia. It is unknown whether these progressive processes predate the onset of psychosis. We examined gray matter reduction of the superior temporal gyrus over time in individuals at risk for psychosis (UHR) and first-episode psychosis (FEP) patients. Subjects included: 35 UHR individuals (12 later developed psychosis [UHRP] and 23 did not [UHRNP]), 23 first-episode psychosis (FEP) patients, and 22 controls. Volumes of STG subregions (planum polare, Heschl's gyrus, planum temporale [PT], and rostral and caudal regions) were measured at baseline and follow-up (mean, 1.8 years) scans. Cross-sectional comparisons: only FEP had significantly smaller PT and caudal STG than other groups at baseline, while male UHRP subjects had smaller PT compared to controls at follow-up. Longitudinal comparisons: UHRP and FEP patients showed significant gray matter reduction (2–6%/year) in the planum polare, planum temporale, and caudal region compared with controls and/or UHRNP. FEP patients also exhibited progressive gray matter loss in left Heschl's gyrus (3.0%/year) and rostral region (3.8%/year), which were correlated with severity of delusions at follow-up. These data indicate that a progressive process in the STG precedes the first expression of florid psychosis. These findings provide further evidence for progressive structural changes in temporal lobe regions at the earliest stages of psychotic illness (Pantelis et al. Schizophr Bull, 2005), and have implications for early intervention during or before the first episode of psychosis.
ID: 551051

NEURAL PLASTICITY AND STRUCTURAL BRAIN CHANGE IN SCHIZOPHRENIA: ARE WE ASKING THE RIGHT QUESTIONS?

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There is growing evidence that structural brain change can be detected in healthy volunteers following short-term changes in physical and/or cognitive activity. Colcombe et al. (2006) showed that significant increases in brain volume could be detected in healthy elderly volunteers following six months of aerobic exercise training, including the anterior cingulate, right inferior frontal gyrus and the left superior temporal gyrus. Draganski et al. (2006) studied medical students who showed significant increases in gray matter in posterior and lateral parietal regions whilst studying highly abstract information, and a more pronounced increase in the posterior hippocampus three months after their exams. Ilg et al. (2008) showed that increased gray matter following practice in mirror reading was associated with decreased activation in in the right superior parietal cortex and increased activation in the right dorsolateral occipital cortex that was linked to increased task-related gray matter increases in young healthy volunteers. Boyke et al. (2008) found gray-matter changes in the middle temporal area of the visual cortex in healthy elderly subjects and young healthy volunteers who learned a juggling task. Additional transient increases in gray matter in the left hippocampus and bilateral nucleus accumbens were found in elderly volunteers who learned to juggle. Taken together, these data suggest alternative explanations for longitudinal structural and functional brain changes described during the transition to psychosis or observed in longitudinal studies of patients with established schizophrenia. Such studies involve patients whose physical or cognitive activity has changed over the time intervals between repeat scans, and the results obtained may reflect changes in inter-scan activity rather than changes in diagnostic status (reflecting changes in psychopathology) or treatment effects as are currently posited to explain the structural and functional changes reported in studies of first episode psychosis or schizophrenia. It is possible that treatment-related changes in metabolic status may also impact on physical fitness in patients with first-episode psychosis or schizophrenia, leading to further variance in observed structural functional brain changes.

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ID: 551045

ENDOPHENOTYPES FOR SCHIZOPHRENIA AND BIPOLAR DISORDER DETERMINED USING BRAIN IMAGING

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Structural and functional brain abnormalities have been identified in both schizophrenia and bipolar disorder and some of these findings may be relevant to their predominantly genetic aetiology. Using structural and functional imaging, individuals with schizophrenia, bipolar disorder, their relatives and those at high risk for genetic reasons will be compared with a view to identifying heritable endophenotypes. Secondly, the neural correlates of specific susceptibility-associated genes for both schizophrenia and bipolar disorder will be identified by comparing those with and without the risk genotypes. Our results show that schizophrenia and bipolar disorder are characterised by largely shared structural findings and largely separate functional findings. These findings are also related to susceptibility variants in the genes encoding NRG1 and G72. These findings suggest that strategies targeted to the identification of specific and overlapping endophenotypes may be a fruitful means of understanding the genetic mechanisms underlying these disorders.
ID: 551032

PROGRESSIVE BRAIN CHANGES IN EARLY-ONSET PSYCHOSIS

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Progressive loss of cortical gray matter volume and increase in ventricular volume have been reported in patients with childhood-onset schizophrenia (COS) during adolescence. In addition, some studies show that, although less exaggerated, progressive changes are also present in non-schizophrenia early-onset psychosis. However, the previous studies were conducted in patients with early-onset schizophrenia or psychosis with a mean duration of illness of several years. In a multicenter, longitudinal, follow-up study of first-episode early-onset psychosis, we aimed to assess whether progressive changes were present in this less biased population and if the baseline or progressive changes were predictors of diagnosis or prognosis. Magnetic resonance imaging studies were obtained at baseline and 2 years later in 66 children and adolescents (mean age 15.5 ± 1.8) with a first psychotic episode and 93 healthy controls matched for age, gender, and years of education. Length of illness was 2.1 ± 1.7 months at the time of the MRI scan. The diagnosis was assessed with the K-SADS, both at baseline and at follow-up (2 patients had schizophrenia, 12 bipolar disorder, and 27 other psychoses). Whole-brain volumes and gray matter (GM) and cerebrospinal fluid (CSF) volumes of the frontal, parietal, temporal, and occipital lobes were measured at baseline and at 2-year follow-up. In the frontal lobe, the rate of GM volume loss was significantly higher in male patients (3.1% and 2.2%, respectively, at left and right) than in controls (1.4% and 0.9%, respectively, at left and right). In the left frontal lobe, male patients showed a significantly higher rate of CSF volume increase than controls (3.1% vs. 0.9%). These differences in volume change rates were observed in male and female patients, with significant time x group interactions. An exploratory analysis revealed that schizophrenia and non-schizophrenia psychotic disorders showed similar volume change patterns relative to controls. Change in clinical status did not correlate with longitudinal brain changes. Our results support progression of frontal lobe changes in males with childhood- and adolescent-onset psychosis.
ID: 551030

GREY MATTER VOLUME CORRELATES OF ACTIVITIES OF DAILY LIVING IN SCHIZOPHRENIA

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Schizophrenia is often associated with impairments of occupational and social functioning which may impact the individual's ability to live in the community. While many researchers have studied the association between lab-based neuropsychological performance and regional brain volumes in schizophrenia there has been less investigation of the relationship between regional brain volumes and 'real life', purposeful activities. In a prospective cohort study we acquired structural MRI scans to investigate the relationship between daily functioning, as assessed by the Instrumental Activities of Daily Living (IADL) scale (Lawton and Brody, 1969) and regional grey matter volumes. The IADL scale assesses performance in 8 domains comprising the ability to use a telephone, grocery shopping, preparing meals, doing laundry, getting to places beyond walking distance, doing housework, taking medications and managing money. 53 patients satisfying DSM IV diagnoses of schizophrenia or schizoaffective disorder were recruited, and underwent comprehensive neuropsychological assessment. Patients were 33 ± 7 years old, had an illness duration of 8.5 ± 6 years and a premorbid IQ of 105 ± 8. All patients completed the IADL scale with a member of the team by rating their present ability to perform specified tasks. Within a week of initial assessment, a high resolution 3D T1- weighted dataset was acquired in the sagittal plane, using a magnetization prepared rapid acquisition gradient echo (MP- RAGE) technique (TR = 10.5ms; TE = 4.8ms) at 3T. Imaging data obtained from scanning were processed using VBM in SPM2. IADL scores were entered into a simple regression analysis with whole brain grey matter segmented maps. Patients scored 13 ± 2.6 out of 16 on the IADL scale. Simple regression with IADL scores showed a correlation with reduced grey matter density in right dorsolateral prefrontal cortex (DLPFC; BA9), bilateral inferior prefrontal cortex (BA47), $P = .001$ uncorrected. These prefrontal regions have been implicated in such process as self monitoring, response reversal and suppression. Hence they may be involved in behavioural modulation in everyday life. Funded by MRC (UK), Career Establishment Grant to SAS.

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CORTICAL THICKNESS IN SCHIZOPHRENIA

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Introduction: Schizophrenia is characterized by excessive reductions in cerebral gray matter volume. Interestingly, in first-degree relatives the same abnormalities are found although less pronounced. Few studies have examined cortical thickness (CorT) in patients with schizophrenia but these include relatively small samples. Methods: Magnetic Resonance Imaging (MRI) brain scans were obtained from 159 patients and 158 healthy controls (age 16–57 years). In-house software was used to segment cerebral gray (GM) and white matter (WM) [1]. These segments were used as input for an advanced neural net classifier. A surface deformation algorithm was applied that first fits the white matter surface and then expands outward to find the gray matter-cerebrospinal fluid intersection (software Montreal Neurological Institute: CLASP [2]). For each subject, CorT is calculated for every vertex. Group difference in CorT was calculated by using regression analyses with age and gender as covariates. The statistics were corrected for multiple comparisons by applying a false discovery rate of alpha = 0.05. In a second independent sample we obtained Magnetic Resonance Imaging brain scans from 175 schizophrenia patients, 185 of their siblings and 125 healthy control subjects (age 17–56 years). The analyses of this second study will be done with Structural equation modeling. Results: Application of false discovery rate correction lead to significance thresholds of $F = 14.8$ (left hemisphere) and $F = 10.6$ (right hemisphere). In patients excessive decreases in CorT relative to controls were found, predominantly in left and right frontal, temporal and cingular cortices. Interestingly, left Wernicke area showed cortical thinning in patients. Increases were found in bilateral occipital cortex, left precentral and postcentral gyrus, and right parietal cortex. Conclusions: These findings show cortical thinning, predominantly in left and right frontal, temporal and cingular cortices of schizophrenia patients relative to controls. We hypothesize that siblings of patients with schizophrenia also show cortical thinning in the frontal and temporal cortices although less pronounced.

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ID: 550991

ASSOCIATION BETWEEN DURATION OF UNTREATED PSYCHOSIS, OUTCOME AND BRAIN MORPHOLOGY IN SCHIZOPHRENIA WITHIN THE NORTHERN FINLAND 1966 BIRTH COHORT

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Long duration of untreated psychosis (DUP) has been reported to associate with poor outcome in schizophrenia, possibly reflecting a neurodegenerative process after the onset of overt psychosis. Hypothetically these neurodegenerative processes may be cause or consequence of changes in brain structures. Our aim was to define differences in clinical and social outcome and volumes of gray and white matter, intracranial cerebrospinal fluid (CSF), regional gray matter in temporal, frontal, limbic, parietal and occipital cortices and subcortical gray matter between schizophrenia subjects with long and short DUP. Subjects with psychosis from the Northern Finland 1966 Birth Cohort were invited to MRI scan of the brain conducted in 1999-2001 (average follow-up ten years). DUP (mean~38 weeks, median~20 weeks) was assessed from medical records. It was categorized as short (under 6 months, $n = 28$) and long (over 6 months, $n = 20$). DUP was also assessed as logarithmic transformation. MRI-data and DUP was available for 48 and outcome for 52 subjects with DSM-III-R schizophrenia. Outcome was measured with PANSS, SOFAS and working ability. Covariates used in adjustment were onset age, intracranial volume and current use of antipsychotic medication. Longer DUP was correlated with smaller volume of left ($P = .041$) and right limbic area ($P = .003$). Logarithmic transformation of DUP was significantly correlated with volumes of right central ($P = .013$) and right limbic area ($P = .036$). DUP did not correlate with total gray or white matter or CSF. In group of long DUP symptomatic outcome was somewhat poorer, although not statistically significantly (total PANSS mean 55.3 vs 61.7 $P = .21$; positive 13.5 vs 15.0 $P = .27$, negative 16.6 vs 18.7 $P = .45$). SOFAS and working ability did not differ between two groups. At least some brain abnormalities were associated with long DUP in schizophrenia. There was trend linking long DUP and poor symptomatic outcome. This study provides new detailed information on developmental pathways of schizophrenia utilising longitudinal birth cohort design.
ID: 550984

CORTICAL THINNING IN THE POSTERIOR CINGULATE GYRUS: AN ENDOPHENOTYPE FOR SCHIZOPHRENIA?

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Background: Studies investigating cortical thickness in schizophrenia using genetically sensitive samples are still scarce. The evidence to date suggests that decreased cortical thickness of the posterior cingulate and temporal gyrus may be influenced by genetic factors, which is based on regions of interest analyses. The present family study examined whether decreased cortical thickness can be found as an indicator of genetic liability for the disorder, using a whole brain analyses approach. Methods: T1-weighted MRI scans were acquired on a 3 Tesla scanner from 92 patients with schizophrenia, 98 non-psychotic siblings and 91 controls. BrainVoyager QX was used to measure cortical thickness using the Laplace method. Group differences were assessed with whole brain, vertex-based, analyses (ANCOVA), performed in surface space after cortex based alignment of segmented cortices, and adjusted for potential confounders. Results: Analysis showed significant clusters of cortical thinning in patients compared to controls in the left and right superior parietal lobe, the right postcentral gyrus, the left collateral sulcus, the left middle occipital gyrus, the left extrastriate cortex, the left lateral occipitotemporal gyrus and the right posterior cingulate gyrus; increases were found in the left precentral gyrus. Siblings showed thinner cortex compared to the controls in the right collateral sulcus and the right posterior cingulate gyrus; increases were found in the right inferior frontal gyrus, the left lateral sulcus, the right postcentral sulcus, the left middle temporal gyrus and the left cingulate sulcus. Patients had thinner cortices than their siblings in the left and right superior frontal gyrus, the left postcentral gyrus and sulcus, the right precuneus, the right intraparietal sulcus, the left inferior temporal sulcus, the right collateral sulcus, the left lateral occipitotemporal gyrus, the left middle occipital gyrus, the left medial occipitotemporal gyrus and the left cuneus. Conclusions: Psychotic patients and their non-psychotic siblings were found to have widespread cortical thickness alterations compared to controls, as evinced by decreases and increases in several brain regions. Decreased cortical thickness in the right posterior cingulate gyrus was present in both patients with psychosis and their siblings. Thus, decreased cortical thickness in the right posterior cingulate gyrus may be influenced by genes that are associated with schizophrenia.
ID: 550977

POST ONSET PROGRESSION OF BRAIN ABNORMALITIES IN FIRST EPISODE PSYCHOSIS: WHO, WHERE, WHEN, AND HOW MUCH

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This study presents new, never-presented data and newly re-analyzed data relevant to determining the "who, where, when, and how much" of post-onset brain abnormality progression. We used a naturalistic design of tracking individuals with first episode schizophrenic psychosis (FESZ) or affective psychosis (FEAFF, almost all manic) and using structural MRI and mismatch negativity (MMN) ERPs to document brain changes between first hospitalization and 1.5 years later (total Ns of 40) and 3 years later (total Ns of 26). Highly reliable manual Region of Interest (ROI) analyses were used on the 1.5 T scans. All changes were significant at P's < 0.05. We first describe the "who", "where", and "how much" of progression at 1.5 years after first hospitalization. FESZ have a progressive loss of neocortical gray matter (GM, 1.7%), most pronounced in temporal and frontal lobes (2.5%), and associated with a worse outcome on positive symptom measures. FESZ showed a complementary progressive increase in lateral ventricular (10.4%) and sulcal CSF (7.2%) associated with a worse outcome on negative symptoms measures. In middle and inferior temporal gyri there was no progression, but superior temporal gyrus (STG) FESZ showed postonset GM reduction in left posterior STG and Heschl Gyrus (HG), a progression associated with more cognitive disorganization and thought disorder. Moreover, there was a conjoint progression of reduced HG GM and MMN amplitude. FESZ also showed progressive GM reduction in the posterior cingulate cortex (CC, 2.0%) and anterior CC subdivisions

of subgenual (4.2%), cognitive (4.9%), and affective (6.1%). In marked contrast, FEAFF showed post-onset progression of GM loss only in subgenual CC (5.6%) but not in any STG subregion. The present data suggest protective effects of antipsychotics on GM reduction in FESZ ($P = .085$), with mood stabilizers acting to increase GM; however, the GM increase observed in FEAFF (3.6%) was not associated with changes in clinical outcome. At the 3 years retest interval FESZ show continued reduction in neocortical GM and increase in sulcal CSF. The "when" of changes differed by region, FESZ STG reductions being most rapid. In summary, FESZ show certain ROI "hot spots" of greater GM reduction that are associated with worse clinical outcome and worse MMN measures. Of note, almost all ROI with progressive changes in FESZ also showed abnormalities at initial scan, suggesting the possibility of progression in the prodromal period.
ID: 550856

THE EFFECTS OF ANTIPSYCHOTIC MEDICATION ON CORTICAL THICKNESS IN PATIENTS WITH SCHIZOPHRENIA; A FIVE-YEAR LONGITUDINAL MRI STUDY

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In schizophrenia overall gray matter volume reduces over the course of the illness. Progressive gray matter volume reduction is not only related to the disease process, but also to the cumulative amount of antipsychotic medication (Cahn et al. 2002, van Haren et al. 2008). Nevertheless, it is unclear whether (the type of) antipsychotic medication influences some cortical areas more than others. This five-year longitudinal study included 96 patients with schizophrenia and 113 healthy controls Magnetic Resonance Imaging was performed at inclusion (T0) and after five years (T5). Every patient was monitored carefully for the amount and type of medication prescribed between base line and follow-up. Antipsychotic medication (intake per year during the scan interval of typical and atypical antipsychotics in haloperidol equivalents, clozapine in mgs) was calculated. For each subject cortical thickness (CortT) change over time was computed using in-house software (Schnack et al. 2001) and CLASP (Kim et al. 2005). Group difference in CortT change was calculated by using regression analyses with age and gender as covariates. The statistics were corrected for multiple comparisons by applying a false discovery rate of alpha = 0.05. Spearman's rank correlations were performed on the significant cortical areas to examine the effects of antipsychotic medication. Excessive decreases over time in CortT in patients relative to controls were found predominantly in the frontal and temporal cortices. Cumulative typical antipsychotic medication correlated with change over time in CortT in the left post central area (rho = −.36, $P = .008$), atypical antipsychotic medication with change in CortT in the right paracentral lobule (rho = .32, $P = .008$) and clozapine with the cortical areas of the right medial superior frontal (rho = .36, $P = .005$), right lateral middle frontal (rho = .41, $P = .002$) and right cingulate (rho = .41, $P = .001$). These findings suggest that the progressive cortical changes in patients with schizophrenia are also affected by antipsychotic medication and that different types of medication might affect different cortical brain areas.

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ID: 550833

THALAMUS VOLUME AND COGNITIVE FUNCTION IN FIRST-EPISODE PSYCHOSIS PATIENTS AND HEALTHY CONTROLS

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Introduction: Thalamus abnormalities have been implicated in the pathophysiology of Schizophrenia, placing it in the centre of dysfunctional neural connectivity. This structure is also suppose to be involved in a number of different cognitive functions but, until present moment, only few studies have investigated the relation between thalamic volume and cognitive functioning in patients with First Episode Psychosis. Methods: 70 first episode psychosis patients (35 males, 25 females; mean age: 28.48 ±7.3) and 50 healthy controls (33 males, 17 females; mean age: 29.2 ± 7.47) were scanned using a 1.5 Tesla scanner. Thalamus volumes were calculated using stereological principles with the software MEASURE. Patients and healthy controls completed a comprehensive battery of neuropsychological tests, assessing executive functioning, verbal memory, general intellectual ability and IQ. Results: Analyses of (Co)variance (ANCOVA) were conducted, with age and whole brain volume as covariate's on the thalamic volume. Thalamic volume was then correlated with neuropsychological scores. First episode psychosis patients display significantly reduced thalamic volume compared to controls ($F_{1,90} = 9.493$), $P = .03$). No significant correlation was found between thalamic volume and cognitive performance, in either of the cognitive dimension assessed. Conclusion: In our study we demonstrated significant thalamic volumes differences in patients with first-episode psychosis relative to healthy controls, suggesting a potential abnormal thalamic circuitry. These data suggest no relation between thalamic volume and cognitive performance in first-episode psychosis.
ID: 551996

A COMPARISON OF CAUDATE VOLUME AND COGNITIVE FUNCTION BETWEEN FIRST-EPISODE PSYCHOSIS PATIENTS AND HEALTHY CONTROLS

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The caudate volume is a structure often implicated in the pathogenesis of schizophrenia. This structure also regulates a number of cognitive functions. However, only few studies have investigated the correlation of cognitive functioning with caudate volume in patients with psychosis. The aim of this study was to investigate the comparison of caudate volume in first episode psychosis patients between healthy controls and to further examine the relationship between caudate volume and cognitive functioning. 95 first episode psychosis patients (60 males, 35 females; mean age (27.49) ±7.8; 47 schizophrenia, 29 Affective disorders, 18 Other) and 91 healthy controls (54 Males, 37 females; mean age (30.2) ±8.72) were scanned using a 1.5 Tesla scanner. The software MEASURE was used to estimate caudate volume. Executive functioning, verbal memory, general intellectual ability and IQ were examined in a neuropsychological test battery. Analyses of (Co)variance (ANCOVA) were conducted with whole brain volume and age and as covariate's on the caudate volume, diagnosis and pharmacological data. Caudate volume was then correlated with neuropsychological scores. The results showed that patients had larger caudate volume than healthy controls, albeit only at trend level

(P = .069). Within the patient group, there was a positive correlation between caudate volume and performance on the Ravens task (P = .008) and the trail making task (P = .006). These data suggest that a smaller caudate volume in schizophrenia is associated with a poorer performance in tests of general intellectual ability and executive function. It would be interesting, next to investigate this data longitudinally with information collected at a follow up.
ID: 564775

FRACTIONAL ANISOTROPY AND MOVEMENT DISORDER IN SCHIZOPHRENIA

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Diffusion tensor imaging (DTI) studies in patients with schizophrenia generally demonstrate decreased fractional anisotropy (FA) in white matter (WM) in patients compared to controls, which is thought to reflect impaired WM connectivity. To date, there are no studies addressing the relationship between WM changes with neurologic movement disorders, which can be manifestations of schizophrenia, or a side effect of antipsychotic medication experienced by some patients. We examined the relationship of FA indices to measures of parkinsonism, akathisia, and dyskinesia in a large sample of patients with chronic (CSZ) and first episode (FEP) schizophrenia to test the hypothesis that patients with lower FA have higher rates of movement disorders. Patients with CSZ (n = 83) and FEP (n = 31) were recruited from either the University of Minnesota, University of New Mexico, Massachusetts General Hospital, or the University of Iowa, sites participating in the Mind Clinical Imaging Consortium project. Due to differences in scanning hardware and procedures, FA measures were z-transformed within each site before combining the measures for group analyses. Abnormal movements were rated using the Simpson-Angus (SA), Barnes Akathisia (BA), and Abnormal Involuntary Movement Scale (AIMS) rating scales for parkinsonism, akathisia, and dyskinesia, respectively. Results showed no significant correlations between the whole brain FA measures and any of the movement ratings, either in the group as a whole, or in CSZ alone. As expected, FEP patients, who were all on atypical antipsychotics, had low rates of movement symptoms. Spearman rank order correlations with regional FA brain measures suggested higher SA ratings were associated with lower FA in the left cerebellum (P = .012, CSZ; P = .004, CSZ and FEP combined), but not measures of FA in the frontal, temporal, parietal, or occipital lobes. Tardive dyskinesia was identified in only 4 of the 83 SCZ patients and was associated with age and cumulative dose-years of treatment, but FA measures did not differ between affected and unaffected patients. Further analyses of the data will be presented. These results suggest a possible association between parkinsonian symptoms and cerebellar FA, but future studies controlling for antipsychotic dosing and samples enriched for patients with dyskinesia will be needed to clarify possible relationships between WM connectivity and movement disorders in schizophrenia.
ID: 554803

INTERLEUKIN-1BETA GENE MODULATES PREFRONTAL AND TEMPORAL BRAIN STRUCTURE IN SCHIZOPHRENIA

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Introduction: Interleukin-1beta (IL-1b, chromosome 2q13) has a key role in differentiation of dopaminergic neurons and dendrite growth in developing cortical neurons. Previous studies by our group and others have shown that IL1b genotype a) is associated with schizophrenia and b) modulates activity in the dorsolateral prefrontal cortex. Here we investigated the effect of the risk allele (−511 T) on brain structure using voxel-based morphometry. Methods: 61 patients with DSM IV schizophrenia (mean age 31.8 yrs; SD 11.53 yrs) and 54 healthy subjects (mean age 29 yrs; SD 9.87 yrs) were genotyped for a functional single nucleotide polymorphism of IL-1B (rs16944) and grouped into risk-allele carriers (A2 homozygotes and A1/A2 heterozygotes) vs. A1 homozygotes. Grey matter volume was analyzed using optimised voxel based morphometry on T1-weighted high-resolution anatomical images (TR = 15ms, TE = 5ms, flip angle = 300, FOV = 256mm, matrix = 256X256, sagittal slices = 192, slice thickness = 1 mm, voxel dimension 1X1X1 mm3). Results: Main effect of diagnosis showed grey matter (GM) volume loss in bilateral DLPFC, bilateral caudate, bilateral insula, left fusiform gyrus (P < .001, uncorr.). In healthy controls, risk allele carriers showed grey matter reduction in the left insula. In schizophrenia patients, risk allele carriers showed grey matter increase in the left inferior temporal cortex. We found a significant (P < .01, uncorr.) effect of group X genotype interaction in bilateral superior lateral prefrontal cortex, superior temporal gyrus, anterior temporal pole, and left posterior temporal cortex. Only the left fusiform gyrus showed increased grey matter in patients who are A1 homozygous compared to the other groups. Conclusions: This study demonstrates effects of IL-1b in prefrontal and temporal cortical areas, which have been associated with cognitive deficits in schizophrenia. Given the role of IL-1b in early development, this might reflect higher vulnerability of A2 risk allele carriers for brain structural deficits in these areas.
ID: 554460

16. 16. Neuropathology, Histology

THE NEUREGULIN-1 ISOFORMS ALPHA AND BETA ARE DIFFERENTLY EXPRESSED IN THE PRE-FRONTAL CORTEX IN SCHIZOPHRENIA AND AFFECTIVE DISORDER

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Neuregulin-1 proteins play important roles in neuronal migration, differentiation and signal mediation, as well as in the survival of oligodendrocytes. The NRG-1 gene codes for 15 different isoforms. At least five different haplotypes of the NRG-1 gene may be associated with schizophrenia. An abnormal expression pattern of NRG-1 mRNA was found in the prefrontal cortex of schizophrenic patients and patients suffering from depression. Here we investigated in postmortem brains the expression of the two NRG-1 isoforms alpha and beta, which differ with regard to their EGF-like domains, in schizophrenia and depression. NRG-1alpha was immunohistochemically visualized on brain sections of 22 schizophrenics, 12 patients with affective disorders and 22 matched controls, NRG-1beta in brains of 7 schizophrenics, 6 patients with affective disorders and 8 matched controls. The number of NRG-1alpha immunoreactive neurons per hemisphere was counted using a computer assisted analysis system. NRG-1beta immunopositive cells were counted in den DLPFC and ACC by using a light microscope. Normal anatomical distribution showed for NRG-1alpha only few immunopositive interneurons located in the prefrontal gray and white matter, whereas for NRG-1beta a widespread immunoreactivity in pyramidal cells and interneurons was observed. In schizophrenia stereologic analysis revealed a significant reduction of NRG-1αlpha cells in the white as well as in the gray cortical matter. In patients with unipolar depression the density of NRG-1alpha immunoreactive neurons was also significantly reduced in the prefrontal gray matter. In contrast to the 1alpha-isoform, NRG-1beta immunopositive interneurons and pyramidal cells in DLPFC and ACC were significantly increased in schizophrenics in comparison to controls. Interneurons of the DLPFC differed significantly between cases of affective disorders and schizophrenics.The diminished expression of NRG-1alpha in interstitial white matter neurons supports a neurodevelopmental component to schizophrenia (disturbed migration). With regard to NRG-1beta we suppose that the increase of the immunopositive neurons in schizophrenics leads to a hypofunction of NMDA-receptors via enhanced binding of this NRG-1 isoform to its receptor, ErbB4 (Hahn et al. 2006). However the increased expression of NRG-1beta could also be due to the chronic administration of antipsychotics.
ID: 540132

ENDOCANNABINOID SYNTHESIZING AND METABOLIZING ENZYMES IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Cannabis use in schizophrenia is increasingly recognized as a major public health concern. For example, cannabis use worsens prefrontal cortex (PFC)-related cognitive impairments in subjects with schizophrenia. Interesting, cognitive deficits in schizophrenia are linked to reduced GABA signaling in the PFC, and activation of the cannabinoid 1 receptor (CB1R) reduces the release of GABA. Thus, cannabis use may worsen cognitive deficits in schizophrenia by exogenously activating the CB1R which further impairs PFC GABA signaling. Direct investigations of the endogenous cannabinoid (eCB) system may help clarify the biological basis for the negative effects of cannabis use in schizophrenia. For example, lower CB1R mRNA and protein levels have been reported in the PFC in schizophrenia. However, do lower CB1R levels reflect an overall deficiency in eCB signaling in the disease, or are CB1R levels downregulated in response to excessive eCB signaling? Discriminating between these possibilities requires knowledge of the eCB ligands that bind to the CB1R. For example, the eCB 2-arachidonoylglycerol (2-AG) is synthesized by diacylglycerol lipase (DAGL) and is degraded by monoglyceride lipase (MGL). Inhibiting DAGL lowers 2-AG levels and enhances GABA signaling; conversely, inhibiting MGL raises 2-AG levels and further suppresses GABA signaling. While it is not possible to directly measure 2-AG levels in postmortem human brain tissue, determining the levels of DAGL and/or MGL may help elucidate the status of 2-AG signaling in schizophrenia. Therefore, using postmortem brain tissue from a cohort of 23 schizophrenia subjects with decreased CB1R mRNA levels compared to matched control subjects, we are using quantitative PCR (qPCR) to quantify relative mRNA levels for DAGL and MGL in the PFC. The comparative threshold cycle (Ct) method is used in which transcript levels are expressed as normalized values to the geometric mean of 3 control genes. The specificity and efficiency of the qPCR amplification of DAGL and MGL mRNA in human brain have been confirmed in pilot experiments. Final data collection is ongoing with experimenters blinded to diagnosis. We predict that DAGL mRNA levels are reduced and MGL mRNA levels are increased in the PFC in schizophrenia. These findings, in concert with lower CB1R levels, would suggest an overall decrease in 2-AG signaling which may have a compensatory effect for impaired GABA signaling in schizophrenia.
ID: 550361

QUETIAPINE ALLEVIATES THE CUPRIZONE-INDUCED WHITE MATTER PATHOLOGY IN THE BRAIN OF C57BL/6 MOUSE

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Recent human studies employing new magnetic resonance imaging techniques and micro-array analyses feature schizophrenia as a brain disease with alterations in white matter (WM), which is mainly composed of oligodendrocytes (OLs) and their processes wrapping around neuronal axons. To examine the putative role of OLs in the pathophysiology and treatment of schizophrenia, animal studies are essential. In the present study, C57BL/6 mice were given 0.2% cuprizone (CPZ) in their diet for five weeks during which they drank distilled water without or with quetiapine (QTP, 10 mg/kg). The mice fed with normal chow were used as controls. CPZ is a copper chelator and has been reported to induce consistent demyelination in the brain of C57BL/6 mouse by specifically damaging OLs. QTP is an atypical antipsychotic widely used in the treatment of schizophrenia and other psychotic disorders. In accordance with previous studies, CPZ-exposed mice showed pervasive myelin breakdown and demyelination. The amount of myelin basic protein (MBP) in the cerebral cortex was decreased by CPZ-exposure as shown in Western-blot analysis. In addition, the demyelinated sites were teemed with activated microglia and astrocytes but a few myelin forming OLs. Moreover, the activity of copper-zinc superoxide dismutase decreased in the cerebral cortex of CPZ-exposed mice. However, all of these pathological changes in WM were either

prevented or alleviated in CPZ-exposed mice co-administered with QTP. These results suggest that the CPZ-exposed C57BL/6 mouse is a potential animal model to study possible roles of OLs in the pathogenesis and treatment of schizophrenia.
ID: 550211

GAD67 PROTEIN LEVELS AT THE AXON TERMINAL IN THE DORSOLATERAL PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA

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Impaired GABA neurotransmission in the dorsolateral prefrontal cortex (DLPFC) may contribute to the cognitive deficits of schizophrenia. The presynaptic strength of GABA neurotransmission is partially determined by the amount of GABA in the axon terminal available for release. Terminal GABA is synthesized locally by the 67- and 65-kDa isoforms of glutamic acid decarboxylase (GAD67 and GAD65). In the DLPFC of subjects with schizophrenia, a reduction in GAD67, but not GAD65, mRNA has been widely-replicated. This deficit appears to be present in the subclass of GABA neurons that contain the calcium-binding protein parvalbumin (PV). However, it is unknown if the deficit in GAD67 mRNA is accompanied by a comparable decrease in GAD67 protein in PV terminals. To answer this question, we have developed a novel fluorescence intensity/ morphological segmentation protocol, that in combination with immunocytochemistry, spinning disk confocal microscopy, and stereological sampling, permits the unbiased assessment of both the relative density of axon terminals and relative protein levels per terminal. We are utilizing this approach in a cohort of 20 matched pairs of schizophrenia and control subjects, all with RNA integrity number > 7 and postmortem interval < 20 hours. The latter is associated with good preservation of GAD67 and GAD65 protein, as determined by Western blot. Blind to diagnosis, we are quantifying GAD67 protein levels in puncta (putative axon terminals) triple-labeled for GAD67, GAD65, and PV in layers 3 and 4 of DLPFC area 9. A reduction in the levels of GAD67 protein in GAD65/PV terminals, but no change in the density of triple-labeled terminals, in subjects with schizophrenia would parallel the mRNA data and support the hypothesis of reduced GABA synthesis and neurotransmission in PV-containing GABA neurons in schizophrenia.
ID: 549927

DECREASED COX ACTIVITY IN THE PUTAMEN IN SCHIZOPHRENIA.

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Schizophrenia (SZ) is a very heterogeneous disease with a spectrum of symptoms, risk factors and probably etiology. The striatum, a brain region involved in motor, cognitive and emotional skills, is abnormal in patients with SZ. Abnormalities in mitochondria, the energy producing organelles of the cell, have been observed in subjects with SZ in the striatum and elsewhere. Mitochondrial function can be assessed by measuring the activity of cytochrome oxidase (COX), a component of complex IV of the electron transport chain. In the present study, COX histochemistry was performed in postmortem striatal tissue from subjects with SZ and normal controls (NCs), and in rats treated chronically (4 months) with the antipsychotic drugs (APD) clozapine or haloperidol. Postmortem human brain tissue was obtained with family permission from the Maryland Brain Collection. SZ cases ($n = 12$) and NCs ($n = 6$) were matched using age, sex, post mortem interval (PMI), and race as criteria. SZ cases were divided into two subgroups: on APD and off APD ($n = 6$ per group). The mean ages were: NCs, 56.8 ± 15.8y; SZ on APD 54.2 ± 17.0y; SZ off APD, 47.3 ± 21.3y. The mean PMIs were NCs, 12 ± 6.7h; SZ on APD, 9.0 ± 8.1h; SZ off APD, 15.7 ± 4.9h). There was significantly ($P < .001$) less COX (a decrease of 20%) in the putamen of the combined SZ group (0.341 ± 0.01) vs. NCs (0.423 ± 0.01). Both subgroups with SZ had lower ($P < .001$) putamen COX values (SZ on APD, 0.340 ± 0.01; SZ off APD, 0.342 ± 0.01) than that of NCs (0.423 ± 0.01). In the caudate, there were no differences in COX levels in the two group (NCs, 0.405 ± 0.01; SZ, 0.396 ± 0.02) or three group analyses (NCs, 0.405 ± 0.01; SZ on APDs, 0.395 ± 0.009; SZ off APDs, 0.397 ± 0.01. In rats, COX activity was not decreased by either haloperidol (0.453 ± 0.004) or clozapine (0.416 ± 0.002) compared to that of controls (0.398 ± 0.004). The similar decrease in COX activity in the putamen of SZ on and off APD, together with the rat data suggests that the decrease in COX activity in the putamen of SZs does not seem to be caused by APDs. The data suggest mitochondrial abnormalities in the putamen in SZ.
ID: 549892

EXPRESSION OF CORTICAL GABA_A RECEPTOR SUBUNIT TRANSCRIPTS IN SCHIZOPHRENIA: ALTERED INHIBITORY NEUROTRANSMISSION IN SPECIFIC CORTICAL CIRCUITS

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Disturbances in working memory and prefrontal cortex (PFC) function in schizophrenia may reflect abnormalities in the intrinsic circuitry of this region. Previous studies have described alterations in presynaptic markers in certain classes of PFC GABA neurons in schizophrenia. At the postsynaptic site, the effects of GABA are mediated by $GABA_A$ receptors whose subunit composition and subcellular location are specific to different local cortical circuits. To determine the postsynaptic circuit specificity of altered GABA neurotransmission in schizophrenia, we examined the expression of $GABA_A$ receptor α1, α2, α3, and α5 subunits and their assembly partners β2 and β3. We used in situ hybridization in DLPFC samples from 23 matched pairs of schizophrenia and control subjects. For each subunit, we determined the overall level and laminar pattern of mRNA expression. In a parallel study, the potential effects of antipsychotic medications on $GABA_A$ receptor subunit expression were assessed in male macaque monkeys chronically exposed to haloperidol, olanzapine, or placebo. Each $GABA_A$ α subunit had a distinct laminar pattern of expression that was similar in control and schizophrenia subjects. In schizophrenia, mean $GABA_A$ α1 mRNA expression was 16% lower in layers 3–5, α2 mRNA was 14% higher in layer 2, and α5 was 15% lower in layer 4 relative to matched controls. In contrast, α3 mRNA expression did not differ from controls. Absence of alterations in the antipsychotic-exposed monkeys suggested that the abnormal expression of those transcripts in schizophrenia was not due to medication effects. Blinded quantification of $GABA_A$ β2 and β3 mRNA expression is in progress. Our results suggest that GABA neurotransmission in the DLPFC of subjects with schizophrenia is altered at the postsynaptic level in a receptor subunit- and layer-specific manner. Given the predisposition for receptors containing these different subunits to be preferentially located at synaptic contacts from axon terminals of specific classes of GABA neurons and at specific locations on pyramidal neurons, our results suggest that altered GABA neurotransmission in schizophrenia is circuit-specific and affects the firing of pyramidal neurons in different ways. Supporting

ARRESTED NEUROPLASTICITY?: ALTERED AGEING EFFECTS REVEAL A DYNAMIC NEUROPATHOLOGY OF SCHIZOPHRENIA

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Recent hypotheses concerning synaptic deficits in schizophrenia do not explain why the degree of abnormality is not more catastrophic. It indicates that the problem may be relatively discrete and lie with a particular component of the repertoire of neuroplastic mechanisms. Here we demonstrate that normal age-associated changes in association cortex neuron spacing are not found in schizophrenia. These age-associated changes are reported in an adult population (age range 29–90yrs) and are not found in primary sensory cortex, indicating that they are selective to the more plastic regions of association cortex involved in cognition. The deviation of patients from the normal ageing curve of controls was found to correlate with age of onset (linear regression, $P < .01$). On the basis of these findings a meta-analysis of the neuropathology literature (56 studies of neuron density) was conducted and revealed a negative correlation between the mean age of the subjects and the size of the cell density change in schizophrenia ($r^2 = -0.46, P < .01$). The contrast between patients and controls depends on when in adulthood the cell density is measured. Additional meta-analysis of post-mortem brain weight (1367 subjects) indicated accelerating brain size reduction with age in patients. The literature on neuron number in the cortex implicates cell loss as the cause. The neurodevelopmental hypothesis proposed that "a fixed 'lesion' early in life interacts with normal brain maturational events that occur much later" (Weinberger, 1987), however the findings presented are consistent with abnormal maturation. Healthy maturation involves an expansion and later reduction of neuropil (tissue between cells). In schizophrenia the neurons are more closely packed to begin with but show little change in adulthood. An arrest of plasticity may confer vulnerability to cell loss and brain volume reduction when adult neuroplastic demands are not met. The inference is that the size of the plasticity deficit is linked to the timing of the arrest and the age of illness onset.
ID: 551873

CANNABINOID 1 (CB1) RECEPTOR PROTEIN EXPRESSION IN THE PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA OR MAJOR DEPRESSION

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Cannabis use causes impairments in cognitive processes, such as working memory, that are also present in schizophrenia. Working memory impairments in schizophrenia are associated with reduced GABA signaling in the dorsolateral prefrontal cortex (DLPFC). The cannabinoid 1 receptor (CB1R) is highly expressed in the DLPFC, is contained in the axon terminals of a subpopulation of perisomatic-targeting GABA neurons, and when activated, inhibits the release of GABA. These data suggest that altered signaling via the CB1R may be involved in the pathophysiology of schizophrenia. Indeed, we recently demonstrated that the expression of CB1R mRNA and protein was significantly reduced bilaterally in DLPFC area 9 in a cohort of 23 pairs of subjects with schizophrenia and matched control subjects. In this study, we determined whether the reduction in CB1R protein levels 1) is also present in DLPFC area 46 in the same subjects with schizophrenia, 2) is present in area 46 in a new subject cohort, and 3) is specific to schizophrenia or also present in subjects with major depression (MDD). We used immunocytochemical techniques to examine the levels and laminar distribution of CB1R protein in area 46 in 12 pairs of subjects from the previously studied cohort and from a new cohort of 14 matched triads of schizophrenia, MDD, and control subjects. In the 12 pair cohort, optical density analysis revealed that the levels of CB1R immunoreactivity in area 46 were significantly reduced by 19% in schizophrenia subjects. The within-pair percent changes in CB1R immunoreactivity in area 46 significantly correlated with those previously observed in area 9 of the same subjects with schizophrenia. In the cohort of 14 triads, CB1R immunoreactivity was reduced by 20% and 23% in subjects with schizophrenia compared to matched control and MDD subjects, respectively. Levels of CB1R immunoreactivity did not differ between MDD and comparison groups. Laminar analysis revealed that CB1R immunoreactivity was decreased across all cortical layers in subjects with schizophrenia. These results demonstrate that reductions in CB1R protein are 1) common in schizophrenia, 2) conserved across DLPFC regions in schizophrenia, and 3) not present in subjects with MDD. Thus, altered inhibition from CB1-containing GABA neurons may be a critical component of the disease process underlying DLPFC dysfunction in schizophrenia.
ID: 551825

A DISC1 MOUSE MODEL OF GENE-ENVIRONMENT INTERACTIONS IN THE PATHOGENESIS OF SCHIZOPHRENIA

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Interplay between genetic and environmental factors likely plays a major role in development of schizophrenia and related psychiatric conditions. However, mechanistic studies of potential interactions have been difficult due to the paucity of experimental models directly relevant to human epidemiological data. Recent discoveries of candidate genes and a better understanding of the nature of immune response of the body to aversive environmental factors have facilitated the development of novel in vitro and in vivo models. We have developed a mouse model of inducible expression of mutant human Disrupted-in-Schizophrenia-1, DISC1, a predicted truncated protein product of the chromosomal translocation previously shown to segregate with psychiatric illness. We use this model to elucidate the mechanism of interactions between mutant DISC1 and prenatal immune activation with a synthetic analog of double-stranded RNA (poly IC) that induces immune activation in pregnant dams similar to that associated with viral infections during pregnancy. We found that prenatal immune challenge significantly up-regulated pro-inflammatory cytokines in the serum of pregnant mice and embryonic brains, indicating immune activation in mutant DISC1 mice. Compared to saline-treated DISC1 mice, poly IC-challenged DISC1 mice exhibited increased anxiety in elevated plus maze, dark-light box emergency test, and open field, decreased exploration of social and non-social targets and depression-like phenotype in Porsolt test, suggesting the synergistic effects of immune activation and mutant DISC1 in the adult offspring. Poly IC treatment increased the volumes of the lateral ventricles in control mice and did not significantly affect the already enlarged lateral ventricles in mutant DISC1 mice. Our preliminary data showed that prenatal stimulation decreased the density of dendritic spines in the dentate gyrus of the hippocampus in mutant DISC1 mice without altering the spine density in control animals. The present results suggest significant interactions between mutant DISC1 and environmental challenge during neurodevelopment and lend additional support to the use

of our model for elucidating the molecular pathways that mediate gene-environment interactions in schizophrenia and related mental disorders.
ID: 551818

CEREBROVASCULAR DISEASE, MYELIN, AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

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Introduction: Severe cognitive dysfunction is common in elderly individuals with schizophrenia. The neuropathological basis of this decline is unknown. We previously reported evidence for reduced tolerance to Alzheimer-type pathology in chronically institutionalized patients with schizophrenia; however, many instances of severe cognitive decline remained unexplained. We now explore the possibility that cognitive decline in schizophrenia might be related to white matter deficits resulting from cerebrovascular disease or from schizophrenia itself. Methods: Semiquantitative evaluations of Verhoeff myelin stain were performed on white matter from the dorsal half of one frontal lobe at the level of the rostral pole of the lateral ventricle in autopsy brains of 81 elderly individuals with schizophrenia who died in state hospitals, and 21 individuals without psychiatric disease or dementia. Cognitive function in the schizophrenia subjects was quantified with the Scales of Cognitive Impairment Rated From Institutional Records for the beginning and end of the illness, and for intervening 10 year intervals. Hypertensive, atherosclerotic, or amyloidotic vascular disease was diagnosed by neuropathological examination. Results: Two-way ANOVA yielded, as expected, a significant effect of vascular disease on myelin integrity ($P = .02$). Schizophrenia ($P = 0.29$) and the interaction of vascular disease and schizophrenia ($P = .81$) did not affect the histological integrity of myelin in this region. Over the entire course of illness, schizophrenia subjects with vascular disease had nearly 50% greater cognitive decline than schizophrenia subjects without vascular disease ($P = .003$), whose cognitive decline was nonetheless many times greater than reported for normal aging. The cognitive decrement associated with vascular disease in schizophrenia was itself much greater than the effects of normal aging. Curiously, in both the schizophrenia and nonpsychiatric groups, the effect of vascular disease on myelin was greater in females, while the effect of vascular disease on cognitive change was similar for male and female schizophrenia subjects. Conclusion: These findings suggest that in schizophrenia, there is a heightened susceptibility to the cognitive effects of cerebrovascular disease.
ID: 551697

HOW TO RUN A BRAIN BANK FOR PSYCHIATRIC DISORDERS—DO WE NEED AN INTERNATIONAL CONCENSUS?

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Current developments in research of psychiatric disorders are partly due to the progress and growth in the field of brain tissue/Bio (BTB) banking. We have recently proposed a new standardized version of golden standards for brain banking (Ravid 2008a,b; these include organization, methodology of collecting, handling and storing specimens for high quality and modern research, the standard operating procedures (SOP's),legal /ethical /social/ moral issues and the Code of Conduct. Psychiatric brain banks are important as they form a bridge between donors, their relatives, clinicians, neuropathologists , scientists and the pharmaceutical companies, looking for targets and developing drugs. We have developed parameters for quality control and matching of samples to correct for the enormous variability in patient material; these include age, gender, clinical history, medication, agonal state / pH, seasonal and annual variation, post mortem-delay, handling methods, fixation time and storage time. As the aetiology and pathophysiology of psychiatric disorders are still unknown, we have also identified several brain regions as regions of interest for assessments, specifically the area of the prefrontal cortex, which was followed by developing new dissection protocols for post-mortem brain at rapid autopsy. The availability of autopsy material from patients with psychiatric disorders is very limited while the interest from the international scientific community is ever-growing. To solve this problem we introduced an intense collaboration with psychiatric departments and research institutions to implement a post-mortem research program including genetic research and search for gene-expression profiles. The global decline in autopsy rates is a worrying situation which makes well operating and efficient brain banks even more vital. The legislative /ethical framework needed to run brain banks is still a matter of debate and will determine the future and the continuity of research on psychiatric disorders. We are preparing an Inter-national consensus for protocols and procedures of sample acquisition in psychiatric disorders which will hopefully facilitate a breakthrough in research.

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ID: 551671

VA/VL THALAMIC CELL NUMBER IN SCHIZOPHRENIA AND MOOD DISORDERS

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The thalamus has been found to be a site of anatomical disturbance in schizophrenia and mood disorders. We have previously reported increased volume and neuron number in the mediodorsal and anteroventral/anteromedial nuclei of the thalamus in major depression, with no change in the number of neurons in schizophrenia in these nuclei in subjects of moderate age (average age = 45; Young et al., 2004 Am J. Psychiatry 161: 1270–1277). In the present post-mortem investigation of specimens from the Stanley Foundation Brain Collection diagnosed with schizophrenia, major depression and bipolar disorder, we performed stereological study of the ventroanterior/ventrolateral nucleus (VA/VL), a large nuclear group which projects primarily to the cingulate, premotor and motor cortex. We observed in subjects with major depression that volume and neuron number of the VA/VL was nearly double that of controls, while schizophrenia subjects had a normal complement of neurons and a normal volume. Bipolar subjects were observed to have an intermediate volume and neuron number which was not statistically different from controls. We also observed that prior treatment with antidepressants was associated with a reduced volume (but no change in neuron number) of the AV/AM, a finding previously reported for whole thalamic volume (Young et al., 2008, British Journal of Psychiatry 192, 285–289). The present finding supports a robust alteration in neuron number in major depression in several thalamic nuclei

that project to the anterior portions of the cortex in middle-aged subjects, with no major changes in this region in schizophrenia.
ID: 551595

SIMILARITIES AND DIFFERENCES IN SCHIZO-PHRENIA OR BIPOLAR DISORDER: EVIDENCE FROM POSTMORTEM INVESTIGATIONS

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In postmortem studies, microscopic, cytochemical, molecular and genetic approaches are demonstrating both similarities and differences between schizophrenia (SZ) and bipolar disorder (BD). These two disorders affect largely overlapping brain regions, neural circuits and neurotransmitter systems. However, there is also evidence for divergent pathophysiological mechanisms. This talk will review neuropathological investigations comparing SZ to BD and will give particular focus to recent findings in the amygdala and entorhinal cortex. In the amygdala of SZ subjects, but not BDs, fibers expressing dopamine transporter are reduced, while tyrosine hydroxylase-positive fibers were normal. These findings suggest that dopamine uptake may be impaired in SZ, potentially causing a state of hyperdopaminergia. Lack of similar changes in BD may contribute to pharmacological differences between these disorders. Marked increases of glial cells expressing extracellular matrix proteoglicans were also detected in the amygdala of SZ subjects. These changes suggest that a disruption of glial cell functions and extracellular matrix properties may contribute to the pathophysiology of amygdala in SZ. Dopamine transporter and extracellular matrix changes were not detected in BD. However, the amygdala of these subjects is markedly altered, as indicated by substantial neuron number reductions in specific amygdala nuclei in BD. These abnormalities are postulated to contribute to the impairment of emotion processing encountered in BD. Distinct sets of abnormalities also affect the superficial layers of the entorhinal cortex in SZ and BD subjects. Glial and extracellular matrix abnormalities affect specifically layer II only in SZ. Decreases of neurons expressing parvalbumin in layer II and III were found only in BD. Thus, processing and outflow of cortical inputs directed to the hippocampus may be altered in both diseases, although the mechanisms, and likely pathophysiological outcome, are disease-specific. In conclusion, disease-specific patterns of anomalies in SZ and BD suggest that distinct pathophysiological mechanisms may underlie disruption of amygdala and entorhinal cortex functions in the two disorders. Clinical, genetic and pharmacological similarities and differences between SZ and BD may reflect an overlap/mismatch pattern of affected brain regions, neurotransmitter, cellular and molecular systems. Funded by NIH MH066280, MH066955 and MH083222.
ID: 551411

EXTRACELLULAR MATRIX-GLIAL ABNORMALI-TIES IN THE AMYGDALA AND ENTORHINAL CORTEX OF SUBJECTS DIAGNOSED WITH SCHIZOPHRENIA

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Chondroitin sulfate proteoglycans (CSPGs), a main component of the brain extracellular matrix (ECM), regulate neuronal functions throughout development and adulthood. CSPGs functions, such as neuronal migration, synaptic regulation and interactions with the GABAergic, glutamatergic and dopaminergic systems bear direct relevance to the pathophysiology of schizophrenia. Furthermore, CSPGs are one of the main components of perineuronal nets (PNNs), ECM aggregates enveloping neuronal soma and dendrites and known to play a crucial role in the regulation of neuronal functions in adults. With the present postmortem study, we tested the hypothesis that SZ may be associated with CSPG abnormalities in the amygdala and entorhinal cortex (ECx). We have recently shown that astrocytes are the main cell types expressing detectable levels of CSPG in the normal human amygdala. To assess the involvement of glial cells in CSPG abnormalities, we measured numerical densities of CSPG-positive glial cells. To test whether increases of CSPG-positive glial cells are associated with CSPG changes within the ECM, we measured numerical densities of PNNs. Our subject cohort consisted of 15 normal controls, 11 SZ and 11 BD subjects. CSPG-positive glial cells were massively increased in the deep nuclei of the amygdala (419–1162 %) and in ECx layer II of subjects with SZ (567-1560 %). These changes were not accompanied by astrocytosis, suggesting CSPG-specific glial abnormalities. PNNs were instead reduced in LN and layer II of ECx-L in absence of altered PVB-positive neuron numbers, a finding consistent with CSPG anomalies within the ECM, rather than loss of PNN-associated neurons. CSPG changes were negligible in subjects with bipolar disorder. These results point to substantial, specific, and thus far unsuspected anomalies affecting CSPG expression in glial cells and ECM perineuronal aggregates in SZ, but not BD. The large effect size of changes in schizophrenia points to a pivotal role for ECM-glial interactions in the pathogenesis of this disease. A disruption of these interactions, unsuspected thus far, may represent a unifying factor contributing to disturbances of neuronal migration, synaptic connectivity, and neurotransmission in schizophrenia. Lack of CSPG abnormalities in bipolar disorder points to a distinctive aspect of the pathophysiology of schizophrenia in key medial temporal lobe regions. Funded by NIH MH066280, MH066955 and MH083222.
ID: 551936

17. 17. Neuropathology, Biochemistry

EARLY-STAGE SCHIZOPHRENIA AND NORMAL AGING SHARE COMMON MOLECULAR PROFILES

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Kraepelin described schizophrenia as a chronic deteriorating psychiatric disorder characterized by rapid cognitive disintegration, calling it "dementia praecox" (premature dementia). To investigate the aging process in schizophrenia, we examined genome-wide expression datasets from human frontal cortex of normal and schizophrenic individuals ranging from 19 to 81 years of age. We found that changes in gene expression that are correlated with aging in normal subjects differ dramatically from those observed with aging in schizophrenic subjects. Only 2.5% of genes were correlated with age in both cohorts. Real-time PCR analysis confirmed expression differences for the top correlated genes in young (19–26 yrs) vs. older (42–80 yrs) age control groups, changes that were not observed in schizophrenic subjects. Surprisingly, we also found a significant overlap (29–34%) between those genes whose expression was correlated with aging in normal subjects and those significantly altered in subjects with early-stage schizophrenia (within 5 years from initial diagnosis). Furthermore, Gene Ontology terms associated with normal aging were similar to those related to early-stage schizophrenia. These data demonstrate that the molecular basis for aging differs in schizophrenic and normal subjects. In particular, normal aging and early-stage schizophrenia share common molecular signatures, suggesting that onset of schizophrenia anticipates the normal aging process.
ID: 546523

THE RELATIONSHIP BETWEEN GENE EXPRESSION OF NMDA RECEPTOR SUBUNITS AND A NEUREGULIN-1 SNP IN THE CEREBELLUM OF SCHIZOPHRENIA PATIENTS

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Schizophrenia patients show cognitive and subtle motor deficits which may be related to disturbances of the prefronto-thalamo-cerebellar neuronal circuit. The volume of the cerebellar vermis has been shown to be reduced in schizophrenia, but the underlying neurobiological processes remain to be elusive and may involve alterations of the glutamatergic system. To determine if N-methyl-D-aspartate (NMDA) receptor alterations are present in the cerebellum in schizophrenia, we measured NMDA receptor binding and gene expression of the NMDA receptor subunits in a post-mortem study of elderly patients with schizophrenia and non-affected subjects. Furthermore we assessed influence of genetic variation in the candidate gene neuregulin1 (NRG-1) on the expression of NMDA receptor subunits in an exploratory study. Cerebellar post-mortem samples from 10 schizophrenia patients were compared with 9 healthy subjects. We investigated NMDA receptor binding by receptor autoradiography and gene expression of the NMDA receptor subunits NR1, NR2A, NR2B, NR2C and NR2D by in-situ hybridization. For the genetic study, we genotyped the NRG-1 polymorphism

SNP8NRG221533. Additionally, we treated rats with the antipsychotics haloperidol or clozapine and assessed cerebellar NMDA receptor binding and gene expression of subunits to examine effects of antipsychotic treatment. Gene expression of the NR2D subunit was increased in the right cerebellum of schizophrenic patients compared to controls. Individuals carrying at least one C allele of SNP8NRG221533 showed decreased expression of the NR2C subunit in the right cerebellum, compared to individuals homozygous for the T allele. Correlation with medication parameters and the animal model revealed no treatment effects. Increased NR2D expression results in an hyperexcitable NMDA receptor suggesting an adaptive effect due to receptor hypofunction. The decreased NR2C expression in NRG-1 risk variant may cause an additional deficit in NMDA receptor function. This supports the hypothesis of an abnormal glutamatergic neurotransmission in the right cerebellum in the pathophysiology of schizophrenia. However, due to the small sample size, results should be confirmed in a larger study group.
ID: 550326

EPIGENETIC MECHANISMS FOR TRANSCRIPTIONAL DYSREGULATION IN SCHIZOPHRENIA

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DNA modifications and chromatin remodeling represent important mechanisms in the regulation of gene expression. Recently, increased evidence has indicated that epigenetic factors, specifically resulting in decreased gene expression, could represent a pathogenic mechanism in schizophrenia. Previously published studies have reported increased methylation of DNA at promoter sites of certain genes as marker for epigenetic regulation of gene expression. DNA methylation is intricately associated to patterns of histone remodeling, such as histone methylation and histone deacetylation, however these have not been widely studied in relation to schizophrenia. Recent microarray analyses, including our own, have revealed many altered gene expression patterns in postmortem brain samples from schizophrenic subjects. The most dramatic expression changes were decreases in gene expression. In addition to glutamate decarboxylase 1 (GAD1), one of the most abnormally expressed genes in schizophrenia, the mRNAs encoding myelin basic protein (MBP), UDP glycosyltransferase 8 (UGT8), and translocase of outer mitochondrial membrane 70 homolog A (TOMM70A) were also down-regulated. Using Chromatin Immunoprecipitation (CHIP) assay, with antibodies directed against histone H3 and total H3, we find that histones associated with the promoters of GAD1, MBP, UGT8 and TUMM70A were hypoacetylated in brain of subjects with schizophrenia. This effect coincides with the observed decreases in expression of these four genes. These findings indicate that the acetylation status of histones represents an important epigenetic mechanism for gene expression regulation in schizophrenia.
ID: 549932

MODULATION OF NEURONAL MARKERS OF SYNAPTIC PLASTICITY BY THE MGLUR5 PAM, CDPPB, IN THE HIPPOCAMPUS AND PREFRONTAL CORTEX OF RATS

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The hypoglutamatergic hypothesis of schizophrenia has led to the development of novel therapeutic strategies modulating NMDA receptor function.

One of these strategies targets the activation of the metabotropic glutamate receptor 5 (mGluR5) using positive allosteric modulators (PAMs). CDPPB was the first discovered brain penetrant selective mGluR5 PAMs (O'Brien et al., Mol. Pharm., 2003 and JPET, 2004) and displayed antipsychotic like activity in rats (Kinney et al., JPET, 2005). However, CDDPB has also recently been shown to improve cognitive performance in Y maze, passive avoidance, object recognition and set shifting assays (Balshun et al. 2006, Uslaner et al., 2009). Although the molecular mechanisms of how CDPPB exerts these pro-cognitive activities still remain to be defined. In this study, we examined the effects of CDPPB in rats at behaviorally effective doses on markers of synaptic plasticity including NMDA receptor NR1 subunit phosphorylation, ERK phopshorylation, PSD95, synaptophysin, AMPA receptor GluR1, and Cam KII expression in hippocampus and prefrontal cortex (PFC) using western blot analysis. Consistent with enhancement of NMDA glutamate-mediated signal transduction mechanisms by mGluR5 activation, CDPPB increased phosphorylation of ERK to similar levels in the PFC and hippocampus whereas phosphorylation levels of NR1 was increased earlier and reached higher levels in PFC as compared with hippocampus. These data suggest that activation of mGluR5 receptors with CDPPB can regulate both PFC and hippocampal NMDA receptors and other proteins involved in neuronal plasticity.
ID: 549918

DECREASED GYRIFICATION-INDEX (GI) IN THE CEREBELLAR VERMIS OF SCHIZOPHRENIA PATIENTS AND AN ANIMAL MODEL OF SCHIZOPHRENIA

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An increased gyrification index (GI) has been demonstrated in the frontal lobe of patients with schizophrenia. This hypergyria may serve as a neurodevelopmental or endophenotypic marker in this disease. Schizophrenia patients show subtle motor symptoms and cognitive deficits possibly related to the dysfunction of a fronto-thalamo-cerebellar network including the cerebellum. Additionally, the cerebellar vermis showed volume reductions in schizophrenia. Alterations in gyrification of the cerebellum may indicate neurodevelopmental disturbances of migration and brain folding. Hence, in a post-mortem study we investigated the GI in cerebellar subregions of schizophrenia patients and GI in the cerebellum of a probable animal model of schizophrenia, the reeler mouse. Using a stereological workstation, consisting of a light microscope (Olympus), motorized specimen, PC and stereology software (Stereoinvestigator, MBF Bioscience) we determined the GI (inner contour of the gyri/outer contour of the cerebellum) according to the methods of Vogeley et al. (2000) and Zilles et al. (1998). We investigated 4 coronal sections (20μm) of the medial cerebellum in 9 schizophrenia patients and 10 healthy controls as well as 6 sagittal sections of the cerebellum of 11 homozygous, 23 heterozygous reeler mice and 17 wildtype mice. In the vermis of schizophrenia patients, the GI was reduced compared to controls (method of Vogeley et al.: $P = .015$, method of Zilles et al.: $P = .020$). In contrast, in both hemispheres of the cerebellum, no differences have been detected. In the cerebellum of homozygous reeler mice compared to heterozygous reeler mice and wildtype mice, GI was decreased ($P < .001$). The decreased GI in the vermis of schizophrenia patients points to neurodevelopmental disturbances since the GI is mainly determined during the perinatal period. However, the underlying neurobiological processes remain to be determined. Reelin is a protein involved in migration of neurons during development and the heterozygous reeler mouse may represent an animal model of behavioral disturbances in schizophrenia, while the homozygous mutation is lethal during the postnatal period. Decreased expression of reelin may lead to gyrification disturbances,

which has been shown in our study in homozygous reeler mice. The further role of reelin in gyrification disturbances of the vermis in schizophrenia patients should be investigated.
ID: 549872

HISTONE MODIFICATIONS (H3K9K14AC AND H3K9ME2) IN SCHIZOPHRENIA; EVIDENCE FOR AN EXCESS OF RESTRICTIVE CHROMATIN

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Objective: To survey chromatin assemblies in a population of schizophrenia and bipolar subjects and identify unique histone modifications that are aberrantly expressed. Measures of H3K9K14ac (acetylated histones), and H3K9me2 (dimethylated histones) representing facilitative and restrictive chromatin respectively, were measured in clinical subjects along with an epigenetically regulated schizophrenia candidate gene GAD1. Method: Fresh mononuclear cells were extracted from blood samples of normals and clinical patients recruited at the UICMC. Primary cell cultures were established using standard *in-vitro* procedures. Histone protein and mRNA measurements were performed to investigate a) baseline differences; b) response of cultured cells to HDAC inhibitors; c) response to clinical treatment across four weeks with the HDAC inhibitor valproic acid. Histone protein modifications were measured by Western blot, and GAD1 mRNA expression was measured using quantitative RT-PCR. Results: a) Schizophrenia subjects have significantly lower levels of H3K9K14ac histones compared to normals subjects as measured in fresh mononuclear cells (schizophrenia ($n = 23$), normals ($n = 21$); $P < .04$). b) Levels of H3K9me2 histones are significantly elevated in fresh mononuclear cells in patients with schizophrenia ($P < .02$). c) primary mononuclear cultures from schizophrenia subjects manifest significantly blunted acetylation of histones when incubated for 24 hrs with the HDAC inhibitor Trichostatin-A ($P < .01$). c) similarly, clinical levels of valproic acid applied over four weeks in clinically treated subjects are far less effective in modifying histones in schizophrenia patients when compared to bipolar patients ($P < .04$). Conclusions: Chromatin is the DNA-protein platform required for the focusing and assembly of regulatory proteins especially on the promoter sequence of a given gene. Our results suggest that schizophrenia is associated with an excess of restrictive type chromatin. These results support the investigation into the relationship of chromatin modifications to gender, metabolism, chronicity, medication use, and selective augmentation with an HDAC inhibitor.
ID: 549769

SELECTIVE REDUCTION OF OLIGODENDRO-CYTES IN THE POSTERIOR HIPPOCAMPUS OF SCHIZOPHRENIC PATIENTS AND A MURINE MODEL OF SCHIZOPHRENIA WITH A SELECTIVE PARIETAL LOBE LESION

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The bilateral volume reduction of the hippocampus is one of the best replicated findings in schizophrenia and is correlated with disturbed verbal memory functions being one of the best predictors for the unfavourable outcome in schizophrenia. Nevertheless, there is very limited knowledge concerning the underlying pathophysiological processes. In this respect we investigated numbers and densities of neurons, oligodendrocytes and astrocytes in the posterior hippocampal subregions in post-mortem brains from 10 patients with schizophrenia and 10 matched controls using design-based stereology performed on Nissl-stained sections. Compared to the controls, the patients with schizophrenia showed a significant decrease in the mean number of oligodendrocytes in the left and right CA4. This is the first finding of reduced numbers of oligodendrocytes in CA4 of the posterior part of the hippocampus in schizophrenia. Our results are in line with earlier findings in the literature concerning decreased numbers of oligodendrocytes in the prefrontal cortex in schizophrenia. To gain mechanistic insight into the pathophysiological processes involved we performed an experimental study aiming at modelling degenerative aspects of schizophrenia. Applying a small cryolesion onto the right parietal cortex of juvenile mice, we induced late-onset global brain atrophy with memory impairments, reminiscent of cognitive decline and progressive brain matter loss in schizophrenia. Whereas the total number of neurons and astrocytes in cingulate cortex and hippocampus remained unaltered and pointed to a non-gliotic neurodegeneration (as seen in schizophrenia), we found reduced expression of the myelin protein CNPase (cyclic nucleotide phosphodiesterase) together with a reduction of oligodendrocytes. Remarkably, early intervention with recombinant human erythropoietin (EPO), a hematopoietic growth factor with multifaceted neuroprotective properties, prevented these neurodegenerative changes. In summary, the outlined human post-mortem study reveals a selective reduction of oligodendrocytes in the posterior hippocampus in schizophrenia. The animal study nicely demonstrates that a small parietal cortical lesion in juvenile mice can induce a selective loss of oligodendrocytes in a non-gliotic degenerative process as it potentially underlies the pathophysiology of schizophrenia.

ID: 549687

IDENTIFICATION OF A MUSCARINIC RECEPTOR DEFICIT SCHIZOPHRENIA

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We have shown decreased cortical muscarinic M1 receptors (CHRM1) in schizophrenia and wished to determine the extent of this deficit in subjects with the disorder. We have now gone on to determine levels of [3H]pirenzepine binding in Brodmann's area 9 from controls ($n = 74$) and subjects with schizophrenia ($n = 80$) and CHRM1 genotype in DNA from their CNS tissue. The data from this study showed that there was no relationship between levels of [3H]pirenzepine binding and CHRM1 genotype. However, [3H]pirenzepine binding was significantly decreased in subjects with the schizophrenia compared to controls (Mean ± SEM: 133.9 ± 7.25 vs. 182.7 ± 4.50 fmol/mg ETE; $P < .0001$). Moreover, a Kernel Density Analyses showed that the control data was consistent with a single population in which the data was binomially distributed. By contrast the data from the subjects with schizophrenia was consistent with two-populations, one ($n = 22$) had very low levels of pirenzepine binding (Mean ± SEM: 44.3 ± 6.88) and another ($n = 58$) had levels of radioligand binding (Mean ± SEM: 167.8 ± 4.52 fmol/mg ETE) similar to that observed in controls. From these data we conclude that subjects with a marked reduction in cortical CHRM1 receptors (76%) may represent a discrete endophenotype within the syndrome of schizophrenia
ID: 549569

PHOSPHOLIPID CONCENTRATIONS IN DORSOLATERAL PREFRONTAL GREY AND WHITE MATTER IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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The 'membrane hypothesis of schizophrenia' proposes that brain phospholipid metabolism is altered in this disorder. While lower levels of membrane lipid components, including phospholipids and fatty acids, have been reported in schizophrenia, most studies have examined peripheral markers rather than brain tissue. However, previous post-mortem studies have identified lower phosphatidyl ethanolamine (PE) levels in the cholesterol ester fraction of the frontal cortex and lower phosphatidyl choline (PC) levels in the caudate and thalamus in this disorder. Although membrane alterations have also been proposed in bipolar disorder, brain phospholipid levels have not yet been assessed in this disorder. Lipid content is known to differ between white and grey matter, mainly due to higher levels of myelin in the former. Considering recent reports of white matter alterations in schizophrenia and bipolar disorder, our aim was to quantify phospholipid levels in grey and white matter in these disorders in order to assess region and disease specificity of membrane alterations. Samples of grey and underlying white matter were obtained from the dorsolateral prefrontal region (Brodmann area 9), courtesy of the Stanley Medical Research Institute brain collection (35 schizophrenia, 34 bipolar disorder, 35 control). Groups were matched for age and post-mortem interval. Lipids were quantified using high-pressure liquid chromatography. PE and PC peaks were measured and concentrations compared between groups using repeated measures analysis of variance. We observed a significant effect of region, with PE and PC levels higher in white matter than in grey matter. Overall, there was a significant effect of diagnosis ($F = 3.297$, $P = .041$), with contrasts indicating that phospholipid levels were altered in both the schizophrenia ($P = .025$) and bipolar disorder ($P = .033$) groups. We observed no significant region by diagnosis, or lipid by diagnosis effect. In white matter both PE and PC levels were lower by 3% in the schizophrenia group and by 5% in the bipolar disorder group. In grey matter both PE and PC levels were lower by 7% in the schizophrenia group and by 5% in the bipolar disorder group. The results are consistent with a small but significant reduction in phospholipid levels in both grey and white matter in schizophrenia and bipolar disorder, suggestive of a global membrane abnormality.

ID: 550820

CANNABIS AND PREFRONTAL CORTICAL CIRCUITRY IN SCHIZOPHRENIA

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Cannabis use during adolescence is associated with an increased risk of schizophrenia, and cannabis exposure causes impairments in a number of cognitive processes, such as working memory, that are also exhibited by individuals with schizophrenia. Working memory impairments in schizophrenia are associated with both reduced GABA neurotransmission in the dorsolateral prefrontal cortex (DLPFC) and altered gamma oscillations. The effects of cannabis are mediated by the cannabinoid CB1 receptor (CB1R), which is highly expressed in the DLPFC, is present in high density on the axon terminals of a subset of GABA neurons, and when activated, suppresses the release of GABA and alters gamma oscillations. Thus, understanding the normal role of the CB1R receptor in regulating GABA neurotransmission in the DLPFC, and the status of this receptor in schizophrenia, is essential. In this presentation, we will review recent and unpublished findings demonstrating 1) the distribution and development of the CB1R in primate DLPFC, 2) lower CB1R mRNA and protein levels in the DLPFC of subjects with schizophrenia, 3) the replication of these findings in another subject cohort and their presence in another prefrontal region, 4) the absence of altered CB1R levels in major depression, and 5) improvement in working memory and gamma oscillations in schizophrenia with a novel compound that augments GABA neurotransmission at GABAA receptors post-synaptic to GABA axon terminals bearing CB1Rs. Together, these findings provide a potential mechanistic basis for the observations of cannabis exposure and adverse outcomes in schizophrenia.
ID: 551844

ANALYSIS OF POSTYSYNAPTIC DENSITY PROTEINS AND THEIR LOCALIZATION IN SCHIZOPHRENIA

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Converging evidence implicates NMDA receptor dysfunction in schizophrenia. Chronic blockade of NMDA receptors with PCP alters the expression levels of NMDA receptors and changes the stoichiometry of NMDA receptor subunits. Treatment with NMDA receptor modulators such as glycine or D-serine reduced negative symptoms, and several postmortem studies have found altered expression of NMDA receptor subunits and binding sites in schizophrenia. Recent work found increased expression of the alternatively spliced NR1C2' NMDA receptor subunit, which is associated with increased transit of the NMDA receptor from ER to the postsynaptic density. These data suggest that the deficits in schizophrenia may not simply be a problem of increased or decreased receptor expression, but an alteration in the intracellular localization of the NMDA receptor. Specifically, we hypothesize that there is decreased trafficking and localization of NMDA receptors to the postsynaptic density, contributing to altered glutamatergic transmission in schizophrenia. To identify any alterations in the composition of the postsynaptic density (PSD), we are using an anti-PSD95 antibody bound to agarose beads to enrich a fraction specific for PSD from human postmortem tissue. SynGAP, a RasGTPase that directly binds to PSD95 via MUPP1 (a multi-PDZ domain containing scaffolding protein) and localizes to the PSD, is co-enriched in our PSD fraction. This technique will be used to quantify the fraction of PSD components that are trafficked to the PSD in schizophrenia. In addition to our PSD studies, we have performed Western blot analysis on proteins that create a complex within the postsynaptic density that is critical for scaffolding and proper orientation of activating proteins. Scaffolding proteins PSD95 and MUPP1 form a complex with SynGAP which has functional relevance to NMDA receptor mediated glutamatergic neurotransmission. We found a significant reduction of PSD95 in anterior cingulate cortex (ACC), with no changes in other areas. SynGAP showed no change in any of the areas analyzed. Data for the expression of MUPP1 in schizophrenia will be presented. The ACC is reported to process some executive functions such as: error and expectation awareness, conflict monitoring, reward anticipation

and reward based learning, which are abnormal in schizophrenia. This finding supports the hypothesis of dysregulated NMDA receptor stabilization at the PSD.
ID: 551713

BRAIN REGIONAL EXPRESSION PATTERN OF THE VOLTAGE-GATED POTASSIUM CHANNEL, KV3.2 IN SCHIZOPHRENIA

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Accumulating evidence suggests that individuals with schizophrenia exhibit a reduction in stimulus-mediated gamma oscillations in brain. Gamma oscillations are fast frequency bands of electroencephalography (EEG) rhythms at 30–100Hz. Fast-spiking GABA-containing interneurons are presumed to participate in the generation of these gamma oscillations. Parvalbumin-containing GABA interneurons, which comprise only a subset of GABA interneurons, have fast-spiking properties, and are thought to have a primary role in gamma oscillations. Altered expression of GABA related proteins has been found in schizophrenia tissue, in particular, proteins which are related to these parvalbumin-positive GABA-containing interneurons in schizophrenia prefrontal cortex. Kv3 channels are voltage-gated K+ channels involved in the rapid repolarization of the action potential, and four Kv3 genes (Kv3.1-Kv3.4) are found in both rodents and humans. Kv3.1 and Kv3.2 channels are expressed prominently in GABA neurons in the cortex of rodents where they facilitate fast-spiking of the neurons. Furthermore, the Kv3.1 channel specifically is reported to play a role in the generation and maintenance of gamma oscillations. These convergent lines of evidence suggest that Kv3.1 and Kv3.2 channels could contribute to mechanisms involved in some of the manifestations of schizophrenia. Thus, we determined the expression and distribution of Kv3.1 and Kv3.2 channel proteins in human postmortem brain and compared the expression between schizophrenia and control tissue. We examined the expressions of Kv3.1 and Kv3.2 proteins using Western blots in dorsolateral-prefrontal, cingulate, orbito-frontal, parietal, and occipital cortices, and in cerebellum, caudate nucleus, nucleus accumbens, thalamus, and hippocampus from normal control tissue. Immunoreactivity of Kv3.2 was strongly seen in these regions, although that of Kv3.1was not strong enough to detect reliably in any of the regions. We quantified the immunoreactivity of Kv3.2 in 12 cases with schizophrenia and 12 controls in these ten regions. No differences emerged in Kv3.2 expression levels between schizophrenia and controls except a small yet significant difference in nucleus accumbens. Our results suggest that the expression levels of the Kv3.2 protein do not distinguish schizophrenia from normal brain tissue, and that alterations in the concentration of these proteins do not account for alterations in neo- or sub-cortical function.
ID: 551674

GABA-RELATED MRNA EXPRESSION IN THE DORSOLATERAL PREFRONTAL CORTEX (DLPFC) OF SUBJECTS WITH BIPOLAR OR MAJOR DEPRESSIVE DISORDER

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In schizophrenia, disturbances in cognitive functions, such as working memory, are associated with alterations in the inhibitory circuitry of the DLPFC. These alterations seem to be specific to certain subpopulations of GABA-containing interneurons. For example, transcripts that encode for somatostatin (SST) and parvalbumin (PV), each expressed in separate subpopulations of interneurons, are robustly reduced; in contrast,

calretinin (CR) mRNA, expressed in a third subpopulation of interneurons, is not altered in schizophrenia. In addition, the magnitude of the reductions in SST and PV mRNAs were greater than for the mRNA encoding the 67-kilodalton isoform of glutamic acid decarboxylase (GAD67), the enzyme principally responsible for GABA synthesis, and little to no change was detected for the mRNA encoding the 65-kilodalton isoform of GAD (GAD65). Assessing the expression of these GABA-related transcripts in other psychiatric populations is necessary to determine if this pattern of transcript alterations is specific to schizophrenia. Bipolar (BPD), but not major depressive (MDD), disorder appears to share some genetic risks with schizophrenia, although many individuals with each of these disorders have similar environmental consequences associated with a severe and persistent psychiatric illness. Therefore, we utilized qPCR to examine the expression of GAD67, GAD65, PV, SST, and CR mRNAs in DLPFC area 9 from 19 matched triads of subjects with BPD, MDD and control subjects. Each qPCR run included 3 subjects from a triad and amplified the 5 transcripts of interest and 3 internal control transcripts in quadruplicate. ANCOVA and subsequent multiple comparisons correction revealed a significant ($F2,49 = 10.73$; corrected $P < .0007$) effect of diagnosis for PV mRNA expression. Post-hoc analysis demonstrated that BPD subjects had a 16% reduction in PV mRNA expression compared to control subjects and an 18% reduction compared to MDD subjects. In contrast, expression levels for the other four transcripts were very similar across the 3 groups of subjects. These results suggest that altered PV expression in the DLPFC might be common to both schizophrenia and BPD, but the profile of GABA-related gene expression alterations is diagnosis-specific. Furthermore, the lack of alterations in MDD subjects suggests that the findings in schizophrenia and BPD may reflect the disease process and are not a common consequence of severe psychiatric illness.
ID: 551669

ABNORMALITIES OF EXCITATORY AMINO ACID TRANSPORTER-1 GLYCOSYLATION IN SCHIZOPHRENIA

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Several studies have demonstrated cortical abnormalities in glutamate neurotransmission in schizophrenia. The excitatory amino acid transporters (EAATs) facilitate the vast majority of synaptic glutamate clearance and thus are critical to normal glutamatergic signaling. Genetic and gene expression studies have recently implicated the glial glutamate transporter EAAT1 in schizophrenia. We have previously described increased mRNA expression and decreased protein expression of EAAT1 in prefrontal cortex in schizophrenia. EAAT1 function can be modified at additional levels beyond transcript and protein expression, including post-translational modifications such as glycosylation, which is required for EAAT1 trafficking and multimerization. We hypothesize that EAAT1 glycosylation is altered in prefrontal cortex in schizophrenia. In this study, we digested postmortem brain homogenates from subjects with schizophrenia and controls with the deglycosylating enzymes endoglycosidase H and PNGase F and measured shifts in molecular weight using Western blot analysis. We found an increase in the PNGase F induced molecular weight shift in the anterior cingulate cortex in patients with schizophrenia versus controls, but no changes in endoglycosidase H induced shifts. We found no difference in shifts in controls or subjects with schizophrenia in the dorsal lateral prefrontal cortex following treatment with either glycosidase. These data suggest that EAAT1 N-linked glycosylation may be selectively altered in the anterior cingulate cortex in schizophrenia. To further investigate these differences at the level of specific glycosyl residues, we immunoprecipitated EAAT1 for two types of analysis: mass spectrometry and lectin-based carbohydrate detection. We have successfully detected mannose and glucosamine residues in our EAAT1 immunoprecipitates using biotinylated

lectins, including concanavalin A, wheat germ agglutinin, and lens culinaris agglutinin. Data from these lectin studies probing for alterations in specific glycosyl residues in subjects with schizophrenia and controls will be presented. Our results suggest an increase in EAAT1 glycosylation in schizophrenia which may impact EAAT1 trafficking and multimerization, leading to alterations in EAAT1 surface expression and activity. These data represent an important new lead for understanding abnormalities of the glutamate cycle in schizophrenia.
ID: 551624

CHARACTERIZATION OF A UNIQUE, DEVELOPMENTALLY REGULATED SPLICE VARIANT OF HUMAN NRG1 TYPE IV. IMPLICATIONS FOR SCHIZOPHRENIA

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Genetic studies implicate NRG1 in risk for schizophrenia and a clinically-associated polymorphism (rs6994992) represents a cis regulatory element associated with transcription of NRG1, type IV in the adult human brain (Law et al. 2006; Tan et al. 2007). Type IV is 3.5 fold higher in the human fetal brain compared to the adult however its role in neurodevelopment and its relationship to schizophrenia risk are unknown. We have cloned and characterized NRG1, type IV transcripts in the human fetal brain and reveal a complex pattern of alternative splicing. Of particular interest is the identification of a novel splice isoform (termed NFIV1) whose expression is restricted to a critical period of human neurodevelopment and regulated by rs6994992. The NRG1, type IV family was cloned from cDNA libraries of fetal human brain. Utilizing real time QRT-PCR we then measured quantitative expression traits of NFIV1 in a cohort of human fetal brains ($N = 45$; 14–20 weeks gestation) and individuals across the lifespan ($n = 195$ Age range 0–80 years). All individuals were genotyped for rs6994992. To assess the biological function of NFIV1 we developed Myc-tagged constructs for transfection of rat primary hippocampal neurons. Translation characteristics, subcellular localization and dendritic spine development were examined. NFIV1 is a unique NRG1 transcript characterized by the absence of exon E24 which codes for the α-secretase cleavage domain and a premature stop codon in the cytoplasmic domain. Expression of NFIV1 in the human brain emerges in the second trimester were it was highly expressed and remains so until approximately 12 months postnatal. NFIV1 was not identified in adult brain. Risk genotypes at rs6994992 predict lower expression of NFIV1 during development. Fusion protein studies reveal that the NFIV1 transcript is translated into a truncated protein which is resistant to biochemical processing mediated via α-secretase and shows a diffuse cytoplasmic and dendritic localization with intense nuclear expression. NFIV1 expression affected the maturation and growth of dendritic spines in rat primary hippocampal neurons. Our results demonstrate a role for NRG1, type IV in human brain development and demonstrate a complex pattern of splicing during critical developmental periods which has implications for type IV's involvement in genetic risk for schizophrenia.

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ID: 551491

INVESTIGATING THE CONSEQUENCES OF ELEVATED D-AMINO ACID OXIDASE (DAO) IN SCHIZOPHRENIA: STUDIES OF D-SERINE METABOLISM AND TRANSPORT IN C6 GLIOMA CELLS

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The glial enzyme D-amino acid oxidase (DAO) metabolizes D-serine, a co-agonist of the NMDA receptor. We and others have demonstrated an increase in the expression and activity of DAO in schizophrenia, which may reduce brain D-serine concentrations, and thence contribute towards NMDAR hypofunction in the disorder. This hypothesis, however, requires that DAO has access to D-serine from the synapse (via the D-serine transporter), and that the increased DAO is not counter-balanced by an elevation in serine racemase (SRR), the D-serine synthesizing enzyme. We have been using rat C6 glioma cells as a model system to investigate the effect of increased DAO expression on SRR and D-serine uptake. We have established that C6 cells normally express SRR, DAO, and the D-serine transporter ASCT2, and have over-expressed DAO protein in the cells using recombinant DAO transfections; this was confirmed using western blotting normalized to beta-actin (control cells: $1.22 + 0.1$ vs over-expressing cells : $2.1 + 0.1$, $P < .01$, $n = 6$, paired t-test). The over-expression of DAO did not alter levels of SRR (control cells: $0.97 + 0.2$ vs over-expressing cells: $1.01 + 0.16$, $n = 6$, $P = .184$). The kinetics of extra-cellular D-serine uptake into C6 cells were examined by measuring the incorporation of radioactivity one hour after the addition of [3H]-D-serine to the culture medium. DAO over-expression did not alter the uptake of [3H]-D-serine (control cells: $30 + 1$ vs over-expressing cells: $32 + 2$ pmol/min/mg protein, $n = 6$, $P = .241$). We quantified ASCT2 mRNA using RT-PCR and its expression, normalized to GAPDH mRNA, was also unaffected (control cells: $0.56 + 0.04$; over-expressing = $0.53 + 0.04$, $n = 6$, $P = .311$). These data show that a two-fold elevation of DAO expression in C6 cells does not affect the levels of the D-serine synthetic enzyme SRR, nor D-serine uptake nor ASCT2 expression. If a similar absence of compensatory changes pertains in the brain in vivo, it supports the possibility that the increased DAO expression and activity seen in schizophrenia may indeed impact upon D-serine availability. In ongoing work in this cell model, we are measuring intracellular D-serine concentrations, and studying the consequences of lowering DAO by RNAi and of manipulating SRR expression. Integrative studies of this kind will clarify the likely functional implications of increased DAO in schizophrenia, and help to evaluate DAO and other D-serine related molecules as therapeutic candidates.
ID: 551449

GROUP I AND II METABOTROPIC GLUTAMATE RECEPTORS IN THE HUMAN PREFRONTAL AND TEMPORAL CORTEX: DIFFERENCES IN SCHIZOPHRENIA

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Schizophrenia is a chronic brain disease of unknown etiology. There have been several hypotheses proposed for explaining schizophrenia pathophysiology, the most recent of which proposes a disruption of glutamatergic neurotransmission. It is based on the ability of N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP) and ketamine, to produce a syndrome that is clinically indistinguishable from schizophrenia. The group I (mGluR 1 and 5) and group II (mGluR 2 and 3) have been implicated in this illness. The group II mGluR agonists attenuate neurochemical and behavioral effects of PCP, similar to actions of atypical antipsychotic medications. A recent Phase 2 clinical trial with an mGluR2/3 agonist, LY 2140023, demonstrates antipsychotic activity in patients with schizophrenia. Animal and human post mortem studies suggest that mGluR 1 and 5 may also be important in the pathophysiology of schizophrenia. This study was designed to distinguish the expression of mGluR1, 2, 3 and 5 receptor proteins in schizophrenia using human post mortem brain tissue. Receptor-specific antibodies were used in immunoblotting experiments to determine differences in expression levels of each mGluR in the prefrontal (PFC) and temporal (TC) in 15 matched cases of schizophrenia and normal controls. Six month chronic antipsychotic treatment in rodents was conducted to examine the potential effect of antipsychotic drugs on protein expression. We find a significant reduction of mGluR3, but not mGluR1, 2 or 5, in the PFC in schizophrenia. Chronic antipsychotic treatment in rodents did not influence mGluR3 levels. There were no significant differences in any of the mGluRs in the TC. These data suggest that reduced signaling at the mGluR3 receptor in the PFC may be important in the pathophysiology of schizophrenia. Further, these data implicate the mGluR3 receptor in the antipsychotic action of mGluR2/3 agonists.
ID: 551420

ISOLATION AND ANALYSIS OF ENDOSOMES IN SCHIZOPHRENIA

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Accumulating evidence suggests that glutamate receptor dysfunction in schizophrenia is not a problem of too much or too little receptor expression, but instead a problem of receptor trafficking. Trafficking of receptors is controlled, in part, by phosphorylation of specific residues on the AMPA receptor subunits. Phosphorylation may lead to stabilization of a receptor at the synapse or internalization of the receptor in endosomes. Turnover of receptors via endosomes is a critical event for regulation of neuronal transmission at the synapse. We postulate that alterations in endosome content may underlie neuropathological alterations in schizophrenia. We hypothesize that there is an increase in AMPA receptor containing early endosomes in schizophrenia, suggesting increased turnover of AMPA receptors in this illness. The aim of this study is to isolate the early endosomes from postmortem human brain tissue and to use a modified subcellular fractionation technique to probe for alterations in endosome content and AMPA receptor subunit expression. Tissue homogenates were pre-cleared of non-specific binding via incubation with magnetic beads. Using this pre-cleared tissue homogenate, we targeted endosomes for immunoisolation using a magnetic bead-antibody complex (specific binding) or using magnetic beads only (negative control). Captured material was removed from the beads and analyzed by Western blot analysis. The early endosome marker, Early Endosome Antigen 1 (EEA1) was detected in the pre-clear pellet (non-specific binding) and in the immunoisolation (specific binding) lanes, but not in the negative control lane. As confirmation of endosomal isolation, electron microscopy (EM) imaging was used. By double-blind evaluation, we observed a 6.15 fold enrichment of endosomes in the immunoisolation (specific binding) sample compared to the pre-clear (non-specific) pellet sample. Data on expression of EEA1 and AMPA receptor subunits in endosome fraction for subjects with schizophrenia and a comparison group will be presented. Overall protein expression of EEA1, Rab4, and Rab7 in anterior cingulate cortex and dorsolateral prefrontal cortex will be presented. In summary, we have developed a modified immunoisolation protocol to isolate early endosomes from postmortem tissue. This technique will permit us to test the hypothesis that there is an alteration in trafficking of AMPA glutamate receptor subunits in the endosomal compartment in schizophrenia.
ID: 551407

ROLE OF c-Cbl (AN E3 UBIQUITIN LIGASE) IN BDNF/ TRKB SIGNALING IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Brain derived neurotrophic factor (BDNF) through its receptor, TrkB plays a crucial role in neuroplasticity (ie, growth and branching of dendrites, remodeling of synaptic contacts and neurogenesis). TrkB dysregulation has been associated with several pathophysiological conditions including neurodegenerative diseases and psychiatric disorders such as schizophrenia and depression. Understanding the mechanisms regulating TrkB may provide new strategies for the prevention and treatment of the pathologies associated with TrkB dysregulation. The present study has explored the role of ubiquitination in the regulation of TrkB signaling in schizophrenia. We have identified an E3 ubiquitin ligase, c-Cbl that associates with TrkB in the postmortem brain samples from schizophrenia and bipolar disorder subjects. c-Cbl gene expression was analyzed in dorsolateral prefrontal cortex samples from the Stanley Array Collection. Quantitative real-time PCR analysis of RNA in 100 individuals (35 with schizophrenia, 31 with bipolar disorder, and 34 psychiatrically normal controls) showed significantly increased expression of c-Cbl in both schizophrenia and bipolar disorder. Our study also showed that the binding of c-Cbl to TrkB leads to the ubiquitination and downregulation of TrkB in mouse cortical neurons. Our results suggest that ubiquitination of TrkB may be involved in the downregulation of BDNF signaling in schizophrenia and bipolar disorder. The identification of a specific E3 ubiquitin ligase molecule represents a potential mechanism to control the levels of TrkB function in psychiatric disorders.
ID: 551321

DECREASED PROTEIN EXPRESSION AND ALTERATION OF N-GLYCOSYLATION OF THE GLUR2 AMPA RECEPTOR SUBUNIT IN SCHIZOPHRENIA

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Abnormalities in glutamate neurotransmission have been proposed to underlie some aspects of schizophrenia. We and others have demonstrated significant abnormalities in schizophrenia of ionotropic glutamate receptor transcripts that are region- and receptor subunit-specific. For example, we have demonstrated that transcript levels for some AMPA receptor subunits (GluR2, GluR3 and GluR4) are decreased in dorsolateral prefrontal cortex (DLPFC) in schizophrenia. Further, we have reported alterations in expression of AMPA receptor-associated proteins that regulate AMPA receptor trafficking and expression at the plasma membrane. We have found decreased PICK2 mRNA and elevated stargazin mRNA in DLPFC in schizophrenia. Interestingly, both of these proteins play a critical role in AMPA receptor trafficking: PICK1 regulates GluR2 recycling at the post-synaptic cell membrane by favoring retention of internalized GluR2 in recycling pools, while stargazin promotes AMPA receptor trafficking through an early biosynthetic pathway. Abnormalities of PICK1 and stargazin expression may thus result in abnormal AMPA receptors trafficking and/or postranslational modification (N-glycosylation) in schizophrenia. N-glycosylation takes place early in AMPA receptor biosynthesis, and is postulated to regulate trafficking, proteolysis and to modulate AMPA receptor function at the synapse. In this study, we investigated total protein expression, as well as N-glycosylation state of the GluR2 AMPA receptor subunit. Total protein levels and N-glycosylation of GluR2 were determined in DFPLC and anterior cingulate cortex (ACC) in schizophrenia and a comparison group by western blotting analysis. N-glycosylation was assessed in brain samples following digestion with endoglycosidase H (Endo H), which removes immature high mannose sugars, and with peptide-N-glycosidase

F (PNGase F), which removes all N-linked sugars. We discovered that GluR2 protein levels were decreased in schizophrenia and that a GluR2 protein pool was significantly less sensitive to Endo H-driven deglycosylation in schizophrenia. These data suggest that GluR2 may be differentially glycosylated in schizophrenia and controls. In the future, we plan to expand the current study and determine protein levels for all four of the AMPA receptor subunits and their N-glycosylation status in DLPFC and ACC in this illness.
ID: 551313

PHARMACOLOGICAL MODULATION OF CANNABINOID SYSTEM DIFFERENTLY AFFECTS SCHIZOPHRENIA-LIKE SYMPTOMS IN ANIMAL MODELS

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Evidences suggest an involvement of the endogenous cannabinoid system in the pathophysiology of schizophrenia. We demonstrated that chronic phencyclidine (PCP) treatment, a model of cognitive symptoms of schizophrenia, altered the cannabinoid system in the rat prefrontal cortex. Moreover, we demonstrated that prolonged delta-9-tetraydrocannabinol exposure worsened behavioural and biochemical effects induced by PCP (Viganò et al., 2008). This study put forward the hypothesis of potential antipsychotic properties of cannabinoid receptor antagonists. On this basis, we evaluated behavioural and biochemical responses induced by chronic administration of low dose of AM251 (0.5mg/kg), a CB1 receptor antagonist, in rats co-exposed to chronic PCP (2.5mg/kg). Chronic AM251 co-treatment improved the PCP-altered recognition memory in a novel object recognition task and reduced the immobility induced by PCP in the forced swim test. Additionally, the behavioural improvement induced by the CB1 receptor antagonist was accompanied by the counteraction of the reduction in CB1 receptor functionality produced by PCP. These results suggest a potential beneficial role of AM251 for cognitive and negative schizophrenia-like symptoms induced by PCP. Moreover, to better understand the role of endocannabinoid ligands in all the behavioural aspects induce by PCP, we studied the effects of direct and indirect cannabinoid agonists in positive schizophrenia-like symptoms. To this aim, rats received an acute administration of the CB1 receptor agonist delta9-THC (0.5mg/kg) and the anandamide uptake inhibitor AM404 (3mg/kg) before acute PCP (3.5mg/kg). Both these compounds counteracted PCP-induced psychotic-like symptoms, inhibiting the increase of the locomotor activity and ataxia, and reducing stereotypies. The relative involvement of cannabinoid or vanilloid receptors in the protective effects of AM404 was assessed through the pre-treatment with the cannabinoid antagonist AM251 (0.5mg/kg) or vanilloid antagonist capsazepine (10mg/kg). AM251 reversed the protective effect of AM404 on locomotion whereas capsazepine better reversed AM404 protective effects on stereotypies and ataxia suggesting a dual role of CB1 and TRPV1 receptors in modulating beneficial effect of cannabinoids. In conclusion, CB1 receptor agonists and antagonists seem to be promising candidates for novel approaches in the treatment of different symptoms of schizophrenic disorders depending on the frequency use.
ID: 551254

ALTERED EXPRESSION OF DENDRITIC SPINE-RELATED GENE PRODUCTS IN THE DORSOLATERAL PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA

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Spine density on the basilar dendrites of deep layer 3 pyramidal neurons is decreased in the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia. The mRNA expression of CDC42, which promotes spine formation, is decreased in the DLPFC in schizophrenia, and CDC42 mRNA levels correlated with spine density. However, CDC42 mRNA was decreased in deep layer 3, as well as in layer 6 where spine density was not altered. To determine the molecular mechanisms contributing to laminar-specific spine deficits in schizophrenia, we used real-time qPCR to measure mRNA levels of two downstream targets of CDC42, CDC42EP3 and CDC42EP4, which are preferentially expressed in layers 2 and 3, in the DLPFC from two cohorts of matched pairs of schizophrenia and control subjects (cohort 1 = 12 pairs; cohort 2 = 19 pairs). We also measured the mRNA levels for interacting gene products [septins (SEPT2, 3, 5, 6, 7, 8 and 11), PUM2, ANLN] and other spine-specific gene products (spinophilin, PSD95, synaptopodin). ANCOVA analyses (including age, sex, PMI, RNA integrity number, pH, storage time and cohort as covariates) showed significant increases in CDC42EP3 (26.6%, 15.3%, $P = .002$), PUM2 (16.5%, 8.7%, $P = .005$) and SEPT11 (20.6%, 19.8%, $P = .02$), and a significant decrease in SEPT7 (-8.6%, -6.0%, $P = .02$) mRNA expression in schizophrenia. Although SEPT7 is a spine neck component and its mRNA levels significantly correlate with CDC42 mRNA, and in situ hybridization confirmed decreased SEPT7 mRNA in schizophrenia (-8%, $P = .03$), the decrease was found in both layer 3 (-9%, $P = .046$) and layer 6 (-13%, $P = .005$). However, PUM2 could control spine formation through regulating dendritic translation of spine related genes possibly including CDC42EP3 or septins. Thus, the altered expression of PUM2, SEPT11 and/or CDC42EP3 might contribute to the reductions in spine density predominantly in layer 3. In situ hybridization studies are in process to determine the laminar-specificity of these findings. Molecules regulating the downstream signaling of CDC42 could be novel molecular targets for therapeutic interventions in the illness.
ID: 551150

SIMILAR INFLAMMATORY PROFILE IN BIPOLAR DISORDER AND SCHIZOPHRENIA: SELECTIVE INCREASE IN SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR I AND VON WILLEBRAND FACTOR

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Alterations in the inflammatory system have been associated with schizophrenia and mood disorders. Bipolar disorder has been less studied, and the literature is inconsistent with regard to the specific underlying mechanisms. This study aim was to investigate inflammatory parameters in a representative sample of bipolar disorder and schizophrenia compared to healthy controls. Plasma levels of soluble tumor necrosis factor receptor 1 (sTNFR1), Interleukin 1 receptor type 1 (ILR1), Interleukin 6 (IL6), high-sensitivity CRP (hs-CRP) and von Willebrand factor (vWf) was measured with ELISA techniques in a catchment area based sample of consecutively referred patients with severe mental disorders ($n = 443$; comprising bipolar spectrum disorder ($n = 169$) and schizophrenia spectrum ($n = 274$), and healthy volunteers ($n = 261$)). Plasma levels of sTNFR1 and vWf were highly statistically significantly increased in both bipolar disorder and schizophrenia compared to controls, but with no major differences between the two diagnostic groups. Controlling for age, gender and ethnical differences did not affect the results. There was a trend towards statistically significant elevation of hs-CRP between the two diagnostic groups and the controls. There were no differences in other inflammation factors between the groups. This study indicate specific alterations of endothel related inflammation processes in severe mental disorders.
ID: 551024

THE OLFACTORY EPITHELIAL BIOPSY APPROACH FOR THE STUDY OF NEURODEVELOPMENTAL DYSREGULATION IN SCHIZOPHRENIA

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The olfactory neuroepithelium (OE) is the only neural tissue that is readily obtainable from living human subjects and thus can provide a unique opportunity to examine neurons of patients with neuropsychiatric illnesses. The OE biopsy tissues can be examined under in vivo, ex vivo and in vitro conditions for biochemical, molecular and electrophysiological characteristics in the subjects' neural tissues. Particularly relevant to the pathophysiologic study of schizophrenia is a neurodevelopmental characteristic of the OE; neuronal regeneration continues throughout life. Human OE may differ from the rodent counterpart in molecular processes underlying neurogenesis. In the rodent OE, two distinct cell types in the basal cell layer, horizontal basal cells (HBC) and globose basal cells (GBC) play critical roles in neurogenesis. Subsequent maturation of rodent olfactory neurons (ORNs) occurs in layers of immature and mature ORNs in laminar organization. The basal cell layer of human OE does not contain HBCs, pluripotent cells and laminar organization of ORNs does not exist in the human OE. In vitro organotypic cultures of the OE can be a powerful tool to study neurodevelopmental dysregualtion in schizophrenia. We and others have shown that organotypic cultures of human OE can produce BrdU labeled cells expressing neuronal markers and that neuronal differentiation can partly occur in vitro. In addition, OE cells propagated in dissociated cultures express functionally active D2, 5HT1A, 5HT2A and NMDA receptors, which permit an opportunity to examine dysregulations in neurotransmitter receptor functions in patients' neuronal cells. Cellular heterogeneity and individual variability in the cellular composition of OE tissues pose a special challenge in relating the data from OE cells to the person's characteristics. The OE consists of neuroepithelium as well as respiratory epithelium and each biopsy tissue varies in proportions of neuronal and non-neuronal cell types. Similarly, in vitro OE cultures contain neuronal, non-neuronal cells and some in transition and their compositions appear to vary between individuals and even different passages of the same cell line. As powerful as the OE biopsy approach may be conceptually, it will be important to develop research paradigms to capture stable measures despite the issues of cellular heterogeneity and individual variability.
ID: 550916

THE TOPICAL NIACIN SKIN TEST IN EARLY PSYCHOSIS AND HEALTHY CONTROLS: IDENTIFYING MEANINGFUL SUBTYPES.

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Niacin sensitivity is strongly related to prostaglandin D2, a derivate of arachidonic acid, a bioactive lipid. These lipids have been implicated in the etiology and pathophysiology of psychosis. Studies have demonstrated that a subgroup of psychotic patients show an attenuated response to topical niacin application when compared with controls (CTL). The aim of this study was to compare a group of first episode psychosis (FEP) patients with CTLs on the niacin skin test (NST). A unique two-step cluster analysis of the NST scores was also conducted to identify subgroups. The topical NST was administered to 92 FEP patients and 42 CTLs. The test was scored using a semi-quantitative descriptive scale incorporating oedema and erythema at four different concentrations across four time points. Repeated measures ANOVA across the FEP and CTL cohorts revealed significant main effects for group, $F_{1,132} = 36.40$, $P < .001$, time, $F_{1.88,\ 247.48} = 403.15$, $P < .001$, and the group x time interaction, $F_{1.88,247.48} = 9.08$, $P < .001$. Three clusters were derived from the analysis of the NST matrix: The first two clusters appear to comprise patients who were more similar to controls (Cluster 1 equal distribution FEP and CTL, Cluster 2 predominantly CTLs) and Cluster 3 was primarily FEP patients. There was a significant difference between the three clusters with respect to total niacin sensitivity score, $F_{2,89} = 165.53$, $P < .001$. Post hoc analyses indicated that FEP patients in Cluster 2 exhibited the highest mean niacin sensitivity score. When examining psychopathology across the three clusters (patients only), there were significant differences on Affective Flattening/Blunting, $F_{2,89} = 5.0$, $P = .009$, and Anhedonia/Asociality, $F_{2,\ 89} = 3.9$, $P = .022$, with Cluster 2 having lower mean scores. A novel cluster analysis of the NST data matrix revealed very interesting findings. First, there is a subgroup of FEP patients who, like CTLs, are niacin sensitive and thus do not appear to have disturbed lipid biology during their first illness presentation. Second, there is a subgroup of niacin insensitive FEP patients who also exhibit significantly greater levels of negative symptoms. This may indicate that the niacin sensitive FEP patients have a less schizophrenia-like illness presentation and better outcomes—a hypothesis worthy of further exploration. Our data supports the use of the NST to subtype FEP.
ID: 550879

NEUREGULIN 1 IN SYNAPTIC PLASTICITY AND SCHIZOPHRENIA

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Schizophrenia is a mental disorder that affects 1% of population. It is characterized by abnormal neuronal activity in the brain including hypoglutamatergic function. Molecular pathogenic mechanisms of schizophrenia, however, remain unclear. Recent genetic studies have identified several susceptibility genes including neuregulin 1 (NRG1) and its receptor ErbB4. NRG1 is a family of polypeptides important role in neural development. NRG1 and ErbB4 are expressed in adult brain in addition to the developing nervous system. We showed that ErbB4 is concentrated at the postsynaptic density of excitatory synapses in adult brains and NRG1 suppresses long-term potentiation (LTP) in the hippocampal CA1 region, a cellular model of learning and memory (Neuron 26:443, 2000). Recently, we found that NRG1 stimulates activity-dependent release of GABA, a major inhibitory neurotransmitter, in the prefrontal cortex (PFC) (Neuron 54:599, 2007). This effect requires ErbB4, but not pathways of dopamine, glutamate, acetylcholine, norepinephrine and serotonin. These results indicate that NRG1 plays a role in synaptic plasticity in developed brain in addition to neural development. More recently, we found that PI3 kinase is required for NRG1 regulation of GABA release. This is intriguing because PI3 kinase activation is mediated by CYT-1 ErbB4, an isoform whose expression is higher in schizophrenic PFC. In light of earlier observations that mRNAs of type I and IV NRG1 and NRG1 signaling are increased in schizophrenic PFC, we propose that the gain-of-function of NRG1 signaling contributes to hypoglutamatergic function in the schizophrenic brain. In support of this hypothesis were recent results that NRG1 reduces whereas a neutralizing peptide increases firing frequencies of pyramidal neurons in the PFC. We have also investigate which interneurons are target of NRG1 by analyzing conditional mutant mice. Ablation of ErbB4 in parvalbumin-positive neurons in the brain blocks the NRG1 regulation on GABA release and pyramidal neuron firing in the PFC. The mutant mice appeared to be hyperactive in open field exploration with impaired prepulse inhibition. Together, these observations demonstrate an important role of NRG1 and ErbB4 in synaptic plasticity, and provide intriguing leads to pathogenic mechanisms of schizophrenia. Supported by grants from NIMH, NINDS, and NARSAD. ID: 553068

BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) SPLICE VARIANT AND ENDOGENOUS ANTISENSE TRANSCRIPT EXPRESSION IN PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Altered brain-derived neurotrophic factor (BDNF) signaling has been implicated in the pathophysiology of schizophrenia. Several prior studies have reported reduced expression of BDNF mRNA and protein in prefrontal cortex (PFC) in schizophrenia. We aimed to characterize the expression of BDNF splice variant and endogenous BDNF antisense (opposite strand) transcripts in schizophrenia PFC to provide insights into the mechanisms of altered BDNF expression. Relative quantities (RQ) of total BDNF mRNA (BDNFT), BDNF1 and BDNF4 splice variant mRNAs, and BDNF opposite strand (BDNFOS) mRNA were measured by qPCR and BDNF protein was measured by Western blot in postmortem PFC from individuals with schizophrenia and matched controls. Samples with RNA integrity number (RIN) less than 7.0 were excluded prior to conducting qPCR. Groups did not differ on mean postmortem interval (PMI), pH, RIN, or age. qPCR revealed no difference in BDNF1, BDNF4 or BDNFT RQ between schizophrenia and control groups (BDNF1 RQ: +14%, $P = .5$; BDNF4 RQ: -15%, $P = .2$; BDNFT RQ: -14%, $P = .3$). The schizophrenia group had higher mean BDNFOS RQ compared to the control group (+15%, $P = .02$). In secondary analyses, BDNF1 RQ, BDNF4 RQ, and BDNFT RQ each correlated modestly with PMI (Pearson r -0.28 to -0.32, $P < .05$) and more strongly with age (Pearson r = -0.35 to -0.6, $P < .01$) and RIN (Pearson r 0.6 to 0.7, $P < .0001$). BDNFOS RQ did not correlate with PMI, age, or RIN and remained higher in the schizophrenia group after covarying for PMI, pH, RIN, and age. Data on BDNF protein will also be presented. In summary, BDNF mRNA expression and BDNF splice variant 1 and 4 mRNA expression were not altered in PFC in schizophrenia. However, BDNF antisense mRNA was increased in PFC in schizophrenia. This could represent a post-transcriptional mechanism by which BDNF signaling is altered in the setting of normal total BDNF mRNA levels. Further pathophysiological implications of these data and factors that may have contributed to not replicating lower total BDNF mRNA in schizophrenia will be discussed. ID: 554786

18. 18. Cognitive Neuroscience

AVOIDANT PERSONALITY DISORDER SYMPTOMS IN FIRST-DEGREE RELATIVES OF SCHIZOPHRENICS PREDICT PERFORMANCE ON NEUROCOGNITIVE MEASURES: THE UCLA FAMILY STUDY

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Whether avoidant personality disorder (APD) symptoms (Sxs) are related to putative neurocognitive (neurocog) endophenotypes of schizophrenia (Sz) is unknown. We report the relationship between APD Sxs and performance on neurocog measures in the first-degree relatives (1st Rels) of probands with Sz. 367 1st Rels of probands with Sz and 245 Rels of community controls (CC) were interviewed for the presence of APD Sxs as well as Sxs of paranoid (PD)and schizotypal (SPD) personality disorders. All Rels were also administered neurocog measures. Relationships between neurocog measures and total APD Sxs were analyzed in SAS Proc Mixed using mixed effects regression models with a random effect for family using a variance components structure. Models were fit separately in the Rels of the Sz and CC probands. In addition we fit models with a group by Sx interaction in the combined sample to formally test for differences in the relationship of neurocognition and APD Sxs between Sz and CC relatives. No relationships were found in CCs alone. APD dimensional scores predicted performance on the span of apprehension (Span), 3-7 Continuous Performance Test, and Trail Making Test in Rels, and the group by Sxs interactions were significant in the combined models, confirming a stronger relationship in relatives of SZ versus CC probands. In secondary models. APD dimensional scores predicted performance on the Span and Trails even after adjustment for PD dimensional scores in the Rels. APD dimensional scores predicted performance on the Span after adjustment for SPD dimensional scores. However, the group by Sx interaction term was significant or trending toward significance in all the combined sample models even after adjustments for PD and SPD dimensional scores. Given the substantial correlation between dimensional scores for APD and SPD Sxs, and the assumption that these personality disorders are not independent, we conclude APD dimensional scores and SPD dimensional scores are useful predictors of performance on these neurocog measures that are not fully separable. These findings indicate that APD dimensional scores predict poorer neurocog performance in the Rels of SZ probands, often more strongly than in the Rels of CCs. The relationships between dimensional scores of APD Sxs and probable neurocog endophenotypes for SZ supports the hypothesis that APD is a useful SZ spectrum phenotype for SZ research.
ID: 536960

VISUAL LEARNING AND MEMORY IN THE RODENT: NOVEL OBJECT RECOGNITION AND THE MORRIS WATER MAZE—PROS AND CONS

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Visual learning and memory was identified by the MATRICS process as one of seven key domains of cognitive function impaired in schizophrenia. Visual learning and memory impairments have been identified in schizophrenic patients, and some evidence suggests that such deficits may predate illness onset in high risk individuals. In humans, MATRICS selected the Brief Visual Memory Test-Revised (BVMT-R) to assess visual learning and memory. This paper based task assesses the subjects ability to recall and recognize six geometric figures which are presented for short (10s) periods of time. As such there are both spatial and non-spatial aspects to the task. An important second step to conceptualizing cognitive function in schizophrenia is to consider the precise nature of animal models and tests which should form the focus of future research, and importantly how well, or indeed whether these can map onto the cognitive domains identified by MATRICS. In the rodent, a large number of tasks exist which assess visual learning and memory. This talk will focus on two commonly used rodent tasks: A visuospatial maze-based task (Morris water maze), and a nonspatial test of recognition memory (Novel object recognition). The focus of this discussion will be both practical and theoretical issues associated with their use, and their applicability to cognitive research in schizophrenia.
ID: 550760

PRECLINICAL ASSESSMENT OF VIGILANCE IN RATS AND MICE: TRANSLATIONAL VALIDITY FOR THE CONTINUOUS PERFORMANCE TEST

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Cognitive disruption in schizophrenia correlates closely with functional outcome. Thus the need to develop cognitive therapeutics for this disease has never been greater. The Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS), identified impaired attention/vigilance as one of the core deficits experienced by schizophrenia patients. Vigilance is commonly assessed in humans using the continuous performance test (CPT), which requires a response to signal events and an inhibition of response to non-signal events. Signal detection theory (SDT) is used to evaluate performance in the CPT. In fact MATRICS chose the CPT-identical pairs to assess attention/vigilance in their cognitive test battery. Few rat or mouse paradigms follow these task parameters however. Two tasks available which fulfill these criteria are the rat sustained attention task and the recently developed mouse 5-choice CPT, based on the 5-choice serial reaction task. These tasks have been assessed for translational validity as tests of vigilance and are now being used to develop animal models of impaired vigilance with relevance to schizophrenia. The sustained attention task has been available for over a decade in rats and recent studies have been performed with relevance to schizophrenia. The effects of antipsychotic treatment on normal animals have been investigated, as have putative pro-cognitive drugs. Moreover, the effects of antipychotics have also been investigated in an animal model of schizophrenia. The more recent 5-choice CPT has received only limited investigation to date, although numerous studies in different laboratories are now being conducted. This task utilizes 5-hole chambers. The use of holes as opposed to levers makes this task ideal to assess vigilance in mice. To date, poorer performance of DBA2/J mice relative to C57BL/6J mice has been demonstrated. Moreover, reduced expression of the dopamine D4 receptor in mice resulted in poorer vigilance, consistent with that of schizophrenia patients with reduced prefrontal D4 receptor expression. Two rodent vigilance tasks with translational validity to the CPT exist. Studies continue to explore the neurobiological contribution to performance in these tasks, as well as develop animal models of schizophrenia with face, predictive and construct validity. Once fully developed, these models and tasks can be used in the drug discovery process to investigate future putative therapeutics.
ID: 550759

DISTINCT NEURAL SIGNATURES OF RESPONSE MONITORING DEFICITS IN SCHIZOPHRENIA AND AUTISM: A NEUROCOGNITIVE ENDOPHENOTYPE?

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Adaptive, flexible behavior depends on intact 'response monitoring', which involves evaluating whether the consequences of a behavior are consistent with its intent and, if an error occurred, instituting adjustments to optimize outcomes. Schizophrenia and autism spectrum disorder (ASD) are neurodevelopmental disorders that are characterized by rigid, stereotyped, and perseverative behavior. In the present study we investigated the contribution of anterior cingulate cortex (ACC) structure and function to response monitoring using event-related functional MRI (fMRI) and diffusion tensor imaging (DTI) in 12 ASD participants, 18 schizophrenia patients, and 15 demographically-matched healthy controls. We compared ACC activation following correct and erroneous antisaccade responses with fMRI and examined the microstructural integrity of the white matter underlying ACC as indexed by fractional anisotropy (FA). Both experimental groups made more antisaccade errors than controls. Schizophrenia patients performed correct antisaccade trials more slowly than controls, while ASD participants performed faster. With regard to ACC activation, both experimental groups showed reduced discrimination between error and correct trials, but the basis of this reduction differed by group. In schizophrenia, the reduction reflected a blunted ACC response to errors, while in ASD it reflected a hyperactive response to correct trials, which correlated with Autism Diagnostic Interview-Revised ratings of restricted, repetitive behavior. Relative to controls, both groups showed significantly reduced FA in ACC white matter. These findings demonstrate functional and structural ACC abnormalities that may contribute to behavioral rigidity in both ASD and schizophrenia. However, the behavioral and neural abnormalities differed by group. Given recent evidence of genetic mediation of response monitoring by common polymorphisms, these findings suggest that neuroimaging-based indices of deficient response monitoring are promising candidate endophenotypes that are clinically-relevant and can distinguish between neurodevelopmental disorders.
ID: 550741

INTERACTION BETWEEN WORKING MEMORY LOAD AND GESTURE IMITATION ABILITY IN SCHIZOPHRENIA

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In Imitation one person observes and reproduces the behavior of another person. Imitation plays a key role in skill acquisition, and the development of fundamental social skills such as understanding the goals, intentions and desires of other people. Recent evidence suggests that individuals with schizophrenia (SZ) are impaired in their ability to imitate manual, facial, and vocal gestures. This impairment may be linked to well established difficulties in generating internal representation in working memory (WM). In the present study we used a novel technique to investigate the relationship between WM and imitation ability. Individuals with SZ and demographically matched CO subjects imitated, both online and from memory, a series of manual sequences each consisting of two gestures. Imitation was per-

formed while wearing an electronic data glove that transduced the movement of the subject's fingers as the gesture was reproduced. This allowed precise analysis of the velocity and accuracy of the finger movements. In the online task subjects imitated each sequence concurrently with the stimulus display; in the memory task subjects imitated each sequence after a 2 sec delay. In both conditions each sequence was displayed 8 times, so that gesture learning could be investigated. Clinical symptoms were also assessed. The results revealed a significant interaction between diagnostic status and imitation condition, with SZ producing more errors relative to CO in the memory condition compared to the online condition. This suggests that adding a WM requirement interacts with imitation ability in the disorder. Imitation learning did not differ significantly between groups. However this may have been due to the relatively few errors produced overall. There was also a significant interaction between group and memory condition in premotor planning, the time taken to make the first gesture in a sequence, with SZ requiring significantly longer time to begin the first gesture compared to CO in the memory condition, but not the online condition. Significant correlations were found between negative symptoms in SZ and both the number of errors produced and planning time in the memory condition. Taken together, these results suggest that imitation ability in SZ is particularly sensitive to WM load.
ID: 550691

CORRELATION OF PREPULSE INHIBITION WITH WISCONSIN CARD SORTING TEST PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA AND CONTROLS: EFFECTS OF SMOKING STATUS

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Background: In patients with schizophrenia, cigarette smoking rates are high and smoking appears to alter two important neurocognitive deficits associated with the illness: information processing as measured by prepulse inhibition (PPI) of the acoustic startle response and frontal lobe function as assessed by the Wisconsin Card Sorting Test (WCST). Objective: The goal of this study was to evaluate the relationship between PPI and prefrontal cortical functioning in individuals with schizophrenia and controls and examine how smoking influences this relationship. Design: The study included four groups: (i) schizophrenia smokers (SS; $n = 15$), (ii) schizophrenia nonsmokers (SNS; $n = 11$), (iii) non-psychiatric control smoker (CS; $n = 14$) and (iv) non-psychiatric control nonsmokers (CNS; $n = 10$). All subjects were assessed identically on PPI and WCST. Results: Baseline differences amongst the four groups were observed for PPI on the Diagnosis x Smoking Status x PPI Interval interaction [$F_{11,140}$ = 4.89, $P < .01$]. SNS demonstrated the poorest PPI function, while SS showed comparably high levels of PPI to CNS at the 120 msec pre-pulse to pulse interval. Significant differences also existed between the four groups on categories completed [$F_{3,47}$=3.78, $P = .015$] and perseverative errors [$F_{3,47}$= 3.65, $P = .017$] outcomes on the WCST, with non-psychiatric controls outperforming individuals with schizophrenia irrespective of smoking status. Categories completed on the WCST and PPI at the 120 msec prepulse condition significantly correlated in SS ($r = .61$, $P < .01$). In contrast, there were no significant correlations between PPI and any WCST outcomes in SNS, CS or CNS (all P's >0.20). Discussion: Selected executive function outcomes of WCST (eg, categories completed) are strongly correlated with PPI in smokers with schizophrenia, but not in non-smoking patients, and controls, suggesting that the association between sensorimotor gating and prefrontal executive functioning is enhanced by acute cigarette smoking. Our preliminary findings may contribute to understanding the vulnerability of patients with schizophrenia to nicotine dependence, and may lead to the development of targeted treatments for this co-morbidity. Nicotine receptor-stimulating

drugs are a promising alternative to cigarettes, as they will help alleviate cognitive deficits ie, target executive functioning and PPI deficits, without the adverse health consequences implicated with regular tobacco use.
ID: 550662

MODELLING WORKING MEMORY IN THE RAT: A MISGUIDED EFFORT?

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The lack of effective treatments for the cognitive symptoms of schizophrenia is a prime driver in the search for predictive "animal models". The goal is to find measures of complex cognitions—such as working memory—that have clear "translational" utility. The result is a wide variety of behavioural protocols for the rat and mouse. Nevertheless, there remains a fundamental dissatisfaction with these 'models' and, more significantly, no breakthroughs in treatment. Cognition is a covert operation and must be inferred from carefully measured and well-characterised behavioural analysis. Fortunately, even the most complex behaviour is the product of an assembly of a subset of more basic cognitions acting in concert. We assume that, in psychiatric disorders such as schizophrenia, complex deficits arise from fundamental cognitive impairments. Identifying what these fundamental cognitive impairments are has provided a route 'backwards', from the clinical manifestation (the psychiatric symptomatology) to the core cognitive impairments. For example, the MATRICS initiative has described 'domains' of core cognitive functions that are compromised in schizophrenia. The focus therefore is now on the possibility of translating these 'downwards', back to preclinical research. Here, I propose that translation should not be seen as a movement (in either direction) along a path that leads from the preclinical to the clinical. Rather, there are parallel paths: one is concerned with the neurobiology underlying the symptoms of psychiatric illness (in humans) while the other is concerned with the neurobiology of rodent cognition. 'Translation' is required to ensure that these pathways intersect so that progress towards understanding on either pathway facilitates progress on the other. Thus, we can abandon talk of 'animal models of human cognition' and study instead 'animal cognitions that are translated'. This approach obviates the requirement for the rat to be a model of the human. Instead, the emphasis is to ensure that the appropriate overt behaviours (predictive of functional capacity and clinical outcome) are measured. Examples of behavioural protocols that fulfill these requirements will be reviewed, with particular emphasis on understanding working memory.
ID: 550634

REASONING AND PROBLEM SOLVING—THE ATTENTIONAL SET SHIFTING TASK

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Cognitive inflexibility in schizophrenia is treatment-resistant and predictive of poor outcome. Within the framework of MATRICS, deficits in cognitive flexibility map onto both the problem solving and speed of processing domains, both of which are believed to be dependent upon frontal-lobe function. Evidence for this includes the observation, for example, that tasks that are sensitive to frontal-lobe damage, such as the Wisconsin Card Sort test, are also impaired in schizophrenic patients. Therefore developing a better understanding of the inter-relationship between the neuroanatomical,

and neurochemical substrates, the psychological processes, and pharmacological agents may offer new insight into how theses domains could be better manipulated in the clinic. Recent studies have examined the effect of asenapine, a novel psychopharmacologic agent being developed for schizophrenia and bipolar disorder, on the performance of rats with ibotenic acid-induced lesion of the medial prefrontal cortex (mPFC) in an intradimensional / extradimensional (ID/ED) test of cognitive flexibility. The effect of subcutaneously administered asenapine on ID/ED performance of controls or mPFC lesioned rats was examined using a within-subjects, repeated-measures design. In a second experiment, lesioned and control rats were tested with or without asenapine in a modified version of the task, with multiple set-shifts, before brains were processed for Fos-immunoreactivity in the mPFC. The mPFC lesion-induced deficit in the ID/ED task was stable with repeated testing over more than two months. Asenapine (75μg/kg, $P < .05$) completely restored the performance of lesioned rats. A second experiment replicated these results and demonstrated that it is possible to measure set-shifting multiple times within a test session. Asenapine (75μg/kg) was associated with differential activation of the neurons in the anterior mPFC of lesioned animals, but was without effect in controls. These data show that asenapine can ameliorate mPFC lesion-induced impairment in attentional set-shifting, probably by a greater activation of the spared neurons in the anterior mPFC. As such this gives an insight into the various substrates that mediate this aspect of cognition. Further, with the amelioration by aspenapine, we now have the potential to translate and validated these hypotheses.
ID: 550614

VALIDATION OF SOCIAL COGNITION TESTS FOR SCHIZOPHRENIA PATIENTS IN INDIAN SETTING

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There are no standardized tools in India to test social cognition. This paper describes validation of tools for two social cognition constructs in schizophrenia: theory of mind and attributional bias. Theory of mind (ToM) tests that we validated included, (a) two first order TOM tasks [Sally-Anne (Baron-Cohen et al. 1985) and Smarties task (Perner et al. 1987)], (b) two second order TOM tasks [Ice cream van (Perner and Wimmer, 1985) and Missing cookies story (Stone et al. 1998)], (c) two metaphor-irony tasks (Drury et al. 1998 and Herold et al. 2002) and (d) the faux pas recognition test (Stone et al. 1998). We also validated The Internal, Personal, and Situational Attributions Questionnaire (IPSAQ) (Kinderman and Bentall, 1996). We generated Indian equivalents of these tests and modified the questions slightly. Eighteen mental health professionals rated the tests on likert scale (1 = strongly disagree; 5 = strongly agree) as to whether the modified tasks tested the same construct as in the original and whether they were culturally appropriate in India. Tests which received a score of <4 (not aggreable) from >25% of experts were revised based on their comments. After revision, all tests were administered on 9 schizophrenia patients and 9 healthy individuals to assess discriminant validity. Both first-order and second-order TOM tasks, both metaphor-irony tasks, the stories 1–6, 8–11, 13–18, and 20 of faux pas recognition test and IPSAQ were agreed upon by >75% of the experts and met our criteria for content validity. Significantly greater proportion of patients had first and second order TOM deficits and irony detection deficits. They also identified less number of faux pas situations and had greater scores on externalizing bias on IPSAQ. Indian modification of social cognition tasks has content validity and discriminant validity. Schizophrenia patients have poorer social cognition than healthy controls.

Table. Comparison of cases and controls: The figures are in percent of subjects with deficits (*) or mean (SD) scores (**)

Variable	Cases (n = 9)	Controls (n = 9)	χ²/ Mann-Whitney-U	P
TOM first order*	4 (44%)	0 (0%)	5.14	0.02
TOM second order*	9 (100%)	3 (33%)	9	0.003
Metaphor*	1 (11%)	0 (0%)	1.1	0.30
Irony*	9 (100%)	1 (11%)	14.4	0.002
IPSAQ Externalizing bias**	4.7 (4.9)	0.4 (2.4)	20.5	0.07
IPSAQ Personalizing bias**	0.72 (0.2)	0.79 (0.3)	32.0	0.49
Total faux pas identified correctly**	5.3 (2.6)	8.2 (1.4)	14.5	0.02

ID: 550575

IMPOVERISHED PROSODY PRODUCTION IN SCHIZOTYPAL PERSONALITY DISORDER

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Background: Schizotypal personality disorder (SPD) is epidemiologically and phenotypically related to schizophrenia and is considered part of the schizophrenia spectrum disorders. Social cognition deficits have been more fully studied in schizophrenia despite five out of the nine diagnostic criteria for SPD being in the social domain. One important aspect of social reciprocity and social interactions is the ability to speak with prosody. Research studies have shown schizophrenia subjects to have decreased pitch variation in their speech. The goal of this study is to examine pitch variation and its clinical implications in SPD subjects. Methods: Nineteen neuroleptic-naïve SPD subjects were compared with 23 healthy control subjects in terms of the amount of pitch variation (standard deviation of pitch) analyzed acoustically. In a separate analysis, trained raters also listened to subjects' speech and rated how much the raters would like to hear more from the subjects along a 7-point Likert scale. Pause proportion, the amount of time free of utterances, was calculated. Verbal fluency was measured with the Word Generation Task. Subjects also completed the Alexithymia questionnaire as a measure of their insight into their difficulties verbally communicating their emotions. Results: As predicted SPD subjects had less pitch variation in their speech compared with controls. Less pitch variability correlated with raters not wanting to hear more from them. Not only did SPD subjects have less pitch variability, but they also had more pauses compared with controls. SPD subjects also generated fewer phonemic and semantic words in one minute compared with controls on the Word Generation Task. SPD subjects scored higher on our measure of alexithymia (more alexithymia). Conclusions: We believe these data suggest that SPD subjects compared with controls, have deficits in prosody production. Poor executive functioning may be compounding the difficulties as SPD subjects also had poor word generation. These deficits have clinical repercussions as raters did not want to hear more from them. SPD subjects do, however, have insight into their difficulties—they are aware that they are not communicating their emotions well. Taken together these data suggest that research directed toward enhancing the pitch variation and decreasing pause proportion, may be important toward helping schizophrenia spectrum subjects navigate the social world.
ID: 550550

WORKING MEMORY MAINTENANCE AND MANIPULATION DEFICITS IN SCHIZOPHRENIA

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Encoding and maintenance of information as well as internal manipulation of information are key components of working memory systems. Given the broad pattern of cognitive deficits associated with schizophrenia, manipulation deficits are believed to be more pronounced than encoding/maintenance impairments. However, these two working memory processes have rarely been directly compared. We evaluated chronic schizophrenia patients (n = 25) on stable medication regimens and healthy comparison participants (n = 22) matched on age, education, parental SES, sex, race, and estimated intelligence. Participants were administered a modified verbal span task with four levels of difficulty. Maintenance was assessed using single item verification probes (Was X the 3rd letter?). Maintenance plus manipulation was assessed via double item verification probes which required more complex serial search strategies comparing relative temporal sequence (ie, Was X before Y?). Both groups showed reduced accuracy and increased reaction time for manipulation compared to maintenance processing. Between-subject effect sizes (Cohen's d) indicated medium-large effect sizes for maintenance probes, whereas the magnitude of patient deficit was small-medium for manipulation probes. When participants were retested at 4-weeks, maintenance deficits increased due to greater practice effects in the healthy group, especially at lower working memory loads. The magnitude of impairment for working memory manipulation was more consistent over time. These findings are consistent with meta-analytic findings of impaired encoding and/or early maintenance of information in working memory in schizophrenia. Additionally, the findings suggest that deficits of encoding information in working memory may be greater than deficits in manipulation of information stored in working memory systems.
ID: 550549

fMRI AND BEHAVIOURAL STUDIES OF NORMAL AND ABNORMAL LEARNING IN PSYCHOSIS.

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In a number of recent learning studies from CAMEO, the Cambridge early onset psychosis service, we have shown that in moderately symptomatic psychosis patients, whilst there are very subtle behavioural abnormalities in learning reward and causal associations, the crude learning of simple reward and causal associations is nevertheless broadly intact. Interestingly, in a recent fMRI study of probabilistic reward learning, we showed that this broadly intact learning is accompanied by remarkably abnormal patterns of brain activation as measured by concurrent fMRI BOLD signal change. How can we reconcile these seemingly inconsistent findings of abnormal brain activity, unusual patterns of thought and behaviour on mental state examination, yet comparatively normal behaviour on computerised tests of learning? One possibility that has been previously advanced is that fMRI is a more sensitive investigative tool, which can reveal abnormalities that computerised cognitive testing cannot. A more interesting possibility is that although patients' primary brain systems of learning reward associations may be dysfunctional (for example, meso-limbic dopamine systems and fronto-striatal systems), patients may engage in recruitment of compensatory, secondary, intact neural systems to attain reasonable performance on cognitive learning tasks. Arguments to support this possibility stem from studies of experimental animals, such as genetically engineered dopamine deficient (DD) mice. Although in the DD state, such mice are not motivated to engage in goal directed behaviours, nevertheless DD mice are able to learn about rewards. Although there is extensive evidence for a role for dopamine in reward learning, such experiments show that, perhaps

through compensatory pathways, learning can still occur, even in the absence of dopamine. I will argue that in an analogous fashion, in spite of remarkably dysregulated mesolimbic, mesostriatal and mesocortical systems in psychosis patients, compensatory neural systems are engaged in order to attain successful behavioural performance on computerised cognitive testing. The implications of this will be discussed further in the presentation.
ID: 550499

MIND IN MOTION—PSYCHOPATHOLOGY IN PATIENTS WITH SCHIZOPHRENIA IS REFLECTED IN NONVERBAL BEHAVIOR MEASURED BY MOTION ENERGY ANALYSIS (MEA)

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Motor behavior is prominently affected in schizophrenia. Alterations of nonverbal behavior have been regarded as diagnostically salient and as critically important for functional outcome, eg, in the case of negative symptoms. Nonverbal signs of the disorder can be understood as alterations in complex, organized patterns of functioning, expressing mind in motion. Although nonverbal behavior is both theoretically and clinically important, empirical research on nonverbal behavior in schizophrenia has been mostly confined to rating-based approaches. Traditional objective measures of nonverbal behavior (eg, marker-based movement tracking) are costly, time consuming and scarcely functional outside laboratory settings. Motion energy analysis (MEA) refers to a method by which objective measures of body movement can be extracted from ordinary video recordings. In this study brief videotaped role play scenes with 30 stabilized outpatients were analyzed. Each patient interacted in 14 short scenes with an investigator who portrayed an interpersonal partner. Correlations between movement parameters (percentage of time in movement, movement speed) and psychopathology ratings from independent PANSS interviews were calculated. As predicted, both reduced movement activity and slowness of movement were correlated with negative symptoms and with specific general symptoms, eg, depression and motor retardation. Positive symptoms were generally not related to movement parameters with the exception of suspiciousness being correlated with reduced head movements. Overall, there was a close and theoretically meaningful association between the objective MEA movement parameters and the symptom profiles. Furthermore, there were clear signs of contagion in the interactions, ie, in patients with lower movement rates investigators also showed reduced movement. Lower movement synchrony between patients and investigators was associated with psychopathology, even after controlling for patients' levels of movement. MEA measures of nonverbal behavior in schizophrenia patients seem to be strongly and specifically linked to psychopathological symptoms. The MEA method allows for quantifying nonverbal behavior from a wide range of video recordings. MEA based studies of 'mind in motion' may provide new insights into links between the phenomenological level of psychopathology and its expression on an objective behavioral level.
ID: 550465

ATYPICAL ANTIPSYCHOTICS IMPROVE EMOTION RECOGNITION DEFICITS IN SCHIZOPHRENIA:A LONGITUDINAL STUDY

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Facial Emotion Recognition Deficits [FERD] have been demonstrated in schizophrenia (Kohler et al. 2003). However effect of antipsychotic treatment on FERD in never-treated schizophrenia is yet to be explored. Subjects included 25 antipsychotic naïve schizophrenia patients [DSM-IV] and 30 age-,sex-,education- matched healthy controls. Psychopathology and FERD were assessed with SAPS and SANS and the Tool for Recognition of Emotions in Neuropsychiatric DisorderS [TRENDS] (Behere et al; Award Paper 2008) respectively. TRENDS a culturally appropriate emotion recognition tool with optimal validity, consists of staticanddynamic visual stimuli of seven basic facial expression (neutral, happy, sad, fear, anger, surprise, and disgust). The patient group was then started on Risperidone 4mg and Trihexyphenidyl 2mg per day and reassessed after a mean duration of 38.2 ± 17.1days. At baseline patients made significantly more errors in emotion recognition ($P < .001$) than controls specifically for emotions of fear and disgust ($P < .001$). SANS score showed significant negative correlation with Emotion Recognition Accuracy [ERA] total score ($P = .001$). On follow up, patients showed significant improvement in SAPS and SANS scores. On paired samples't' test there was significant improvement in ERA total score ($P = .02$), specifically for disgust sub-score ($P = .002$). Improvement in ERA scores was significant even after controlling for potential confounding effects of reduction in SANS scores. This longitudinal study for the first time demonstrates beneficial effect of neuroleptics on FERD in antipsychotic naïve schizophrenia patients. This effect is independent of improvement in psychopathology. Specific improvement in disgust sub scores suggests potential effects of antipsychotics on dopaminergic dysfunction. Acknowledgement: This study was financially supported by Indian Council of Medical Research (ICMR).

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ID: 550443

MAINTENANCE OF RESPONSE IN TRIALS OF OLANZAPINE VERSUS OTHER ATYPICALS FOR TREATMENT OF SCHIZOPHRENIA

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Objective: Compare time maintaining response in patients with schizophrenia treated with olanzapine or another atypical antipsychotic. Methods: We conducted post-hoc analyses on data from five long-term (24–28 weeks), double-blind, randomized trials of olanzapine versus risperidone (1 study), ziprasidone (2 studies), quetiapine (1 study), and aripiprazole (1 study). Loss of response was defined as an increase in PANSS Total score of $\geq 20\%$ along with a Clinical Global Impression-Severity Index score (CGI-S) of ≥ 3 in patients who had achieved response at Week 8. For each study individually, between-group comparisons were made for cumulative days spent in response, where response was defined as $\geq 20\%$ decrease in $PANSS_{1-7}$ Total score. Results: Time maintaining response was statistically significantly longer for olanzapine compared to risperidone ($P < .001$, quetiapine ($P = .003$), and ziprasidone ($P = .008$ and $P = .03$). The mean percentage of cumulative days spent in response was statistically significantly greater for olanzapine compared to ziprasidone ($P < .001$ and $P = .035$). Conclusion: Evaluating drug efficacy over time is important for treatment of long-term illnesses such as schizophrenia. In these analyses, patients randomized to olanzapine maintained

response for a longer period of time than patients randomized to risperidone, ziprasidone, or quetiapine and spent more time in response than patients randomized ziprasidone.
ID: 550436

CAUSALITY PERCEPTION AND INTERSENSORY INTEGRATION IN SCHIZOPHRENIA

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Patients with schizophrenia spectrum disorders often maintain deviating views on cause-effect relationships, especially when positive and disorganization symptoms are manifest. Altered perceived causality is prominent in delusional ideation, in ideas of reference, and in the afflicted mentalizing ability or 'Theory of Mind' (ToM) of patients. In the present study, perception of causality was investigated as a pre-attentional cognitive capability, which was considered analogous to processes of cognitive coordination such as perceptual grouping and gestalt perception. Thirty-one patients (24 men and 7 women, mean age 27.7 y) and the same number of healthy control subjects matched to patients with respect to age and sex were included. A visual neuropsychological paradigm was developed in which two identical discs move, from opposite sides of a monitor, steadily toward and then past one another. Their coincidence generates an ambiguous, bistable percept (discs are subjectively perceived as either 'streaming through' or 'bouncing off' one another). The bouncing perception, ie, perceived causality, is enhanced when auditory stimuli were presented at the time of coincidence. Thus, the experimental setup also afforded intersensory integration of visual and auditory stimulation. Psychopathology was assessed in the patient group using the Positive and Negative Syndrome Scale (PANSS) and a personality test in controls. It was found that positive symptoms were associated with increased perceived causality, disorganization with attenuated perceived causality. Multiple regression analysis indicated that psychopathology explained 46 percent of the variance of causality perception. At the same time, perceived causality was unrelated to personality traits. Patients were not significantly different from controls, and timing of the auditory stimulus had similar influences on causality perception in the patients and control groups, pointing to insignificant differences in intersensory integration. Perceived causality may be interpreted as a basic constituent underlying higher cognition such as ToM and social cognition, which appears to be specifically sensitive to symptom states. Conclusions for cognitive remediation therapy may be drawn based on the results. In addition, it is suggested that the present paradigm has value as a language-free, implicit marker of ToM-related cognition.
ID: 550412

CAN VISUAL ORGANIZATION IMPAIRMENT LEAD TO ATTENTIONAL DISENGAGMENT DEFICIT IN SCHIZOPHRENIA?

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Patients with schizophrenia are impaired at organizing visual elements. This capacity involves both automatic perceptual grouping, allowing the binding of elementary features, and top-down control, that is necessary to avoid excessive binding and to allow flexibility during visual exploration. Previous studies have suggested a lack of top-down control, but preserved ability to focus on targets defined by automatic grouping processes in patients (Giersch and Rhein, 2008). Here we explore to what extent lack of top-down control and impaired executive functions reduce flexibility during visual exploration. 26 stabilized patients and matched controls were submitted to 1) a perceptual search task, where an horizontal array with an alternance of squares and circles was presented in each trial, with only two adjacent figures being identical (Beck and Palmer, 2002). Subjects had to identify whether these two targets were circles or squares. Targets were either linked by a connector (within-group target pair) or located between two connectors (between-group target pair), this, at an equal frequency (50% of within-group target pairs block), or within perceptual groups preferentially (75% of within-group target pairs block). 2) a modified Stroop task, requiring to inhibit the automatic reading response of colour names to select their colour ink. Patients were globally impaired to identify targets located between perceptual groups, but were able to focalize efficiently on within-group targets when those were more frequent (75% of within-group target pairs block). Moreover, patients displaying increased interference effects in the Stroop task showed disproportionate difficulties to locate targets that were positioned between perceptual groups, especially when the task incited them to focalize on within-group pairs (75% of within-group target pairs block). These results suggest that preserved automatic mechanisms, together with a lack of top-down control and deficient executive functions, may lead to adverse effects in schizophrenia, reminding of a disengagement deficit. This may in turn lead to decreased flexibility during visual exploration. Hence, restoring flexibility of perceptual organization appears crucial when considering remediation therapies.

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ID: 550347

REPETITION PRIMING OF FACIAL EXPRESSION IN SCHIZOPHRENIA: COGNITIVE AND NEUROIMAGING FINDINGS

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Research has shown that people with schizophrenia have difficulty making explicit judgments about the intentions and feelings of others. In particular, they have difficulty identifying and labeling negative facial affects. Often, however, we do not make conscious decisions about another's facial expression. The processing of expressions, especially threatening ones, is automatic and occurs implicitly without conscious awareness. Here, we examined repetition priming in an indirect memory test to explore implicit processing of emotional expressions in schizophrenia. Repetition priming refers to enhanced processing of a stimulus (faster reaction times, increased accuracy) following prior exposure to the identical stimulus. Our aims were first, to determine whether or not priming for facial expressions was impaired in schizophrenia, and second, to test whether there were differences in patterns of brain activation involved in priming between patients and controls. In the first study, adults with schizophrenia and controls viewed alternating blocks of faces with neutral and fearful expressions and identified each face as male or female. Immediately after each block of expressions, the identical faces were repeated and, again, faces were identified as male or female. Repetition priming was observed for neutral and fearful expressions, as evidenced by faster reaction times to make judgments for repeated versus novel expressions. Priming did not differ as a function of emotional expression. Of greater significance, the magnitude of priming did not differ for the groups. Implicit memory for facial expressions was preserved in schizophrenia; however, as expected, explicit recognition of previously viewed expressions was impaired. We then used fMRI to

determine if activation patterns for repetition priming differed for patients and controls. We again observed priming for neutral and fearful expressions, and there was no difference in priming between the groups. In contrast, brain activation did differ for patients and controls. Priming for neutral faces was associated with activity in the orbitofrontal area and fusiform face area for controls but not for patients. These findings point to abnormal brain mechanisms associated with implicit processing of faces in schizophrenia. Despite normal priming, patients with schizophrenia engage different neural pathways to process facial affect, even when processing occurs implicitly without explicit awareness.
ID: 550314

TOLCAPONE IMPROVES EFFICIENCY IN CORTICAL AREAS UNDERLYING WORKING MEMORY IN PATIENTS WITH SCHIZOPHRENIA

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Converging evidence suggests that decreased prefrontal dopamine (DA) cortical function may underlie some of the cognitive impairments seen in patients with schizophrenia. Catecholamine-O-methyltransferase (COMT), one of the main catabolic pathways for prefrontal cortex (PFC) DA, impacts the regulation of prefrontal DA flux, and COMT variants possessing different levels of activity have been associated with variable prefrontal efficiency. Subjects with the VA/ Val allele (higher enzyme activity and low PFC DA) show less prefrontal cortical efficiency than subjects with the Met/Met allele (lower enzyme activity and high PFC DA). A specific pharmacological approach to modulate cortical DA activity consists in the use of Tolcapone (TOL), a potent COMT inhibitor which penetrates the blood-brain barrier and improves prefrontal efficiency in normal volunteers. In this study, we assessed the ability of TOL to improve cortical efficiency in patients with schizophrenia. Performance analysis using ANOVA with drug and task load as co-factors showed significant decrease in accuracy with increased task load, but no effect of the drug was found in accuracy or reaction time. ANCOVA analysis of neuroimaging data revealed significant task load-related brain activation in the PFC and parietal cortex. During the 2-back task, a paired t-test revealed a significant main effect of TOL with greater cortical activation in brain regions underlying working memory function, particularly the PFC and the parietal cortex, during the placebo condition relative to TOL with no differences in accuracy or reaction time across the two drug conditions (all P-value > 0.05). No significant main effect of drug was observed in either the 1-back or 3-back. These results suggest that TOL improves the efficiency of information processing during working memory in the PFC and parietal cortex in patients with schizophrenia probably through a dopamine mediated enhancement in neurophysiological signal to noise ratio during the working memory task. TOL's ability to improve cortical focusing suggests that it could have several useful neuropsychiatric applications, such as improving cognitive deficits associated with schizophrenia.
ID: 550296

CLINICAL VARIABLES AS PREDICTORS OF COGNITIVE FUNCTIONING IN FIRST EPISODE OF PSYCHOSIS

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Patients with first-episode schizophrenia (FES) seem to have similar neurocognitive deficits to chronic patients. However, little is known about the influence clinical variables on neurocognitive changes in course of illness. The present study analyzes if baseline clinical variables would predict neurocognitive evolution in first episode psychosis patients. 104 first episode psychotic patients and 21 healthy subjects were assessed twice, at baseline and 1-year follow-up. The neurocognitive battery consisted of: Rey Auditory Verbal Learning Test = RAVLT; Rey Complex Figure Test = RCFT; Backward Digits = BD; Digit Symbol = DS; Trail Making Test- *B* = TMT-B; Fluency test = FAS; Brief Attention Test = BTA = ; Finger Tapping = FT; Grooved Pegboard = GP. A composite neurocognitive score was obtained. Clinical symptoms were assessed by means of the Scale for the Assessment of Positive symptoms (SAPS) and Scale for the Assessment of Negative symptoms (SANS). Analyses were carried out using the SPSS 15. We carried out a multiple regression analysis to predict neurocognitive functioning. As independent variables, we included clinical variables. Patients that presented more positive symptoms at baseline have better neurocognitive improvements at 1 year ($r = 0.217$; $P = .029$). Neurocognitive improvements were not mediated by the severity of negative symptoms at baseline. Unexpectedly, the severity of baseline positive symptoms would predict neurocognitive changes at short time in schizophrenia.
ID: 550277

IMPAIRMENTS OF FACIAL EMOTIONAL PERCEPTION IN PEOPLE WITH CLINICAL HIGH-RISK FOR PSYCHOSIS

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The purpose of this study was to investigate whether people with clinical high-risk for psychosis show impairments of facial emotion perception, which is well-known findings in schizophrenia. Participants were people with clinical high-risk for psychosis (CHR), schizophrenia patients (SPR) whose duration if illness is less than 5 years and normal controls (NC). Participants were requested to perform facial emotion recognition tests. The facial emotional stimuli were selected from Ekman's pictures of facial affect (Ekman, 1976) and Matsumoto and Ekman's Japanese and Caucasian Facial Expression of Emotion (JACFEE) and Neutral Faces (JACNeuF). The recognition rates of fear and sadness in Ekman's pictures in CHR were significantly lower than those in NC ($F = 4.11$, $P = .028$ for sad, $F = 6.51$, $P = .005$ for fear). The recognition rates of fear and sadness of JACFEE in CHR significantly lower than those in NC ($F = 8.17$, $P = .002$ for sad, $F = 4.44$, $P = .022$ for fear). These findings suggest that impairments of facial emotion recognition may be already present in prodromal phase of psychosis. The implications with psychopathologies, social and role functioning in CHR and SPR will be discussed.
ID: 550202

VISUAL AND COGNITIVE PROCESSING OF FACE INFORMATION IN SCHIZOPHRENIA: DETECTION, DISCRIMINATION AND WORKING MEMORY

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Face recognition involves several physiological and psychological processes, including those in visual, cognitive and affective domains. Studies

have found that schizophrenia patients have deficient recognition of facial emotion, yet visual and cognitive processing of facial information in this population has not been systematically examined. In this study, we examined visual detection, perceptual discrimination and working memory of faces as well as non-face visual objects in patients. Visual detection was measured by the accuracy when detecting the presence of a briefly displayed sketched face image which contained only the basic configural information of a face. Perceptual discrimination was measured by the discriminability scores for individual identities from face photograph images of which the degree of similarity was systematically varied via morphing. Working memory was measured by the discriminability scores when two comparison face images were separated by 3 or 10 seconds. All measurements were acquired using a psychophysical method (two-alternative forced choice). Relative to controls, patients showed significantly reduced accuracy in visual detection of faces ($P = .003$). Patients exhibited moderately degraded performance in perceptual discrimination of faces ($P = .065$). Furthermore, patients showed significantly impaired performance in working memory of faces ($P < .001$ for both 3 and 10 sec conditions). Performance in face recognition in patients, while degraded, was not correlated with that in recognition of non-face visual objects. This pattern of results indicates that visual and cognitive processing of facial information in schizophrenia requires greater signal strength and is thus inefficient.
ID: 550164

THE VALUE OF MEASURING NEUROCOGNITIVE HOMOLOGUES IN ANIMAL MODELS OF "PATHOGENESIS" IN SCHIZOPHRENIA

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In the development of "animal models of schizophrenia", we strive to model pathogenic mechanisms leading to both the neuropathology and psychopathology of the disorder. In this presentation, we will argue that a continuing evaluation of the many approaches there are to building such models is necessary if the goal is to arrive at animal models with the validity and reliability necessary to help us understand the pathogenesis of the disorder and to screen potential therapeutic strategies. This presentation will briefly review approaches to building models based on "etiologic" (early risk-factor) data versus those based on understanding the "proximal" neuropathophysiology of cognitive and behavioral abnormalities. This will be followed by a discussion, with examples, of how these approaches can intersect. The presentation will highlight the need for studies in schizophrenia patients in which the neurocognitive processes hypothesized to be abnormal are tested with paradigms that have verifiable construct validity and, thus, can be translated to paradigms in animal models. Although not all of the behavioral and cognitive phenomenology of schizophrenia is easily (or even best) conceptualized as an abnormality in a neurocognitive or neurobehavioral construct that has a homologue in rodents, we argue that significant progress can be made by identifying such constructs and utilizing paradigms that measure them in experimental animals. Such paradigms can then be used in animal models designed to examine the effect of risk factors and hypothesized pathogenic mechanisms, or novel treatments, on neurocognitive and neurobehavioral constructs reliably affected in schizophrenia.
ID: 550149

ASSESSING SOCIAL-COGNITIVE DEFICITS IN SCHIZOPHRENIA WITH THE MAYER-SALOVEY-CARUSO EMOTIONAL INTELLIGENCE TEST

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Background: The emotion management subscale of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) has recently been recommended by the MATRICS committee as the sole measure of social cognition for trials of cognitive enhancement in schizophrenia, yet the psychometric properties of this subscale and the larger instrument in schizophrenia patients have not been thoroughly examined. This research sought to conduct a comprehensive psychometric investigation of the MSCEIT for assessing social cognition in schizophrenia. Methods: A total of 64 outpatients with schizophrenia were assessed using the MSCEIT. Scale reliability and validity parameters were estimated through internal consistency analyses; comparisons of patient performance with norms from healthy samples; examinations of convergence with measures of cognition, functional outcome, and psychopathology; and a series of exploratory factor analyses. Results: The MSCEIT demonstrated adequate internal consistency among its branch and total scales, and patient test performance was significantly below normative levels. Estimates of discriminant and concurrent validity indicated that the MSCEIT diverged from measures of neurocognitive functioning and psychopathology, but was only modestly related with objective measures of functional outcome. Convergent validity estimates suggested that, contrary to expectations, the MSCEIT did not correlate with a behavioral measure of social cognition. Finally, exploratory factor analyses suggested the possibility of a shift in the latent structure of emotional intelligence in schizophrenia, compared to studies with healthy individuals. Conclusions: These findings support the use of the MSCEIT as a reliable and potentially valid measure of social cognition in schizophrenia, but also point to the need for further psychometric investigation of the instrument and additional measurement efforts to assess broader social-cognitive domains that may exhibit stronger relations with functional outcome.
ID: 550121

CNTRICS: WHY IT STARTED AND WHERE IT IS GOING

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One of the greatest challenges facing Medicine in the 21st century is the development of procognitive agents or other interventions to enhance cognition and improve functional outcome in schizophrenia. The tools and constructs of cognitive neuroscience provide a potentially powerful translational bridge between our rapidly growing knowledge about brain function and the application of this knowledge in both early and late phases of treatment development. These tools include computer-administered tasks that measure specific cognitive systems (such as attention, working memory, long-term memory, cognitive control) as well as the component cognitive processes that comprise these more overarching systems. The advantages of using these tools include the ability to identify and use homologous animal and human models in the drug discovery and testing process and the ability to incorporate noninvasive functional imaging measures into clinical trial contexts at several different phases of the drug development process. However, despite these advantages a number of barriers exist to their translation from basic science tools to tools for drug discovery. We discuss the development and implementation the Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS) initiative, designed to identify and overcome these barriers. Three meetings over a period of 18 months brought together leaders in basic and clinical cognitive neuroscience, psychometrics and drug development in an unprecedented format. The result was a series of recommendations related to the cognitive

systems to be targeted for treatment development for impaired cognition in schizophrenia, a set of guidelines for establishing the reliability and practicability of administration of tasks, and a set of recommended tasks for further development as measures of treatment effects on cognition in schizophrenia. We will also discuss the proposed next phase of CNTRICS, including a focus on the development of appropriate animal homologues of targeted cognitive constructs as well as biomarker development.
ID: 550053

CNTRICS: DATA AND PRODUCTS FROM THE "CONSTRUCTS", "PSYCHOMETRICS" AND "TASKS" MEETINGS

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The purpose of this talk is to provide an overview of the data and deliberations generated as part of the first three meetings of the CNTRICS initiative. The first CNTRICS meeting focused on identifying cognitive constructs that: 1) had been well validated in the human and animal cognitive neuroscience; and 2) were relevant to understanding cognitive function in schizophrenia. In preparation for this meeting, CNTRICS conducted two on-line surveys. The first asked members of relevant research fields help generate and rank criteria for evaluating potential cognitive constructs. The second asked respondents to rank a number of potential constructs on these criteria, as input for the discussion at the first conference. The first conference had basic science experts present overviews on the cognitive and neural mechanisms involved in each of six domains: 1) working memory; 2) executive control; 3) attention: 4) long term learning and memory; and 5) perception; and 6) social cognition. Following these overview talks, smaller groups "broke-out" to identify 12 cognitive constructs from these 6 domains that were felt to have sufficient cognitive and neural construct validity for further consideration. The second CNTRICS meeting focused on identifying the translational challenges facing research aimed at developed paradigms from basic cognitive neuroscience Prior to the meeting a web based survey asked a wide range of experts in the field to provide rankings on the key issues and challenges related to measurement development that helped focus the discussion. In addition, this survey helped to establish benchmark values for various psychometric properties deemed critical in the task development processing (eg, test-retest reliability, maximum practice effects, etc.). The third meeting focused on identifying promising cognitive tasks to measure each of the constructs selected in the first CNTRICS meeting. Prior to the meeting a web based survey sought nominations for specific tasks for targeted measurement of the constructs identified at Meeting 1 together with documentation of their construct validity, amenability for use in imaging studies, relationship to animal models, psychometric properties, sensitivity to drug effects and existing data in schizophrenia. Breakout groups at the meeting ranked tasks according to specific criteria, recommending 1-2 tasks for further development for each construct.
ID: 550032

DO EARLY CHANGES IN TRIGLYCERIDES PREDICT LATER CHANGES DURING OLANZAPINE TREATMENT?

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Purpose: To characterize changes in fasting serum triglycerides during olanzapine treatment and determine whether changes in triglyceride concentrations early in treatment predict clinically significant changes at 6 months. Methods: Fasting triglyceride data were from three 6-month, active-comparator studies of treatment for schizophrenia or schizoaffective disorder. Minimum age was 18 years for all trials. Maximum age was 75, 60, and 55 years for trials A, B, and C respectively. Analyses included only patients with fasting triglyceride data at all protocol-specified time points. In trials A, B, and C respectively, 277, 202, and 281 patients were randomized to olanzapine; 128, 48, and 134 patients met analysis criterion. Patients were categorized according to change from baseline in triglycerides at Weeks 5–13 and Weeks 22–30. Cut-off points of 20, 30, 40, and 50 mg/dL change in triglycerides from baseline were used for Weeks 5–13. Positive and negative predictive values (PPV, NPV) were calculated for all cut-off points. Results: Mean baseline fasting triglyceride concentrations (standard deviation [SD]) were 133.5 mg/dL (98.1), 210.4 mg/dL (214.8), and 147.1 mg/dL (96.8), respectively for trials A, B, and C. Mean changes from baseline at endpoint (SD) were 41.0 mg/dL (115.7), 9.1 mg/dL (124.4), and 37.2 mg/dL (97.1) for trials A, B, and C. In all trials, the largest change was seen in the first 12 weeks of treatment. Given a <20 mg/dL early change in triglycerides, probability of a $\geq$50-mg/dL change at 6 months ranged from 12% to 17%. NPVs ranged from 83.3% to 87.7%. PPVs ranged from 40.0% to 46.2%. Conclusions: Early assessment of fasting triglyceride concentrations can help identify patients who may be at potential risk for clinically significant changes with longer treatment. While NPV values are informative, potential risk of triglyceride increase is still present. Clinicians should continue to monitor serum triglycerides.
ID: 549884

USING EYE-MOVEMENTS TO ASSESS ITEM-SPECIFIC AND RELATIONAL LONG TERM MEMORY IN SCHIZOPHRENIA

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Episodic long-term memory is among the most severely impaired cognitive domains in schizophrenia, and is also one of the strongest predictors of long-term functional outcome among schizophrenia patients. However, the field has yet to arrive at a precise understanding of the cognitive and neural mechanisms of these memory impairments. Here, we used direct (behavioral performance) and indirect (eye movement monitoring) measures to test the hypothesis that memory deficits observed in schizophrenia are a consequence of a specific impairment in the encoding of inter-item relationships, with encoding of item-specific information largely intact. During study trials, participants viewed several rendered scenes. An orienting question directed attention to a critical item in each scene thereby encouraging participants to process information about the item itself (ie, its precise physical form) or its relationship to other items in the scene. At test, participants were shown repeated (unchanged) scenes, manipulated scenes, and novel scenes. In manipulated scenes, a critical item was either replaced with a different exemplar (item manipulation) or moved to a different location (relational manipulation). Participants were asked to indicate whether the scene was unchanged, old with an item manipulation, old with a relational manipulation, or new. Each response was followed by a confidence rating. Eye movements, monitored throughout the test block, provided an indirect measure of memory for scene repetition (novel vs. repeated scenes), relational memory (original vs. relational manipulation scenes), and item-specific memory (original vs. item manipulation scenes). Preliminary results show that performance on the orienting question was high in both groups, which indicates that all of the participants were

engaged in the task and had attended to the critical region of each scene. In addition, relative to the matched comparison group, schizophrenia patients performed more poorly on the test of relational memory and failed to show some of the normal changes in viewing that are evident in scan paths of neurologically-intact participants when scenes have been manipulated. Further analyses will investigate the relationship between relational memory as expressed in eye movements and overt reports.
ID: 549870

SWITCHING ANTIPSYCHOTIC DRUGS ENHANCES IMPROVEMENT IN PATIENTS WHO SHOW LACK OF AN EARLY RESPONSE TO THEIR INITIAL ANTIPSYCHOTIC THERAPY

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Objective: To examine the utility of switching to an alternative antipsychotic drug for patients who fail to show an early response to their initial antipsychotic therapy. Methods: This randomized, double-blind, flexible-dose, 12-week study enrolled 630 patients diagnosed with schizophrenia or schizoaffective disorder. All patients were initially assigned to risperidone (RIS) therapy (2-6 mg/day) for 2 weeks. Early responders ($\geq$20% improvement PANSS total score from baseline to 2 weeks) continued on RIS ($N = 144$), whereas early non-responders to RIS were randomized at Week 2 (1:1) double-blind to continue on RIS ($N = 192$) or switch to olanzapine (OLZ) (10-20 mg/day; $N = 186$) for 10 additional weeks of therapy. These two early non-responder groups were compared on efficacy and safety parameters. Given observed heterogeneity in response, post-hoc analyses were conducted for patients who were at least moderately ill (58%) at Week 2 and repeated for those who were not (42%). Results: Early non-response to RIS was observed in 72.4% of patients. Early non-responders had significantly less improvement in PANSS total score throughout the 12-week study ($P < .001$) compared to early responders. Switching RIS early non-responders to OLZ resulted in significant symptom improvement in PANSS total score ($P = .020$) and MADRS ($P = .020$) at endpoint (up to 10 weeks). Among the early non-responders, OLZ-treated patients had numerically greater weight gain ($P = .143$), significantly greater increase in triglycerides ($P = .005$), but a greater decrease in prolactin ($P < .001$). Among early non-responders who were still at least moderately ill at Week 2, OLZ-treated patients experienced significantly greater improvement in PANSS total, positive, negative and general psychopathology scores ($P < .05$) and in the MADRS ($P < .001$), with separation between the OLZ and RIS groups evident by 4 weeks after switching. Treatment differences were not observed among early non-responders who were less than moderately ill at randomization (Week 2). Conclusion: Switching RIS early non-responders to OLZ at Week 2 is an effective strategy that facilitates further symptom improvement but is also accompanied by changes in safety parameters, thus warranting individual benefit-risk considerations. Among early non-responders to RIS who continue to be at least moderately ill at Week 2, switching to OLZ is associated with greater symptomatic improvement.
ID: 549817

IDENTIFYING SALIENT FEATURES OF VISUAL PROCESSES FOR EMOTION IDENTIFICATION IN SCHIZOPHRENIA WITH THE BUBBLE TECHNIQUE

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By identifying facial expression of emotion, people can rapidly infer the feelings and thoughts of others. Emotional facial expression communicates socially relevant information needed for adaptive behavior. Schizophrenia patients exhibit difficulties recognizing emotions from facial expression, and this deficit is linked to poor social functioning. It is not known which aspects of visual information processing lead to inadequate recognition of facial emotional expression in schizophrenia. In this study, we used a novel 'Bubble technique' (Gosselin and Schyns, 2001) that has not previously been applied to schizophrenia to determine the salient visual information involved in recognizing facial emotional expression. Seventeen schizophrenia patients and 17 healthy controls (matched for age and gender) received the Bubbles task in which they categorized whether emotional expression of the face stimulus was happy or fear. The Bubble technique creates facial stimuli by sampling features of facial information at random spatial location at five non-overlapping spatial frequency bands, resulting in a final stimulus of face that is partially occluded by 'bubbles'. Online titration of sampling density of bubbles ensured 75 % overall accuracy for each subject. Multiple linear regression analyses between sample space (spatial location and spatial frequency bands) and accuracy revealed salient features of face stimuli for recognizing emotional expression. To correctly recognize a happy face, healthy controls used both eye and mouth regions, whereas schizophrenia patients relied primarily on mouth regions. To recognize fear, both groups utilized eye and mouth regions. However, schizophrenia patients relied more on higher spatial frequency for fear identification, whereas healthy controls utilized lower spatial frequency. By revealing how schizophrenia patients use different regions and different spatial frequencies of visual information to recognize emotion, these findings 1) suggest aspects of basic visual processing that can contribute to identification errors, and 2) suggest possible rehabilitation approaches to improve of facial emotion identification in schizophrenia.
ID: 549807

IDENTIFICATION OF SYMPTOMS THAT PREDICT ANTIPSYCHOTIC RESPONSE IN THE TREATMENT OF SCHIZOPHRENIA

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Objectives: Early non-response to antipsychotics is a robust predictor of subsequent non-response to continued treatment with the same antipsychotic. This analysis pursued simple decision rules using one and two PANSS item groups to predict early response/non-response to antipsychotics in the treatment of moderate-to-severely ill schizophrenia patients with at least moderate positive symptoms. Methods: Data was pooled from 6 randomized double-blind trials of atypical antipsychotics in the treatment of schizophrenia ($N = 1494$). Response was defined as a 30% reduction in PANSS total score at 8 weeks. Predictors of response included change from baseline in PANSS items at Week 2. Classification and regression tree (CART) analysis was used to define a decision tree creating a predictive model for response/non-response. Results: Analysis of individual positive symptoms indicated a composite measure of positive symptoms worked best. The first node of the decision tree used a 2-point decrease in at least 2 of the 5 positive symptoms from baseline to Week 2. If this response criterion was not met, the second node used a 2-point decrease in the excitement item. Using this algorithm, most patients (92%) were classified as responders/non-responders with high positive (79%) and negative (75%) predictive value. Conclusion: Using items selected from the 30-item PANSS, a simple decision tree was found to be predictive of response/non-response based on 2 week change on 6 individual PANSS items.

Findings could lead to the development of a brief evaluation tool to help guide treatment decisions early in the course of antipsychotic drug therapy.
ID: 549730

ALPHA 7 NICOTINIC ACETYLCHOLINE RECEPTOR ACTIVATION PREVENTS SCHIZOPHRENIA-RELEVANT BEHAVIORAL AND MOLECULAR CHANGES INDUCED BY REPEATED PCP TREATMENT IN MICE

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Aim: To study the differential effect of phencyclidine (PCP) and the selective alpha 7 nicotinic acetylcholine receptor (nAChR) agonist SSR180711 on working memory/attention as well as their effect on the expression of genes relevant to schizophrenia. Special focus was put on the ability of SSR180711 to prevent changes produced by PCP. Methods: A modified Y-maze test was used to asses working memory/attentional performance in mice treated repeatedly with PCP and/or SSR180711, and in situ hybridization was used to correlate these data to gene expression in the prefrontal cortex (PFC). We examined the expression of parvalbumin and synaptophysin, which are altered in schizophrenic patients, as well as the activity-regulated cytoskeleton-associated protein (Arc), which is important for synaptic plasticity. Results: Repeated PCP treatment (10 mg/kg/day for 10 days) induced impairments in working memory and attention, as measured in the modified Y-maze. This behavioral impairment was accompanied by a decreased expression of parvalbumin and synaptophysin mRNA in the PFC, which corresponds to the changes seen in patients with schizophrenia. In addition, PCP was found to increase basal mRNA expression of the activity-regulated cytoskeleton-associated protein (Arc) in the PFC. Activation of the alpha 7 nAChR by acute administration of the alpha 7 nAChR agonist SSR180711 (3 mg/kg) reversed the behavioral impairment produced by PCP. Importantly, repeated co-administration of SSR180711 and PCP prevented both the behavioral impairment induced by PCP and the changes in parvalbumin, synaptophysin, and Arc mRNA expression in the PFC. Conclusion: The alpha 7 nAChR agonist SSR180711 is the first compound shown to prevent the deleterious effects induced by repeated PCP treatment. The preventive effect of alpha 7 nAChR agonism in this PCP model suggests an involvement of the alpha 7 nAChR not only in the symptomatic relief, but also the pathophysiology, of cognitive deficits in schizophrenia.
ID: 549623

THE USE OF FORMULAIC EXPRESSIONS IN SCHIZOPHRENIA: A BASIS FOR IDENTIFYING NEURAL SUBSTRATES

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Background: Among various speech and language disturbances that have been reported in schizophrenia (SZ), pragmatics of language are considered the most affected. Within this sphere, certain types of nonliteral language comprehension measures (eg, proverbs, idioms, indirect request) have been investigated in SZ, which have bearing on the ability to relate socially and emotionally. These are formulaic expressions (FEs), which are produced spontaneously in social conversational contexts and have emotional and attitudinal charge. They have linguistic and functional properties indicating that they are a special class of utterances. In healthy individuals, FEs make up over 25% of everyday speech. Studies of brain damaged individuals have shown that FEs are processed mainly by the right hemisphere (RH) and the basal ganglia. This study was the first to examine the production of FEs in social and conversational settings by patients with SZ. Methods: We measured FE production in 6 patients (5 schizophrenic/1 schizoaffective), and 8 healthy controls. Instruments included an audio-recorded structured conversation, and formal tasks used to measure FE knowledge/production. Results: A comparison of the production of FEs in patients diagnosed with SZ and in controls indicated that the SZ group was comparable to the controls in their use of FEs on formal tasks, indicating that they have knowledge of these expressions. However, patients' spontaneous production of FEs in a conversational setting was significantly diminished in comparison to controls ($P < .01$), as was their performance on responsive formulas in social settings ($P < .05$). A significant correlation was observed between the lack of vocal inflections item on the SANS and the proportion of FE production. Conclusions: These results indicate that in SZ the ability to use two modes of language, holistic and analytic, is disturbed. Patients' performance was comparable to individuals with basal ganglia and RH damage. FE production is a well-characterized and quantifiable measure of language communication, which may contribute to the remediation of social cognitive deficits in SZ. A future goal is to correlate these results with a physiological or imaging measure in order to identify possible neural substrates involved in diminished use of formulaic language.
ID: 549453

ROLE OF FRONTO-STRIATAL SYSTEMS IN LEARNING AND EXECUTIVE MECHANISMS RELEVANT TO SCHIZOPHRENIA

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The purpose is to review and re-examine the role of aberrant associative learning mechanisms in fronto-striatal pathways in explaining both positive symptoms and certain cognitive deficits in schizophrenia. The effects of the NMDA antagonist ketamine on associative learning in a functional imaging paradigm utilizing the BOLD response are described in normal volunteers and in schizophrenic patients, using a human causal learning paradigm (collaboration with P. Corlett and PC Fletcher). These responses will be compared with deficits in discrimination learning and set-shifting affected by the atypical stimulant modafinil, using the id/ed paradigm from the CANTAB battery which is related to the Wisconsin Card Sorting Test (collaboration with D Turner and BJ Sahakian). The utility of the id/ed test will also be examined from recent large-scale studies in schizophrenia (collaborations with G Murray, and EM Joyce). Ketamine impaired predictive learning in volunteers and patients with schizophrenia, effects that were associated with BOLD activations in certain regions, including the midbrain, nucleus accumbens and dorso-lateral prefrontal cortex (DL-PFC). The extent of the activation in DL-PFC predicted effects of higher doses of ketamine to induce delusions outside the scanner. Modafinil improved discrimination learning in the intra-/extra-dimensional set-shifting paradigm from the CANTAB battery, (in accordance with similar data in a related animal model of schizophrenia based on NMDA receptor

antagonism). Results from the two parallel investigations illustrate that associative learning may be associated with positive symptoms in schizophrenia such as delusions, and also with impairments in executive function, such as set formation and shifting. These deficits are sensitive to pharmacological modification by both ketamine and modafinil. To explain these data, one hypothesis links positive symptoms to aberrant learning mechanisms within sub-cortical circuitry that impacts at the cortical level, and cognitive impairments to additional deficits in related cortico-striatal networks at the cortical level. The availability of longitudinal data for the id/ed test in a large sample of first episode cases also enables investigation of the contribution of basic deficits at the initial simple discrimination learning phase to the executive impairments in set-shifting, (as well as test-retest reliability of such deficits), over the course of the disorder
ID: 549326

LESSONS LEARNED FROM THE IMPLEMENTATION OF A CLINICAL TRIAL USING THE MATRICS-FDA-NIMH GUIDANCE

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Sanofi-Aventis is currently conducting a large (~700 patients), multi-site (~70), multi-country (US and Canada) study in patients with cognitive impairment diagnosed with schizophrenia, the CONNECT study. We have experienced both opportunities and challenges using the study methodology for this novel therapeutic approach. The study is a 24-week, multicenter, double blind, randomized, parallel-group, dose ranging study of the efficacy and safety of three oral doses of AVE1625, a CB1-receptor antagonist, and placebo on top of an established treatment of either olanzapine, risperidone, paliperidone, quetiapine or aripiprazole monotherapy. The primary endpoint is the MATRICS Consensus Cognitive Battery; the co primary endpoint for functional capacity is the UCSD Performance-Based Skills Assessment University, 2. S-a acknowledges the many positive opportunities this experience has provided our company, both scientifically and professionally. These opportunities include guidance from the FDA regarding requirements for trial design and endpoints, expertise in the use of the MCCB and UPSA2 and the establishment of relationships with many experts in this therapeutic area. S-a's involvement in the MATRICS-CT Scientific Board as a pharmaceutical partner has also been a unique and rewarding experience. Challenges occurred in the following areas: limited number countries in which to perform the study, protocol design, need for increased financial resources and patient retention. The following actions are part of the lessons learned: Increase the number of sites and length of enrollment, use shorter treatment period, consider inclusion of schizoaffective diagnosis, include use of all SGAs, allow some form of combination antipsychotic therapy, reconsider age limit of diagnosis, use abbreviated assessments such as the UPSA Brief, consider all English speaking countries from the beginning (in the absence of translations), plan for 2 day visits for 'heavy' assessments weeks and consider using an inpatient setting if patients are there only for lack of outpatient placement. In conclusion, sanofi-aventis sees this as a positive endeavor that has provided the company with many 'Lessons Learned' which will be beneficial in future clinical trials. Additionally, the translations of the MCCB and development of the co primary functional outcome measures will be of importance for the upcoming studies. The company also recognizes the many experts who have helped us along the way.
ID: 549063

THE mGluR5 POSITIVE ALLOSTERIC MODULATOR, CDPPB, HAS ANTIPSYCHOTIC EFFECTS, IMPROVES MEMORY, AND INCREASES HEDONIA: RELEVANCE TO SCHIZOPHRENIA.

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Schizophrenia is marked by a cluster of behavioral and psychological deficits, generally classified into 3 subgroups: positive symptoms, negative symptoms, and cognitive deficits. Unfortunately, no currently prescribed medication effectively improves all of these symptom domains. Because accumulating evidence suggests that NMDA receptor hypofunction underlies at least some of the behavioral manifestations of schizophrenia and mGluR5 receptor activation is thought to positively regulate NMDA receptor function, we examined the influence an mGluR5 positive allosteric modulator (PAM), CDPPB, on behavioral assays relevant to schizophrenia. CDPPB (30 mg/kg ip) attenuated both amphetamine (1.5 mg/kg sc) and MK-801 (0.23 mg/kg sc) induced psychomotor activity, assays sensitive to compounds with antipsychotic potential. Furthermore, CDPPB (3 and 10 mpk ip) reversed an MK-801 (0.3 mg/kg ip) induced deficit in novel object recognition and passive avoidance learning, indicating that mGluR5 PAMs have pro-cognitive effects. Finally, we report that CDPPB (3 mpk ip) alleviated an MK-801 (0.3 mg/kg ip) induced deficit in hedonic valuation, a core feature of negative symptoms, as measured by the sucrose preference test. These results suggest that mGluR5 PAMs may have a novel therapeutic profile in that they might improve all of the symptoms domains present in schizophrenia.
ID: 549042

SEMANTIC PRIMING ABNORMALITIES AS PUTATIVE ENDOPHENOTYPE OF PSYCHOSIS: AN EVENT-RELATED POTENTIAL STUDY

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Background: Several studies have indicated that patients with psychosis show an abnormal, faster and further spread of activation through the semantic network (eg, Moritz et al., 2001). This has been shown in direct and indirect semantic priming paradigms. The aim of the present study was to investigate whether the direct and indirect semantic priming effect is a putative endophenotypic marker which is also found in first-degree relatives (siblings) of patients. The study used Event-Related potentials, ie, the language specific N400 component, as an indicator of the underlying neural correlates of abnormal semantic priming. Method: Thirteen patients with non-affective psychosis, 14 siblings and 16 controls participated in a lexical decision task with three conditions (directly related, indirectly related and unrelated) and two different stimulus onset asynchronies (SOAs), 250 ms and 500 ms, to disentangle the effect of strength of semantic associations and to control for time differences of stimulus presentation, tapping automatic (short SOA, hereafter SOA250) and more controlled (long SOA, hereafter SOA500) processes. Results: For SOA250, control participants showed a N400 direct priming effect, but no difference in the N400 component between the indirect and unrelated condition. The N400 priming effect was present in all conditions with SOA500, the indirect condition in-between the other two conditions. In patients, the N400 priming effect was similar in the indirect and the direct condition for both SOAs, and was pronounced for SOA500 in both conditions. For SOA250, siblings showed similar results as patients (no difference between the direct and indirect condition compared to the unrelated condition), indicating abnormal semantic priming processes. For SOA500, siblings showed similar results as controls (ie, N400 priming effect for both conditions with the indirect condition in-between). Conclusion: Abnormal spreading of activation in the semantic network is present in patients with psychosis. Siblings also showed abnormal spreading of activation at the level of automatic processing, which dissolve and become normal in more controlled processes. Semantic priming abnormalities can be considered a possible risk marker for psychosis.
ID: 549035

THE CONTRIBUTION OF INTEGRATING DISCONFIRMATORY EVIDENCE AND JUMPING TO CONCLUSIONS TO DELUSIONS IN SCHIZOPHRENIA

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Previous research has consistently demonstrated a bias against disconfirmatory evidence (BADE) and a jumping to conclusions (JTC) bias in schizophrenia, with some studies reporting this effect to be more pronounced in patients currently experiencing delusions compared to those with remitted delusions. We report evidence for correspondences between cognition and delusions in three studies using novel versions of the BADE and JTC tasks.
Study 1. In the first study, participants were administered a version of the BADE test, consisting of 30 delusion-neutral scenarios, for which three increasingly disambiguating sentences were sequentially presented. Participants rated the plausibility of four interpretive statements that were initially rated for plausibility based on a single scenario-descriptive sentence, and were then re-rated against two subsequently presented sentences that were either confirmatory or disconfirmatory in nature. A measure of integration of disconfirmatory evidence discriminated between the delusional schizoprenia patient group and all other groups, including non-delusional schizophrenia patients, bipolar, and healthy control groups. No group differences were observed for other measures derived from the test, such as initial ratings prior to the introduction of disconfirmatory evidence.
Study 2. In the second study, a JTC task was used, for which participants rated the likelihood that a fisherman was catching a series of white and/or black fish from two lakes with differing proportions of white and black fish (lake A or lake B). Probability ratings in favour of the more likely lake were higher for delusional schizophrenia patients compared to non-delusional schizophrenia, bipolar, and healthy control groups. No group differences were observed for ratings of the non-preferred lake.
Study 3. In a third study, individuals with schizophrenia spectrum disorders completed a version of the JTC task involving fishing from lakes at two timepoints 12 weeks apart. The results revealed significant negative correlations between change in the number of fish requested before a decision was made, and change in delusion scores over time. These studies provide evidence for two independent cognitive processes underlying delusions, a BADE and JTC, with JTC additionally demonstrating sensitivity to changes in the severity of delusions in schizophrenia.
ID: 548989

IMPAIRED CAPACITY BUT PRESERVED PRECISION OF VISUAL SHORT-TERM MEMORY IN SCHIZOPHRENIA

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Deficits in short-term memory are consistently reported in patients with schizophrenia, such that fewer items are remembered in delayed match to sample paradigms. The impairment is more prominent with larger set sizes, suggesting reduced memory capacity. However, capacity limitations cannot explain persisting memory deficits at set sizes as small as one item. The underlying problem may instead be that memory representations are imprecise. "Noisy" representations would cause recall impairment at any set size, and would also explain findings that deficits diminish when comparisons between sample and test items do not depend on a differentiated level of encoding. In the present study, 22 patients with a diagnosis of schizophrenia and 19 matched controls performed a visual short-term memory task designed to independently measure memory capacity (K) and precision (Zhang and Luck 2008, Nature 453:233). A sample array of 3 or 4 colored squares was presented for 500 ms. After a 1 or 4 s delay, one of the previous square locations was cued. The task was to match the color remembered at this location as accurately as possible on a color wheel displaying the entire spectrum. A maximum likelihood algorithm was used to derive separate estimates of the number of representations that can be stored (K), and the precision of representations (average distance from true value) when the item was present in memory. Three-factor ANOVA with group as between- and set size and delay as within-subject factors revealed a main effect of group on K ($P = .03$) but not precision ($P > 0.9$), reflecting significantly reduced memory capacity in schizophrenic participants but no indication for noisier memory representations. The reduced K in patients tended to be more prominent with the larger set size, as reflected by a trend-level interaction of group with set size ($P = .07$). In contrast, the impairment did not differ with delay length ($P > 0.4$), consistent with previous reports of normal memory decay rates. The results provide evidence against the hypothesis that short-term memory impairment in schizophrenia is caused by deficits in the precision of memory representations, at least for simple color stimuli. Capacity reduction may limit the number of represented items; however, the quality of these representations seems unimpaired. Alternative explanations for capacity-independent impairment in memory tasks include transient lapses in attention or task set maintenance. Supported by NIMH MH065034.
ID: 548429

GLOBAL COGNITIVE MEASURES AS PRIMARY OUTCOMES IN TREATMENT TRIALS

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Results from large trials of patients with schizophrenia suggest that the amount of cognitive improvement associated with second-generation antipsychotic treatment in chronic schizophrenia and first episode psychosis is minimal, and may not exceed the amount of improvement that would be expected from placebo or practice effects. Clearly, additional pharmacologic and behavioral treatments are needed to improve cognition in schizophrenia. Numerous large-scale trials are underway to investigate treatment effects on cognitive impairment in patients with schizophrenia. While the MATRICS recommendations to FDA suggested a single composite score as the primary outcome measure for these trials, they allowed that some trials may target more specific cognitive outcomes. General cognitive functions measured by composite scores are more highly correlated with real-world functioning, yet refined cognitive tests may measure abnormal brain processes in schizophrenia with greater precision. This presentation will discuss several recent unpublished schizophrenia cognition trials that have used composite scores or general cognitive functions as a primary outcome measure, and will compare these global cognitive measures to more specific domain scores. For example, in one yet unpublished study using the MATRICS Consensus Cognitive Battery (MCCB), preliminary data from 90 patients suggest that these general composite scores have slightly greater test-retest reliability (ICC = 0.88) than domain scores (ICCs ranging from 0.85 to 0.64), and greater sensitivity to impairment (T-score = 28.1 ± SD = 11.5 for patients compared to 50.0±10.0 for controls) than individual

domain scores, which ranged from T = 34.1 for processing speed to T = 39.5 for reasoning and problem solving. In addition, recently analyzed data from 794 patients treated with different antipsychotic medications in the CATIE trial suggest that improvements in overall Quality of Life score (beta = 0.32, *df* = 54,853, *P* < .0001) than are any of the five individual domain scores (beta ranging from 0.09 to 0.16). This series of results suggests that while specific cognitive measures may have utility for early phase studies, currently existing measures of general cognitive functions have proven reliability for multisite clinical trials and clinical relevance for real-world functioning, and should continue to serve as the standard for later phase studies.
ID: 548358

LARGE VERBAL ABILITY CONTRIBUTION TO MSCEIT SCORES OF SOCIAL COGNITION IN SCHIZOPHRENIA

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The Emotion (EM) and Social Management Tasks (SM) tasks from the MSCEIT are included in the MATRICS battery to assess social cognition. Unlike other subtests of the MATRICS, which have ample support from previous literature, these two tasks have not had much prior use in schizophrenia research. Both tasks require verbal comprehension and memory for written narrative. These prerequisite neurocognitive abilities may reduce the validity of these tasks as measures of social cognition. Given the prominence of language function deficits, it is important to consider their potential contributions to performance when using the EM and SM tasks to evaluate social cognition in schizophrenia. Method: 45 stable outpatients with schizophrenia completed a battery of neurocognitive and social cognitive assessments, which included the MATRICS battery. Pearson correlations were computed for scores from the MSCEIT tasks and measures of verbal ability (HVLT Total, WAIS Digit Span, WAIS Vocabulary, WMS Logical Memory I (LM-I), WAIS Letter-Number Sequencing); and also with other social cognitive tasks (Bell Lysaker Emotion Recognition Test (BLERT), Hinting Task, Social Attribution Test—Multiple Choice (SAT-MC)). Results: The MSCEIT social cognition tasks correlate substantially with WMS LM-I (EM: r = .63; SM: r = .63; P's < .001) and WAIS Vocabulary (EM: r = .51; SM: r = .54; P's < .001). MSCEIT tasks do not correlate significantly with Hinting Task nor SAT-MC, although we found smaller associations with the BLERT (EM: r = .37; SM r = .31; P's < .05). However, when partial correlations were computed to remove variance associated with WMS LM-I from r(BLERT, EM) and from r(BLERT, SM), those relationships were no longer significant (EM: r = .20; SM: r = .12). To appreciate the magnitude of the effect, all six verbal tasks were regressed on EM and again on SM. Verbal tasks significantly predicted 37% (P < .01) and 51% (P < .001) of the variance, respectively. In comparison, the verbal tasks failed to significantly predict Hinting Tasks or SAT-MC scores and predicted 32% of the variance on the BLERT (P < .05). Conclusions: Findings indicate that EM and SM may be more closely related to verbal ability, particularly story recall, than they are to social cognition. Given these results, when using EM and SM in schizophrenia research, the effects of compromised verbal abilities must be considered before making inferences about social cognition.
ID: 548117

A REVERSE TRANSLATIONAL APPROACH TO CHARACTERIZING EXPLORATORY BEHAVIOR AND MOTOR ACTIVITY IN SCHIZOPHRENIA AND BIPOLAR-MANIA

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Schizophrenia and bipolar-mania are recognized as separate disorders but share many commonalties and are considered by some to be the same disorder on a continuum. Exploration is a behavior that is fundamental to survival and is dysregulated in neuropsychiatric disorders such as schizophrenia and bipolar-mania. Exploratory behavior in rodents has been studied for decades but surprisingly little work has examined this critical function in humans. In the present study we characterize exploratory behavior as a potential endophenotype that may help distinguish between schizophrenia and bipolar mania and offers promise as a useful translational paradigm. We developed a novel human open field paradigm, the Behavioral Pattern Monitor (BPM), to quantify exploratory behavior of individuals with schizophrenia and bipolar-mania and to identify distinctive phenotypes of these illnesses. We also studied several putative mouse models to determine their consistency with the results of our human studies. We found that schizophrenia subjects demonstrated a pattern of exploratory behavior that was distinct from patients with bipolar-mania. Namely, Bipolar-manic subjects exhibited significantly higher motor activity and object exploration while schizophrenia patients did not show the expected habituation of motor activity. Furthermore, measures from the human BPM classified schizophrenia and bipolar-mania subjects with better sensitivity and specificity than did symptom scores. When testing the mouse models, genetic or selective pharmacological inhibition of the dopamine transporter matched the bipolar-mania phenotype better than the "gold standard" model of mania (amphetamine). These findings serve to validate the human open field paradigm and to distinguish defining characteristics that differentiate schizophrenia and bipolar-mania. This cross-species study of exploration has allowed us to challenge an accepted animal model and develop more accurate human and animal models, which are essential to identify neurobiological underpinnings of neuropsychiatric disorders. Supported by an NIH award R01-MH071916.
ID: 546403

THE SOCIAL ATTRIBUTION TEST IN SCHIZOPHRENIA: COMPARISON WITH HEALTHY CONTROLS AND RELATIONSHIP TO NEUROCOGNITIVE AND SOCIAL COGNITIVE MEASURES

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Impairments in social cognitive processes including attribution failures are a possible source of poor community functioning in schizophrenia and a possible target for interventions. However, there are few procedures available for the study of attributions, particularly measures that are not heavily dependent on verbal ability. In a study of adolescents and adults with Aspergers Syndrome (AS) and high functioning autism, Klin (2000) created a scoring procedure for attributions using Heider and Simmel's 1944 silent cartoon animation in which geometric shapes enact a social plot. Subject narratives were coded in terms of the participants' abilities to attribute social meaning to the geometric cartoon. Results revealed marked deficits in both clinical groups, and these were unrelated to verbal IQ or metalinguistic skills. Based on these findings, a multiple choice version of this task was developed (SAT-MC) and used for the first time in the current study to assess adults with schizophrenia (n = 25). This clinical sample was compared with adults attending community college who were screened for psychiatric illness (Community Controls (CC) n = 85). Correlations between SAT-MC scores and neurocognitive and social cognitive measures were also performed. Results revealed significantly poorer performance for the schizophrenia sample (sz mean (sd) = 9.8 (5.07); CC = 15.3 (2.9) P < .001). As with findings in the AS sample, SAT-MC scores were not significantly related to

WAIS Vocabulary, WMS Logical Memory I or WMS Logical Memory II. Correlations with the MATRICS indices (not including social cognition) were also not significant. However, correlations with other social cognition measures (Bell Lysaker Emotion Recognition Test (BLERT), Hinting Task, Social Management and Emotion Management (from MATRICS) revealed significant associations with the BLERT ($r = .42$, $P < .001$) and with the Hinting Task ($r = .24$, $P < .05$), but not the MATRICS measures. These results support the use of the SAT-MC for further explorations of social attribution deficits in schizophrenia and may serve as a potential link for understanding similarities and differences in the social deficits of autism and schizophrenia.

Reference

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ID: 546123

EMOTION RECOGNITION PERFORMANCE AMONG ADOLESCENTS AT GENETIC HIGH RISK FOR SCHIZOPHRENIA.

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Background: Studies have shown that people with schizophrenia and their non-psychotic relatives have deficits in emotion recognition, a measure of social cognition. There are few published data on emotion recognition in adolescents at risk for schizophrenia. The relation of such deficits to cognitive and psychopathological measures is also unclear. Methods: Participants, recruited through the Pittsburgh Risk Evaluation Program, include 70 first- and second-degree adolescent relatives of individuals with schizophrenia (HR) and 63 healthy comparison (HC) subjects. Subjects were assessed using the Penn Emotion Recognition Test, a timed test which requires subjects to assign emotion (Happy, Sad, Anger, Fear, No emotion) to 40 faces. Results: HR individuals were significantly more likely to over-attribute emotions to neutral faces ($P = .017$), with such individuals frequently misinterpreting neutral faces as negative. In addition, at-risk individuals had significantly greater reaction times when completing emotion recognition tasks, regardless of valence ($P = .002$). Impairments in neuro-cognition were largely independent of social-cognitive performance (range of $r = -.06$ to .19), and emotion recognition impairments persisted after adjusting deficits in neurocognitive function. Further, social-cognitive impairments in the interpretation of neutral faces were significantly associated with greater positive ($r = -.36$, $P = .002$) and general prodromal psychopathology ($r = -.36$, $P = .002$), whereas neurocognitive impairments were only associated with disorganization ($r = -.46$, $P < .0001$). Conclusions: HR children appear to have deficits in emotion recognition, similar to that of patients with schizophrenia, and perhaps independent of non-social cognitive deficits. It is unclear whether these deficits represent an additional risk factor for developing a psychotic disorder. Specific, targeted training may be helpful in reducing the impact of poor social cognition in at-risk individuals. Longitudinal studies are needed to ascertain the long-term impact of social cognition deficiencies.

ID: 542843

TRANSLATING SCIENCE INTO ACTIVE INGREDIENTS: OPTIMIZING COGNITIVE TRAINING APPROACHES IN SCHIZOPHRENIA

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One of the greatest challenges for 21st century biomedicine is to develop an effective treatment for the cognitive dysfunction of schizophrenia. Cognitive remediation trials have demonstrated some efficacy, but recent meta-analytic work reveals a glass ceiling of low to medium effect sizes across a wide variety of methods. How can we break through this glass ceiling and optimize the benefits of cognitive training in schizophrenia? How do we translate science into "active ingredients" for successful behavioral approaches to cognitive enhancement? We will start our analysis with an examination of the basic neuroscience evidence on the "active ingredients" that promote widespread neuroplasticity in cortex and in subcortical neuro-modulatory systems during successful learning. What are the implications of these basic science findings? How can they be successfully translated into human interventions? Next, we will move to the level of the clinical encounter, by exploring the science behind the "active ingredient" of participant engagement and motivation. How does participant motivation relate to outcome? How do findings from educational psychology inform the design of maximally engaging cognitive training programs for persons with schizophrenia? Finally, we will turn to the human laboratory as we investigate the science behind the "active ingredient" of training-induced brain plasticity. We will present fMRI, MEG, and serum biomarker evidence of neural changes associated with intensive computerized cognitive training. What do these findings tell us about the underlying mechanisms of cognitive improvement in patients with schizophrenia? How can we optimally harness these mechanisms in the design of cognitive training exercises? At all levels of analysis, our vision will be to create optimally effective restorative cognitive training approaches for people with schizophrenia.

ID: 542178

EMOTION CATEGORIZATION PERCEPTION IN SCHIZOPHRENIA: EFFECT OF SOCIAL CONTEXT DURING CONVERSATIONS

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Increasing evidence suggests that context plays an important role in the cognitive activities of schizophrenia and their context processing is impaired, it would be necessary to examine the impact of social dyadic interaction to the emotional perception. The purpose of the current study was to investigate the response patterns of patients with schizophrenia within a continuum of facial expression in different scenarios of social context. In particular, it aimed to investigate whether the boundaries between happy and angry emotions of schizophrenia would be influenced by the social context and whether there is any difference in the emotion categorization boundary between schizophrenia and healthy control. Eighteen patients with schizophrenia and sixteen healthy controls were administered a forced-choice emotion identification task in which they were required to attend to a series of conversations with different social context. Stimuli were linear morphed facial expressions between emotion 'happy' and 'angry'. For each type of social context, measures of response slope and the location of the boundary shift point between 'happy' and 'angry' were calculated. The schizophrenia group demonstrated no significant difference in the boundaries of emotion categorization perception of

four types of conversations in different social context. Compared with healthy control, the schizophrenia group demonstrated a steeper slope at the shift point regardless of the conversation type. The results might suggest that the categorization of emotion perception in patients with schizophrenia was less discriminative during the conversations with different social context. However, when the signal strength increased from the left pole to the right one independent of the social context,these patients were more alert to angry facial expression.

Table. Slope and mean signal threshold difference in two groups

Question type	Mean Slope (std)			Mean signal threshold (std)		
	Schizophrenia (n = 18)	Healthy control (n = 16)	t	Schizophrenia (n = 18)	Healthy control (n = 16)	t
blame	1.641 (0.261)	0.825 (0.126)	3.98*	6.176 (0.286)	5.847 (0.143)	1.46
Control mask	1.803 (0.294)	0.766 (0.093)	4.76**	6.386 (0.314)	6.104 (0.106)	1.2
inquiry	1.919 (0.268)	0.749 (0.062)	6.02**	6.415 (0.282)	6.335 (0.071)	0.38
praise	1.899 (0.226)	0.800 (0.116)	6.12**	6.411 (0.238)	6.56 (0.132)	−0.77

*$P < .05$; **$P < .01$
ID: 539298

A NOVEL SCHIZOPHRENIA MODEL ESTABLISHED BY SUBCUTANEOUSLY INJECTING A CYTOKINE TO A CYNOMOLGUS MONKEY NEONATE

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Inflammatory cytokines are implicated in the developmental hypothesis of schizophrenia, as human fetuses and neonates are exposed to high concentrations of these factors in response to infection, inflammation and brain injury. Our previous postmortem studies also support the biological importance of the cytokines (EGF, IL-1, and NRG) to its neuropathology. Based on these findings, we have established rodent models for schizophrenia by subcutaneously administering these cytokines to mouse and rat neonates. For example, the rodent model with EGF exhibits various behavioral abnormalities in acoustic startle response, prepulse inhibition, latent learning, social interaction, and sensitivity to psychostimulants, most of which can be ameliorated by subchronic treatment with atypical antipsychotics. In contrast, its gross learning ability and brain structures appeared to be normal. Because of the given behavioral differences between rodents and human, however, it is difficult to fully evaluate validity and implication of this model in schizophrenia pathology. To address this issue, we attempted to establish a primate model, subcutaneously administering EGF to a cynomolgus monkey neonate (2 week postnatal) in 2002. The monkey has grown without any apparent physical abnormality. After adolescence, however, the monkey exhibits various behavioral abnormalities, including bipedal hyper-locomotion, stereotypic movement, vocalization, cautious stance, and self-injury. The self-injury is always initiated with cautious stance and touching eyes with hands, potentially reflecting visual hallucination. Some of the behavioral deficits are attenuated by subchronic treatment with risperidone. The behavioral abnormalities of this primate model are more distinguished in comparison with those induced by amphetamine or phencyclidine. Although the replication of this study is required, the present observation suggests the possibility that endogenous EGF circulating in the periphery has significant impact on behavioral development of prenatal and perinatal primates including human. Note; The monkey experiments were performed in Shin Nippon Biomedical Laboratories, Ltd (Kagoshima, JAPAN) in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by the Japanese Physiological Society.
ID: 537649

BRIDGING THE GAP BETWEEN SCHIZOPHRENIA AND PSYCHOTIC MOOD DISORDERS: RELATING NEUROCOGNITIVE DEFICITS TO PSYCHOPATHOLOGY

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Background: The neurobiological relationship between schizophrenia and psychotic mood disorders (PMD) is not well understood. Neurocognitive deficits have been described in both types of disorders and have been proposed to reflect underlying neurobiological dysfunction. Examining the relationship between neurocognitive function and psychopathology could help illuminate the neurobiological relationship between schizophrenia and psychotic mood disorders. Methods: Participants included 72 individuals with DSM-IV schizophrenia, 25 individuals with a psychotic mood disorder, and 72 community controls. Standardized scores and correlations between four domains of neurocognition and psychopathology were examined. Results: Individuals with schizophrenia and psychotic mood disorders scored similarly on several dimensions of neurocognitive function and psychopathology. The relationships between neurocognitive function and psychopathology were similar in the two groups. Conclusions: Individuals with schizophrenia and psychotic mood disorders were similar in terms of both the level of impairment in neurocognitive function and psychopathology, as well as in the relationship between the two dimensions of illness. These results suggest that schizophrenia and psychotic mood disorders such as schizoaffective disorder and bipolar disorder with psychotic features are on a neurobiological continuum.

Table. Correlations between Neurocognition and Psychopathology Among SCZ and PMD

	SCZ (n = 72)	PMD (n = 25)	Fisher's z
Working Memory and Negative Symptoms	−0.262*	−0.383+	0.55
Working Memory and Disorganized Symptoms	−0.355**	−0.179	−0.68
Episodic Memory and Negative Symptoms	−0.275*	−0.489*	1.03
Episodic Memory and Disorganized Symptoms	−0.370**	−0.062	−1.33
Executive Function and Negative Symptoms	−0.305**	−0.238	−0.30
Executive Function and Disorganized Symptoms	−0.284*	−0.177	−0.46
IQ and Disorganized Symptoms	−0.231*	−0.091	−0.59

**$P < .01$, *$P < .05$, +$P < .06$ denote significance within group; Fisher's z signifies statistical difference between groups.
ID: 537431

METACOGNITION ACTIVATES A CONSISTENT NETWORK DURING DIFFERENT TASKS

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Metacognition (which can be said to involve monitoring the quality—eg, accuracy—of object-level knowledge and using this to guide behaviour) correlates with insight more strongly than any other neuropsychological test during first episodes of schizophrenia; and recent studies in samples with and without schizophrenia suggest that it is a critical determinant of real-world competence. This study investigated the neural activation produced by metacognitive processes during various cognitive tasks in those without illness, as a precursor to studying sufferers. We hypothesized that meta-level monitoring and control of different object-level cognitive tasks would activate the same specific network. 12 right-handed males without psychiatric illness performed three tasks during fMRI imaging in a 1.5T scanner, using a randomized, repeated block design. One task was a based on set shifting, another word recognition, the third judging line length. Each task had two forms: one with a heavy metacognitive load; and a control with minimal metacognitive load. For each task the response during blocks of control versions of tasks was contrasted with that for metacognitive blocks, using version as a cofactor in ANOVAs for each task. Activation of a consistent, almost entirely bilateral network of clusters was specifically demonstrated by each task contrast: BA8/9/32; middle frontal gyrus; inferior frontal gyrus/insula; inferior parietal lobule; and posterior cerebellum. Contrasting metacognitive and control conditions across all tasks gave a similar result. This form of the construct of metacognition appears meaningful, recruiting consistent processes in different tasks. Activation suggested, for instance, action monitoring, online assessment and calculation; and decision making. Comparison with schizophrenia sufferers is likely to be instructive and may illuminate insight's processes.
ID: 550826

HIGH NAILFOLD PLEXUS VISIBILITY IN SCHIZOPHRENIA IS ASSOCIATED WITH A DISTINCT NEUROPSYCHOLOGICAL PROFILE AND LESS VENTRICULOMEGALY

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High nailfold plexus visibility (High NPV) has been demonstrated to identify a subtype of schizophrenia characterized by more negative symptoms and lower occupational and social functioning. High NPV has been proposed as a schizophrenia endophenotype. We have been further characterizing the High NPV phenotype in preparation for family and genetic studies, using clinical, neuropsychological, and brain imaging measures. Despite the apparent negative functional consequences of this trait, the one previous brain imaging study of High NPV in schizophrenia unexpectedly found that patients with elevated NPV had less ventriculomegaly than their fellow patients. In this preliminary analysis of 30 patients along with their controls, we confirmed that High NPV schizophrenia patients have more negative symptoms on the SANS ($d = .41$). We have previously shown that this trait is independent of the Deficit Syndrome, and this finding is strengthened by controlling for deficit status ($d = 1.07$, $P < .03$). However, the High NPV patients also show higher educational achievement than their fellow patients ($t_{25} = 8.14$, $P < .01$) and score significantly better on several neuropsychological tests, including frontally mediated tasks such as the Delayed Response Test, Verbal Fluency, and the RBANS Visual Constructive Index. Furthermore, the High NPV patients exhibited less ventriculomegaly based on structural MRI ($t_{25} = 4.56$, $P = .04$). This replicates the earlier finding of Curtis et al. Given that most of our findings show better cognitive functioning and more normative brain structure in the High NPV patients, it is surprising that such patients have generally been found to have a poorer social and occupational outcome. Much of this may stem from their elevated level of negative symptomatology. We have also observed evidence of worse white matter tract disruption based on DTI brain imaging in earlier pilot work with High NPV patients. We will be analyzing DTI data in the next steps of the current study.
ID: 551907

BEHAVIORAL DIFFERENCES IN RECOMBINANT INBRED MOUSE STRAINS SELECTED FOR GENETICALLY-INFLUENCED VARIATION IN CORTEX AND THALAMUS VOLUME

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In previous studies, we have shown that patients with schizophrenia have correlated reductions of gray matter in the cerebral cortex and thalamus. In the present study, we tested the hypothesis that these associated neuroanatomical phenotypes may be impacted by shared genetic influences. Using BXD recombinant inbred (RI) mice, we found significant QTLs that related to cortex and thalamus volumes (Dong et al. 2007). To determine the behavioral consequences of this complex neuroanatomical phenotype, we selected 10 BXD strains known to exhibit either large (BXD strains 1, 5, 12, 15 and 22) or small (BXD strains 2, 6, 24a, 29 and 33) cortex and thalamic volumes and tested them on a number of behavioral paradigms related to cortical and thalamic functions as well as schizophrenia. Our results shown the significant differences between strains in terms of an anxiety measure, the elevated plus maze ($P < .05$); a sensory motor battery ($P < .05$); and a measure of higher-order attentional processes, attentional set shifting ($P < .05$). Those strains associated with a larger cortex and thalamus displayed significantly more time in the open arms of the plus maze, finer sensory motor skills, and greater ability to shift attention between relevant dimensions. These results support our hypothesis and previous findings that these behavioral paradigms are dependent on cortex and thalamus function. Moreover, to the behavioral variation observed in the strains with a smaller cortex and thalamus may be relevant to the dysfunctions characteristic to schizophrenia and other neuropsychiatric disorders. Further, we then applied immunohistological techniques using calcium-binding parvalbumin and calbindin in order to characterize strain differences in interneuron number in the mediodorsal thalamic nucleus and the cingulate cortex. While parvalbumin staining analysis did not show any significant differences ($P > 0.05$), the number of calbindin-positive neurons showed a trend favoring an increased number of such interneurons in the strains with larger cortex and thalamus volumes ($P = .054$). Together, these results illustrate the value of recombinant inbred strains of mice as model systems to investigate the genetic basis for neurobiological abnormalities that have been associated with schizophrenia.
ID: 551810

FEAR EXTINCTION STUDIES IN CALCYON TRANSGENIC MICE POINT TO EFFECTS ON PREFRONTAL CORTEX MATURATION AND FUNCTION

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Calcyon is a neuronal protein that regulates clathrin mediated endocytosis of AMPA receptors in brain presumably via interaction with clathrin light chain. The calcyon gene is present only in mammals, and postmortem studies suggest that both the protein and mRNA are significantly elevated in schizophrenics. However, whether calcyon up-regulation relates to etiology of schizophrenia or is merely a bi-product of the disease process is unknown. Thus, we created CalOE transgenic mice that express the human calcyon gene in forebrain in order to learn whether up-regulation of calcyon is sufficient to alter behavior. Initial studies revealed an impact on behavioral control as the CalOE mice are hyperactive and exhibit reduced anxiety or impaired restraint. Here, we examined whether up-regulation of calcyon impairs hippocampal synaptic plasticity and/or cognitive flexibility. We trained CalOE and control littermates to associate a spatial context with an aversive event. Then we tested how quickly they learn that the emotional valence of the context has changed by exposing them to the training context without footshock (extinction). Although both groups learned the initial association equally well, CalOE mice were impaired in extinction. Remarkably, the extinction deficits were reversed by shutting off high levels of calcyon during adolescence with a dose of doxycycline that silences calcyon transgene expression in the hippocampus, cortex and amygdala. These findings suggest that calcyon over-expression in the forebrain leads to cognitive deficits associated with switching the emotional valence of fear-associated stimuli. The data are also consistent with reduced cognitive flexibility potentially due to alterations in prefrontal cortex maturation. As such, they suggest that CalOE mice would be useful for modeling and manipulating this drug refractory aspect of schizophrenia.
ID: 551797

TRANSLATING THE BASIC SCIENCE OF LEARNING-INDUCED NEUROPLASTICITY INTO HUMAN INTERVENTIONS

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A large body of animal and human experiments have now richly documented the neurological basis of "adult (post-critical period) neuroplasticity". Other studies have documented the neurological bases of perceptual, cognitive and motor deficits that limit the performance abilities of a variety of psychiatrically- and neurologically-impaired child and adult patient populations. We have combined these lines of investigation by creating animal models that exhibit deficits that arise in developmental and acquired-adult disabilities or 'disease', then engaged animals in intensive forms of 'cognitive training' designed to ameliorate or reverse those neurological deficits. Combined with human studies, these experiments have now shown that most aspects of negative change paralleling the emergent expressions of psychiatric or neurological illness are reversible. We have used this science to develop specific training strategies targeting developmental (in language, reading and cognition) and acquired adult impairments and disease (schizophrenia, normal and pathological aging, TBI, acquired motor deficits). We shall briefly summarize the basic principles guiding this novel approach, and illustrate and contrast it with more conventional 'cognitive therapy' training strategies.
ID: 551782

EARLY VISUAL PROCESSING DEFICITS AS A PRECURSOR TO EMOTION RECOGNITION DEFICITS IN SCHIZOPHRENIA; AN EVENT-RELATED POTENTIAL STUDY

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The purpose of this study was to investigate contributions of early visual processing deficits to emotion recognition dysfunction in patients with schizophrenia (SCZ). SCZ show deficits in early visual processing, as evidenced by preferential magnocellular (M) system dysfunction. SCZ also show deficits in face emotion recognition, but have been shown to have intact experience of emotion, indicating that emotion recognition deficits are not a result of emotion processing problems per se. Thus, we examined the contribution of physical aspects of faces to emotion processing deficits in SCZ. Ekman and Friesen faces (fear, happy, sad, neutral) were presented (500 ms) at 3 contrasts (4%, 12%, and 96%). The lower contrast images bias processing towards the M pathway. Behavioral performance and event-related potentials (ERPs) (72 channel BioSemi system) were obtained in separate sessions. In the ERP study, attention to task was monitored by an implicit task: participants pressed a button to a target picture of a flower that was shown 20% of the time. In the behavior task, SCZ showed impaired emotion recognition at each contrast. Controls performed well (80% correct) at even the lowest contrast (4%), whereas SCZ only reached 55% correct at this contrast. ERPs showed decreased P1 amplitude at each contrast in SCZ compared to controls. In addition, SCZ needed 96% contrast to obtain or approach control levels at 4% contrast in both behavioral performance and P1 amplitude. In conclusion, the relatively intact behavioral performance by controls at 4% contrast indicates that they are able to recognize emotions using only M-biased information, whereas patients have difficulty using the M-pathway for emotion recognition. Decreased P1 amplitude suggests impaired early visual processing in response to face emotion stimuli in SCZ. These results support the hypothesis that impaired ability to use physical attributes of face emotion stimuli (ie, contrast) contributes to emotion processing deficits in SCZ and builds upon previous studies showing contrast sensitivity deficits to more basic stimuli in SCZ. Supported by NIMH RO1 MH66374, R37 MH49334 and K02 MH01439.
ID: 551781

A META-ANALYTIC REVIEW OF OLFACTORY FUNCTION IN SCHIZOPHRENIA

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The study of olfactory deficits in patients with schizophrenia has been a topic of increasing interest. A previous meta-analysis of this literature by our group revealed large effect sizes across various olfactory tasks that appeared to be relatively unaffected by potential moderator variables. These data suggested that olfactory dysfunction may be a central feature of this disorder and may reflect aberrant neurodevelopment in these sensory brain regions. As this literature has grown exponentially since our original 1999 study, the aim of the current meta-analysis was to expand the prior study through the inclusion of a greater number of studies, examination of different olfactory test types, and expanding the potential moderator

variable analyses. A thorough review of the literature concerning olfactory function in schizophrenia was conducted and relevant studies were extracted using a Quality of Reporting of Meta-analysis standard. Review and application of exclusionary criteria yielded 111 studies out of 56 publications available for meta-analysis. All analyses were subsequently conducted using the Comprehensive Meta-Analysis—2.0 software package. Using a random effects model, results revealed that the overall effect size (d) for olfactory processing tasks across all studies was -0.81 [95% CI = -0.69 < δ<-0.93], which fell in the range of a ''large'' effect using Cohen's 1988 criteria. Homogeneity analysis revealed significant heterogeneity among study effect sizes that supported the examination of possible moderator variables (QB[110]=539.98, $P < .001$). In order to understand the variability among effect sizes, psychophysical, clinical and demographic variables that might explain this heterogeneity were examined. These analyses revealed significant contributions to the magnitude of the olfactory deficit by psychophysical task type (ie, odor identification v. threshold, v. memory, v. hedonics), presentation type (ie, birhinal v. unirhinal), age of onset, duration of illness, medication type, and sex. Overall, the findings from the current meta-analytic review suggest a large magnitude deficit in olfactory function that appears to vary by the domain of olfactory function assessed. In addition, various moderator variables appear to have a significant positive or negative impact on these deficits and warrant consideration in future prospective studies. Funded in part by NIMH grants MH-63381 (Dr. Moberg), MH-59852 (Dr. Turetsky), and an Independent Investigator Award from the NARSAD/Hofmann Trust (Dr. Moberg). ID: 551773

LEARNING-RELATED PATTERNS OF HIPPOCAMPAL FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA

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We explored the brain-behaviour relationship of practice-related learning in schizophrenia in an fMRI experiment using an associative language paradigm developed by Breitenstein and Knecht (J Neuro Methods, 2002). The paradigm measures the acquisition of a novel lexicon by pairing pseudo-words with object drawings. Six subjects with a diagnosis of schizophrenia, stabilized on atypical antipsychotics, were matched with eight healthy control subjects. All participants were tested in two sessions: the first to acclimate to the fMRI scanning environment and practice the task, and the second to learn the novel language in the scanner. Both groups showed equal rates of learning. Imaging data were acquired in 5 successive runs. The data were analyzed using multivariate partial least squares (PLS) analysis to capture the full spatiotemporal pattern as subjects learned. Both groups showed linear decreases in dorsal medial prefrontal and occipitoparietal cortices. Increases were noted in retrosplenial, anterior temporal cortices, and medial fusiform gyrus. Hippocampal engagement occurred early in the session for controls, but much later in patients despite roughly equivalent behavioural performance. Given the theoretical interest in the hippocampus, we examined its functional connectivity across sessions for each group. Consistent with the activation differences, the functional connections in controls were most stable in early in learning with strong interactions of the hippocampus with left inferior frontal, anterior temporal and medial occipitoparietal cortices. Hippocampal functional connectivity in patients was unstable early in learning, gradually becoming more robust by the end of the scanning session. The pattern of connectivity included similar areas as in the controls, with the notable exception of left anterior temporal cortex. Moreover, the region with the strongest hippocampal functional connection was the left anterior prefrontal cortex. These results

are consistent with general observations of distinct patterns of functional connectivity in schizophrenia, but also highlight that these neuroatypical connections can support learning profiles similar to those observed in controls. ID: 551710

IMPAIRMENT IN LONG-TERM RETENTION OF PREFERENCE CONDITIONING IN SCHIZOPHRENIA

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Background: Schizophrenia illness is characterized by significant impairments in long-term episodic memory, which are associated with hippocampal abnormalities. The current study assessed long-term memory for preference conditioning, which is believed to be more strongly based in the basolateral amygdala, in order to determine whether abnormalities in biological systems supporting long-term memory are specific to the hippocampus, or shared across brain regions involved in different types of memory. Methods: 17 schizophrenia (SC) and 16 healthy (HC) subjects, matched on age, sex, and years of education participated in the study. All subjects completed an implicit preference conditioning task which associated different patterns with different frequencies of reward. Subjects were then tested for their preference for the patterns both immediately after training, and following a 24 hour delay. Results. Both SC and HC subjects demonstrated a preference for the more frequently rewarded pattern immediately after training. Following a 24 hour delay, HC subjects continued to prefer the more rewarded pattern in contrast to the less rewarded pattern, but SC subjects did not maintain this differentiation. Conclusions: These data suggest a significant deficit in the ability to maintain stimulus-reward relationships in memory over long delay periods (24 hours) in individuals with schizophrenia. This data is consistent with prior research indicating normal response to emotional stimuli during learning, but impaired long-term memory for the stimuli, and suggest that there may be a common abnormality in biological systems supporting consolidation of long-term memory across multiple types of memory in individuals with schizophrenia. ID: 551698

DISTINGUISHING EFFECTS OF SCHIZOPHRENIA AND IQ DECLINE FROM BEHAVIOURAL PERFORMANCE DURING EXECUTIVE FUNCTIONING

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Neuropsychological studies have consistently identified deficits in attentional set-shifting on tasks such as the Wisconsin Card Sorting Test (WCST), suggesting impaired ability to inhibit previously learned responses and shift attention to relevant stimulus. However, it is not understood if this is due to deficits in motivation, attention, memory or executive function. Findings are often also confounded by differences in intelligence score (IQ) between schizophrenia and control subjects. We investigated set-shifting behaviour in high functioning schizophrenia patients and two groups of healthy volunteers matched on pre-morbid IQ (assessed by WTAR) and current IQ (assessed by WASI) respectively. The 12 schizophrenia patients were matched to the current IQ controls ($n = 12$) on age, education, gender and current IQ and to the pre-morbid IQ group ($n = 12$) on education, gender and pre-morbid IQ. All participants performed a computerised WCST modified to permit separation of response selection and feedback evaluation. In general, the current IQ-matched

controls responded significantly more slowly and more poorly (achieved fewer shifts overall and made more errors per shift; $P < .001$) compared to the pre-morbid IQ group. Schizophrenia patients did not differ significantly in their reaction times, number of shifts or number of errors per shift to either control group (their means on the various tasks generally fell between the two groups). However, we did find a difference for the response selection trial associated with initial positive feedback ("update"). Here schizophrenia patients performed significantly more slowly than pre-morbid IQ controls ($P < .05$) but showed a similar mean to the current IQ controls. This apparent difficulty did not carry over to the subsequent ("maintenance") trials associated with continuing positive feedback. The results suggest that despite a decline in intellectual function, in general schizophrenia patients do not appear to be as disadvantaged on executive function performance measures as healthy controls with the same current IQ. One aspect of cognitive set shifting behavior that does appear disproportionately troublesome for patients with schizophrenia is the process of updating to the new cognitive set. We recommend that where possible, attempts should be made to match for both current as well pre-morbid intellectual functioning in order to interpret patients' performance more fully.
ID: 551648

DECISION MAKING IN FIRST EPISODE SCHIZOPHRENIA AND DRUG-USE DISORDERS: ARE DEFICITS DUE TO A PREFERENCE FOR SHORT-SIGHTED DECISIONS OR FAILURE TO EFFECTIVELY LEARN THE TASK?

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Background: Evaluations of emotion-based decision making in early schizophrenia using the Iowa Gambling Task (IGT) have yielded inconsistent results. This study aims to investigate whether this may be due to the confounding effect of co-morbid drug use which has been shown to be associated with poor IGT performance. Methods: The IGT was administered to 53 first-episode schizophrenia-spectrum psychosis patients and 21 controls; 31 patients and 5 controls met criteria for a lifetime SCID substance use diagnosis. Performance on the IGT was measured as the number of choices from the two advantageous decks minus the number of choices from the two disadvantageous decks. Results: Using a two-way ANOVA we found no significant effect of patient or drug use status on IGT performance and no interaction between the two although there was a trend towards poorer performance amongst patients ($P = .18$) and those with a history of drug use ($P = .18$). To investigate this further we considered whether poor performance in these groups was due to a preference for making short-sighted decisions or a failure to learn the task and hence make more random decisions. We postulate that selecting cards back and forth at a high rate between decks to be indicative of random card selection. There was a strong inverse correlation between performance on the task and the number of such deck switches ($r = -.51$, $P < .001$). This was more pronounced over time as subjects who learned the task persisted in selecting from advantageous decks. A two-way ANOVA showed subjects with substance-use diagnosis had a greater tendency to switch decks ($F_{1,73} = 3.9$, $P = .053$) while there was no significant main effect of patient status on deck switching. IGT performance was re-examined in a two-way ANOVA controlling for deck switching with the intent to isolate the effect of deliberate short-sighted decision making. This showed patients had poorer performance than controls ($F_{1,73} = 4.8$, $P = .032$) while there was no main effect of drug use diagnosis. Conclusion: Although overall performance on the IGT was not significantly affected by patient or drug use status, our results suggest that subjects with a drug-use diagnosis may be less likely to effectively learn the task while first episode schizophrenia patients may have a greater preference for making short-sighted decisions.
ID: 551641

SOCIAL COGNITION TRAINING PRODUCES CHANGES IN NEURAL MECHANISMS SUPPORTING EMOTION RECOGNITION

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Schizophrenia patients have well-documented impairments in facial affect recognition and these impairments contribute to problems in social and occupational functioning. Ability to identify emotions in others depends on an appropriate level of activity in the amygdala. Recent neuroimaging research has shown that emotion recognition deficits in schizophrenia patients may be due to dysfunctional amygdala activity when processing emotional information from faces. Here, we investigated whether neuroplasticity-based targeted cognitive training (TCT) which incorporated intensive training on facial affect recognition would improve behavioral performance and restore proper amygdala function during a facial affect recognition task. 21 schizophrenia patients and 18 healthy control subjects were scanned in high field (4Tesla) fMRI while completing a facial affect recognition task in which subjects were shown positive (happy, flirty, dreamy, and happy-surprised), and negative (sad, angry, fear, disgust) facial expressions and were asked to identify the facial expression in a forced-choice paradigm. In the control condition, using a similar forced-choice paradigm, subjects were asked to identify the color of objects. After the baseline scan, schizophrenia patients were randomly assigned to 40 hours of TCT ($N = 12$) or 40 hours of an active control condition ($N = 9$) which consisted of playing computer games (CG). We found that, before training, TCT subjects did not show amygdala activity to either positive or negative facial expressions as compared to objects, nor was amygdala activity correlated with emotion recognition performance. However, after training, TCT subjects showed significant behavioral improvement in emotion recognition performance. In addition, among the TCT group, there was a significant positive correlation between emotion recognition performance and individual amygdala activity when identifying emotions versus objects. The CG group, on the other hand, did not show behavioral improvement and amygdala activity was not related to performance. These data suggest that intensive TCT which includes facial affect recognition training may engage the amygdala in the process of facial affect recognition, and thus restore the appropriate neural circuitry to facilitate emotion recognition performance.
ID: 551639

LOGITUDINAL CHANGES OF N-ACETYL-ASPARTATE AND COGNITIVE FUNCTION IN EARLY ONSET PSYCHOSIS

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Background: Early-onset psychosis (EOP) is a rare and severe condition which has been associated with a number of developmental disturbances. Low concentrations of N-Acetyl-Aspartate (NAA) are interpreted as a biological marker of changes in neural integrity. Studies using Proton Magnetic Resonance Spectroscopy (H-MRS) have shown reduced NAA levels in the Dorsolateral Prefrontal Cortex (DLPC) in both chronic and first-episode psychotic patients. This reduction of frontal NAA levels has been related to the presence of cognitive deficits in adult onset schizophrenia and has also been described as a good outcome predictor for psychosis. Methods: A sample of 54 first-episode psychotic patients (mean age 17.74) and a matched control sample were longitudinally assessed using a comprehensive neuropsychological battery. This battery included those measures

considered to be related to DLPC functioning (attention, working memory and executive function). The single voxel proton spectra were obtained in a 1.5 T Philips Gyroscan ACS from the DLPC area with and without water suppression at baseline and 2 years follow up. Results: There were significant differences in NAA levels between patients and controls at two years follow-up ($t = -1.15$; $P = .250$) but not at baseline ($t = 2.55$; $P = .013$). Longitudinal changes in NAA levels were significant in the group of controls ($F = 1.79$; $P = .189$) but were not in the group of patients ($F = 1.79$; $P = .189$). Patients had significantly less NAA levels at follow-up. Cognitive function in patients improved over time ($F = 22.59\ 0 = 0.000$) but NAA levels did not explain changes in cognition. Conclusions: The pattern of NAA/water concentrations described for the group of patients at the early course of the illness remained stable during the first two years. Controls presented a specific increase in the left DLPFC NAA/water ratio at two years follow-up. This result replicates previous findings in our group which are congruent with the neurodevelopmental hypothesis of early onset psychosis. Our results indicate that changes in cognitive DLPC function are not related to NAA levels.
ID: 551571

SCHIZOPHRENIA PATIENTS SHOW DEFICITS IN INTRA-STIMULUS SHIFTS OF ATTENTION TO DIFFERENT LEVELS OF GLOBAL-LOCAL STIMULI

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Abnormalities of attention suggesting left hemisphere dysfunction have been well documented in schizophrenia. Schizophrenia patients show a local processing deficit on the global-local task, which has been interpreted as evidence of a left lateralized attention deficit. The global-local task is a measure of attention and perceptual organization that utilizes visual stimuli comprised of large letters (global level) made up of smaller letters (local level). Subjects identify target letters appearing at either the global or local level of the stimulus. In this study, we used a version of the global-local task specifically designed to examine lateralized hemispheric processing and attention shifting in schizophrenia patients and normal controls. Global-local stimuli were presented in couplets (consecutive pairs). Reaction time for the second target in a couplet was compared under conditions in which the target remained at the same level (global-global, local-local) and when the target changed levels (global-local, local-global). Schizophrenia patients were significantly slower shifting attention from the global to the local level, confirming previous findings of a left-lateralized local processing deficit in schizophrenia patients and suggesting that schizophrenia patients have deficits disengaging attention from global to local levels of hierarchically organized stimuli.
ID: 551567

SERUM BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) IN PATIENTS AT ULTRA-HIGH-RISK FOR PSYCHOSIS

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Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the central nervous system and plays a critical role in brain development, function, neuronal survival, and neuroplasticity. In vivo serum BDNF levels in schizophrenia patients are generally reduced compared to healthy subjects, and may be reduced even prior to the onset of psychosis, thereby marking risk for schizophrenia. In this ongoing study, we assess serum BDNF in a sample of patients diagnosed as being at ultra-high-risk for psychosis ($N = 8$; mean age = 18.5), compared to an age-matched sample of first-episode schizophrenia subjects ($N = 10$), healthy controls ($N = 16$), and a group of chronic schizophrenia patients ($N = 54$). Clinical assessments, MATRICS-based neurocognitive assessments and blood draws were conducted at study entry for all subjects. All three patient groups demonstrated lower levels of serum BDNF compared to the healthy controls ($F_{3,78} = 4.20$, $P = .008$). Within the total group of patients, lower BDNF was associated with increased symptom severity and lower functional status, as measured by the Global Assessment of Functioning (GAF) scale ($P = .006$). Within the UHR group, lower BDNF levels were significantly correlated with more severe negative symptoms ($P < .05$), worse disorganized symptoms ($P < .05$) and poorer social functioning ($P < .01$). These preliminary results suggest that reduced BDNF may precede the onset of schizophrenia and may be related to some of the first clinical signs of prodromal psychosis- negative symptoms and poor functioning. Future analyses will assess whether reduced serum BDNF predicts conversion to full psychosis in the UHR group.
ID: 551564

REWARD ASSOCIATIONS ARE INFLUENCED BY MODULATION OF HABENULAR OUTPUT

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Dopamine neuronal activity increases in response to novel rewards or to stimuli that predict their occurrence while transient decreases in activity accompany the absence of an expected reward. Recent developments in the field of reward processing indicate that the habenula is a source of inhibitory input. The habenula communicates with the both the ventral tegmental area and substantial nigra compacta through its sole output pathway, the fasciculus retroflexus (FR). In order to better understand how reward learning is regulated, we electrolytically lesioned the FR, eliminating communication between these brain regions. We also stimulated this same region to create a false habenular signal. The effect of disrupting habenula output on reward association learning was assessed using an autoshaping paradigm. Sucrose rewards were delivered on a variable interval schedule; presentation of a CS+ cue was predictive of reward delivery while the CS− cue was not. The acquisition of stimulus-reward associations was quantified by the comparing the number of approaches to the positive (CS+) and negative (CS−) cues. Once the paradigm had been firmly established, the two cues were reversed, so that the cue that once signaled reward no longer predicted reward and vise versa. FR lesions created prior to acquisition of the task significantly increased the number of approaches to the CS+ during the acquisition. It also slowed extinction of responding to the new CS− when the cues were reversed. The lesion did not affect the amount of pellet dispenser exploration or reward consumption during any portion of the trial. Another group of animals was lesioned between acquisition and reversal to specifically investigate the effects of lesion on reversal. FR lesion after acquisition of the task did not potentiate approach behavior to the new CS+ cue, in contrast, it diminished approach behavior. The affective valence of stimulation of the FR is assessed using conditioned place preference (CPP). Stimulating during CPP did not appear to cause aversion in the subjects. In summary, a FR lesion prior to but not after exposure to the autoshaping paradigm significantly potentiates approach behavior to a newly acquired reward association and delays the reversal of responding to the new rewarded cue. These data are consistent with the notion that the

habenula provides a modulatory input to ventral midbrain dopamine neurons and participates in the reinforcement learning.
ID: 551559

DOES NEUROCOGNITION PREDICT SOCIAL AND OCCUPATIONAL FUNCTIONING IN FIRST-EPISODE PSYCHOSIS?

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Much research has examined neurocognition and functional outcome in chronic schizophrenia. Findings show that neurocognition predicts functioning but this association is weaker upon accounting for symptoms. Few studies have examined the influence of neurocognition on outcome in first-episode psychosis. Our aim was to investigate whether neurocognition predicts social and occupational functioning at entry and one year after specialized early intervention in a schizophrenia-spectrum FEP sample. Method: Neuropsychological assessments were done at baseline and scores were converted into z-scores based on 51 healthy controls. Scores for six domains (Verbal Memory, Processing Speed, Working Memory, Verbal Fluency, Attention, and Reasoning) were computed as the mean of z-scores for tasks comprising these domains. A global neurocognitive score was computed by averaging scores for the six domains. Functioning was assessed with the Social and Occupational Functioning Assessment Scale (SOFAS) at baseline ($N = 151$) and one year ($N = 66$). Symptoms were assessed using the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS). Results: Patients ($N = 151$; mean age 22.8; 71.5 % male) were significantly more impaired on all cognitive domains compared to healthy controls (F's = 4.19–38.69; $P < .05$). At baseline, all six domains (r's = 0.21–0.33; $P < .05$) and the global neurocognitive score were significantly correlated with SOFAS total ($r = 0.33$; $P < .01$). Regression analyses were conducted to examine the contribution of cognition (the global score was used to avoid colinearity) and symptoms to SOFAS. Cognition accounted for 9% of the variance in functioning at baseline. When SAPS and SANS were also included, only SANS was significant and accounted for 15% of variance. The global and individual domains were not significantly correlated with SOFAS at one year. Discussion: At baseline, cognition explained 9% of the variance in social and occupational functioning but this effect disappeared upon accounting for negative symptoms. Further, cognition was not associated with functioning at one year. While our findings are somewhat contrary to the literature, the effect of cognition on functional outcome in these studies is modest, explaining only 3–6% of variance after controlling for symptoms. Factors such as social support, negative symptoms, and intensive case management may buffer the effects of cognitive deficits on functioning, particularly early in the illness course.
ID: 551555

RELATIONSHIPS BETWEEN TEST AND FACTOR SCORES, AND PSYCHOMETRIC PROPERTIES: THE MATRICS CONSENSUS COGNITIVE BATTERY (MCCB) AND THE INTEGNEURO COMPUTERIZED BATTERY IN SCHIZOPHRENIA

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Cognitive impairment is prevalent in schizophrenia, and is related to poorer functional and treatment outcomes. Cognitive assessment is therefore now a routine aspect of clinical trials of new medications for schizophrenia. The current gold-standard for cognitive assessment in clinical trials for schizophrenia is the MATRICS Consensus Cognitive Battery (MCCB), which was developed based on expert consensus, and incorporates paper-and-pencil tests (and one computerized measure) with an established history in the field of neuropsychology. Recently, however, interest has increased in using computerized batteries for clinical trials, due to their ease of administration and smaller error variance that is associated with standardized pre-recorded instruction sets, and automated scoring procedures. In this study, we tested 155 people with schizophrenia and 75 healthy control subjects on both the MCCB and IntegNeuro (a touch-screen based computerized battery with previously demonstrated high levels of reliability and validity) to determine comparability between test scores. In addition, we assessed test-retest reliability over a one-month interval for both batteries, and determined correlations between cognitive test scores and scores on functional outcome measures. Results indicate comparability across the two batteries, with the strongest levels of agreement observed between total battery composite scores ($r > .80$) and in canonical correlation analyses that included all critical single test scores from each battery (rc>.90). Correlations between single test scores, and between cognitive domain composite scores were lower than for full-battery comparisons, but were within the range observed in prior validation studies of other widely used cognitive test batteries for schizophrenia. The batteries demonstrated essentially equivalent sensitivity in discriminating between patients and controls, and adequate test-retest reliability. Correlations between cognitive test scores and functional outcome measures were equivalent between the two batteries, and low in nearly all cases, suggesting that cognitive indices are not proxy measures of real-world functioning. Principal components analyses of the batteries will be reported, as will comparability of these results across batteries. Advantages and disadvantages of computerized vs. paper-and-pencil neurocognitive tests for schizophrenia, as revealed by these batteries will also be discussed.
ID: 551552

THE ROLE OF VISUAL PERCEPTION DEFICITS IN WORKING MEMORY IMPAIRMENT IN SCHIZOPHRENIA

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Deficits in the visual working memory system have been consistently reported in schizophrenia patients. Here we assess the role of visual perception in subjects' performance on object working memory. 37 patients with schizophrenia and 24 nonpsychiatric control subjects were tested on a visual

object recognition working memory task across three delay periods: 200 msec, 3 sec, and 10 sec. Both schizophrenia and control subjects showed a significant decline in performance on the 3 and 10 sec delay intervals compared with the 200 msec delay interval. Performance on the 3 sec delay period did not differ significantly from that in the 10 sec condition in either group. Schizophrenia patients performed significantly less accurately than controls in all three delay intervals. After co-varying the effect of perception (200 msec delay) on performance in the two longer delay periods (3 sec and 10 sec), schizophrenia and control subjects no longer showed a significant difference in accuracy on the 3 sec delay, but the groups remained significantly different for the 10 sec delay interval. After removing the effect of accuracy during the perceptual task, controls did not differ on the 3 sec and 10 sec delays, but SZ patients showed a weak trend to perform worse on the 10 sec delay than on the 3 sec delay. Once the perception component was removed, schizophrenia patients demonstrated intact working memory (3 sec delay). In contrast, although the 10 sec delay period imposes a higher memory load on both groups, it impacted performance only in the patients. These results suggest that an impairment in perception seems to be a major contributor to what appears to be a deficit in the visual object working memory system in schizophrenia patients.
ID: 551545

PHARMACOLOGICAL TREATMENTS OF COGNITION: ONE DRUG FOR ALL DOMAINS?

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The NIMH-funded MATRICS Program (Measurement and Treatment Research to Improve Cognition in Schizophrenia) developed a broad consensus regarding the nature of the cognitive impairments in schizophrenia and how they might best be assessed and treated. MATRICS identified seven domains of cognition of specific relevance for schizophrenia and developed a battery of tests that combines individual assessments of specific domains with a global score of performance across all domains. The subsequent discussions of the CNTRICS (Cognitive Neuroscience measures of Treatment Response of Impaired Cognition in Schizophrenia) program focused on neuroscience- and brain-based translational approaches to the understanding of cognition, with a focus on specific constructs within the field of cognition that are impacted in schizophrenia. The fields of neuroscience and physiological psychology provide extensive evidence that specific cognitive functions are subserved by specific neural circuits. Indeed, much of the neuropsychological literature addressing tests for various cognitive constructs utilizes circuit-based differentiations as tests of the validity of the tests as measuring the specific construct of interest. Similarly, extensive evidence from animal research indicates that different cognitive functions are impacted differentially by pharmacological manipulations. This presentation will provide examples of pharmacologically specific effects of drug treatments on some domains of cognition as distinct from other domains. The possibility that specific treatments for specific cognitive deficits can be predicted from animal model studies will be discussed. The further possibility that cross-species paradigms can be developed to assess domain-specific effects of pharmacological treatments will also be addressed.
ID: 551532

ABNORMAL OSCILLATORY ACTIVITY IN SCHIZOPHRENIA PATIENTS DURING AN AUDITORY STREAMING TASK

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Patients with Schizophrenia have well documented deficits in basic audio-sensory processing. Such dysfunction could contribute to how sequential sounds are integrated in to a coherent percept. In everyday life one is bombarded with a cacophony of sounds from multiple sources, and it is the job of our auditory apparatus to segment these sounds based on the spectral similarity and temporal coincidence. This ability to isolate and perceive auditory streams can be investigated in "auditory streaming" experiments: In our streaming experiment subjects were presented with tones organized in triplets (ABA_ABA…), with individual tones separated by 50 msec and triplets separated by 100 msec. Tone A was always 1000Hz. There were two conditions, depending upon the pitch of tone B. In the first condition, tone B was either 950Hz or 1100Hz and the sequence was perceived as a single stream of galloping triplets. In the second condition, tone B was either 500Hz or 2000Hz. In this latter condition subjects typically perceived that low and high tones separated into two alternate streams much like counterpoint in music (Sussman, et al., 1999). We examined total and evoked gamma oscillations to these two conditions to 24 controls and 22 schizophrenia patients. We found that patients with schizophrenia had significantly higher total gamma power than healthy subjects across both conditions. Control subjects exhibited increased total gamma power during the 'single stream' condition vs. the 'dual stream' condition, but patients failed to show this modulation with condition. Furthermore, while controls displayed a sequential decrease in gamma power to each tone of the ABA triplet during 'single stream' stimulation, patients displayed the opposite pattern of increasing evoked gamma activity following each subsequent stimulus. These findings together suggest increased gamma activity in patients disrupts the stimulus-evoked modulation of gamma responses that is necessary for integrated auditory perception.
ID: 551516

NEUROCOGNITIVE DEFICITS ARE ASSOCIATED WITH PSYCHOTIC-LIKE EXPERIENCES AFTER CANNABIS.

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Background: The relationship between cannabis and psychotic disorders is still under debate. It is clear however that in some individuals even recreational use of cannabis can lead to a transient period where some symptoms of psychosis are experienced. There is extensive anecdotal evidence for individual differences in the experiences which people have after smoking cannabis. Previous work has shown that schizotypy may mediate the experiences which people have when smoking cannabis (Barkus et al., 2006; Barkus and Lewis, 2008). Specifically, those who score higher on schizotypy are more likely to experience psychotic-like immediate effects and report more after effects from cannabis use. Given that altered cognitive performance has been associated with both schizotypal trait and cannabis use, it is possible that cognition may have a role in mediating the experiences which people have when they use cannabis. We hypothesised that individuals who reported psychotic-like experiences after cannabis use would have impaired cognitive performance across multiple domains of cognition. Method: We tested fifty participants (mean age 23 years) who had been selected on the basis of their scores on the psychotic-dysphoric subscale on the Cannabis Experiences Questionnaire (Barkus et al., 2006). They were tested on measures of working memory, spatial working memory, executive functioning and learning. Groups were well matched on other recreational drug use and patterns of cannabis use. Results: Those who reported psychotic-like experiences after cannabis reported higher scores on neuroticism and emotional reactivity ($t = 2.479$, $P < 0.05$ and $t = 2.739$, $P < .05$ respectively), these effects were independent of gender. Those who had psychotic-like experiences had more between search errors on the spatial working memory task and longer latencies on a working memory task; while there were no differences on attention and Trails A and B. Conclusion: In the absence of differences in patterns of cannabis use, individuals who have psychotic-like

experiences after cannabis do demonstrate some cognitive deficits, particular in working memory. These cognitive deficits occur in the absence of differences in patterns of cannabis use.
ID: 551498

THE TEMPORAL STABILITY OF THE BEADS TASK

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Background: Cognitive accounts of delusions implicate reasoning biases in the formation and maintenance of delusions. People with delusions display a jumping to conclusions bias (JTC): a tendency to reach a decision on little evidence and high confidence. The bias is found in the actively deluded, delusion prone and first degree relatives of schizophrenia patients. It has been associated with formation as well as the maintenance of delusional beliefs. The beads task is a commonly used measure of the JTC bias. In its simplest form, two jars of beads are presented in opposing ratios of two colours eg, 85:15 red to blue beads in one jar and the reverse in the other jar. Participant's are then shown a sequence of beads and are asked when they have seen enough beads to decide which jar the beads are being drawn from. The aim of this study was to assess the temporal stability of the beads task administered on two separate occasions without intervention. Method: The beads task was administered on two separate occasions to 30 healthy (13 male, 17 female and mean age 23.90 years) volunteers in a paired study design. There were a number of different ratios and number of jars used in the trials. Results: There was no difference found between the number of beads to reach a decision for the two administrations of the task indicating that the beads task has a good temporal stability (t -1.987, $df = 29$, $P = .06$). There was no significant correlation between performance over time and personality characteristics such as schizotypy and delusional proneness. Conclusions: This finding demonstrates the strength of the beads task in producing similar scores in the same individuals over time. There were no associations between change in performance over time and psychosis-like traits suggesting test retest regardless of trait psychosis proneness.
ID: 551475

MEG, fMRI, AND SERUM BIOMARKER FINDINGS ASSOCIATED WITH PLASTICITY-BASED COGNITIVE TRAINING

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Although a great deal of recent work has focused on cognitive enhancing medications in schizophrenia, and on their underlying neurobiological mechanisms, very little work has focused on the underlying neurobiology of behavioral cognitive treatments. This is somewhat surprising, given that behavioral treatments such as cognitive remediation have demonstrated efficacy, and could potentially be a critical component of the therapeutic armementarium in schizophrenia. We report longitudinal MEG, fMRI, and serum biomarker data obtained in clinically stable adult outpatients with schizophrenia who were randomly assigned to participate either in 50 hours of "neuroplasticity-based" computerized cognitive training or 50 hours of a computer games control condition. In this innovative form of behavioral cognitive enhancing treatment, participants engage in a heavy schedule of computerized training that places implicit, increasing demands on auditory perception and accurate aural speech reception. This psychophysical training is embedded within a suite of increasingly complex auditory and verbal working memory/verbal learning exercises. A fundamental goal of this treatment is to increase the accuracy, the temporally-detailed resolution, and the power of aural speech inputs feeding working and long-term memory processes. We present the following evidence of neurobiological effects as a function of training, obtained in the active condition but not the control subjects: 1) MEG data indicating improved efficiency in early auditory processing; 2) fMRI data showing "normalization" of brain activation patterns during a verbal memory task; 3) significant increases in serum BDNF and d-serine levels. Taken together, these data indicate that 50 hours of "neuroplasticity-based" cognitive training drives neurobiological changes consistent with restoration and enhancement of key neurocognitive processes.
ID: 551473

THE EFFECT OF CHANGING THE VIEWPOINT AND THE COLOR OF OBJECTS ON FALSE RECOGNITION IN FIRST EPISODE OF NON-AFFECTIVE PSYCHOSIS PATIENTS

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People with schizophrenia consistently show recognition memory impairment but we currently know little about potential faulty processes that contribute to this problem. Recognition memory accuracy relies on how well someone remembers encoded items but also on how well he classifies never presented items as new. Sometimes, new items act as lures because they share similarities with encoded items. When someone is unable to differentiate the lures from the encoded item, he tends to classify the lure as an old item and commits a false recognition. People with schizophrenia have been shown to exhibit heightened sensitivity to false recognition as compared to healthy people. Lures were however essentially induced at a conceptual (ie, semantic) level. In our on-going project, we tested false recognition induced at a perceptual level in conditions simulating real-life situations potentially causing such false recognition. This idea was motivated by the fact that people with schizophrenia are known to exhibit several visual impairments and that might exacerbate their proneness to false recognition. To date, participants include 10 first episode of non-affective psychosis (FEP) patients and 11 healthy controls. There were two blocks of a classic yes/no memory recognition task. Overall, 240 photos of common objects were presented sequentially during the encoding phase. In the recognition phase, 120 of the encoded objects were presented randomly with 120 lures. The lures were objects never presented before. They were exemplars of the encoded objects with which they share up to two dimensions: 1) 30 were of identical position and color, 2) 30 were of identical position, 3) 30 were of identical color, and 4) 30 were in different position and color. Preliminary behavioural results indicate that FEP participants were more prone to false recognition than healthy controls only for the less similar lure. In conditions of strong lures induced by a similarity of object's position and/or color, the two groups performed similarly. The false recognition proneness of FEP participants thus emerged only when evidence against false recognition cumulated, likely because they were unable to take advantage of this combination of evidence as healthy controls did.
ID: 551472

RELATIONSHIP OF CONTEXT MAINTENANCE TO POSITIVE SYMPTOMS AND CREATIVITY

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Making unusual associations relative to current context is associated with both "creativity" and positive symptoms in schizophrenia spectrum disorders, but creativity and these disorders are not necessarily related to each other. The following studies investigate this divergence. It was hypothesized that a combination of reduced context maintenance (right frontal activation of remote associates) with reduced evaluation (frontal executive function) leads to positive symptoms, whereas reduced context maintenance coupled with intact context evaluation manifests as creativity. Study 1: Healthy individuals completed neuropsychological, creativity, and schizotypy measures, and a recognition memory paradigm that indexes context maintenance. Two groups were created according to lure accuracy on the memory paradigm. Those with high accuracy had higher scores on frontal lobe measures and lower scores on Magical Ideation and Unusual Perceptual Experiences, indicating stronger executive function and less psychopathology. Groups did not differ on the Remote Associates Test (RAT), an index of "creativity". However, the RAT was negatively correlated with Odd Beliefs within the high accuracy group indicating that "creativity" was associated with low psychopathology in individuals who could differentiate between presented words and lures. In contrast, the RAT was positively correlated with Odd Beliefs within the low lure-accuracy group, indicating that creativity is positively associated with psychopathology in individuals who do not evaluate or monitor associations well. As predicted, individuals with weaker executive function and recognition memory accuracy showed a relationship between "creativity" and positive symptoms. Study 2: Lure accuracy does not differ between patients with schizophrenia and controls. Perhaps this finding differs according to frontal measures and positive symptoms as in the low-accuracy group in Study 1. Preliminary analyses indicate that lure accuracy is negatively correlated with Magical Ideation, and neuropsychological measures of right hemisphere function in patients with schizophrenia. As data collection continues, we will investigate the associated symptoms and neural mechanisms (using ERP and fMRI) of context maintenance and evaluation and determine how they are related to the manifestation of either creativity or positive symptoms.
ID: 551457

SELF-REFLECTIVENESS IS ASSOCIATED WITH DELUSIONS IN FIRST-EPISODE PSYCHOSIS

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In cognitive insight studies, an association between delusions and a tendency to show increased confidence in one's beliefs and judgments ("Self-Certainty") has been reported in chronic psychotic patients and for healthy people who report delusion proneness. Individuals who are delusion prone also show more willingness to acknowledge fallibility and incorrigibleness ("Self-Reflectiveness") than those who show low delusion proneness. Chronic psychotic patients without delusions report lower Self-Reflectiveness than deluded patients. A direct assessment of the cognitive insight/delusions link early in the disease process after a first episode of psychosis (FEP) has not yet been done. In our study, sixty-two individuals with a FEP (48 non-delusional, 14 delusional at the time of evaluation) were administered a clinical examination and delusional severity was assessed with the Positive and Negative Syndrome Scale. Cognitive insight was measured with the Beck Cognitive Insight Scale (BCIS). Delusion groups differed on depression and anxiety (t_{60} = 0.21, P = 0.04; t_{60} = 0.45, P < .01). As the present study's goal was to evaluate the unique relationship of cognitive insight to delusion groups, these scores were entered as covariates. Delusional FEP individuals showed a trend for lower Self-Reflectivity, $F_{1, 55}$ = 3.64, P = .06 than non-delusional FEP individuals. BCIS Self-Certainty scores did not significantly discriminate between delusional and nondelusional FEP individuals, $F_{1, 55}$ = 1.03, P = .32. In an exploratory correlational analysis between delusions scores and BCIS indices, no significant associations emerged (all rs < 0.22, ps > 0.09). These data suggest that the cognitive system involved in Self-Reflectiveness is functioning suboptimally in FEP individuals with active delusions. Taken together, a psychopathological model of cognitive insight may consider whether (1) diminished Self-Reflectiveness may be a vulnerability factor for psychosis, (2) the association between low Self-Reflectiveness and the absence of delusions in chronic psychosis may be a confound of the effects of illness chronicity or lengthy antipsychotic exposure, (3) delusions may contribute to overconfidence in later phases of the illness.
ID: 551447

SOUND LOCALIZATION IMPAIRMENTS IN INDIVIDUALS WITH SCHIZOPHRENIA

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Schizophrenia is associated with sensory processing difficulties. Deficits in the ability to discriminate simple features of auditory stimuli such as pitch and duration are extensively documented. Ability to detect tone location has been studied to a lesser degree and has been primarily assessed using cues derived from interaural delays, rather than free field sound. Such assessments provide limited information about the severity of impairment because they can only accurately assess differences in perceived location relative to the midline. The present study compared performance between individuals with schizophrenia (n = 16) and healthy controls (n = 12) on spatial location and discrimination tasks using low frequency tones. Free field sound was generated by seven speakers concavely arranged with 30 degrees separation. In the location task, a tone was randomly presented from one speaker and subjects indicated which speaker the tone came from. In the discrimination task, two tones were sequentially presented from the same or different speakers. Subjects reported whether both originated from the same speaker or not. In the location task, repeated measures analysis of variance revealed significant main effects for group status (individuals with schizophrenia vs. controls) and speaker location. Both groups were more accurate at detecting location when tones were closest to the midline. Although individuals with schizophrenia were less accurate than controls across all speakers, significant differences were observed at the midline and 30 degrees to the right of the midline. Comparable results were found for the discrimination task. Individuals with schizophrenia had more difficulty distinguishing between tones originating from different speakers, especially for pairs crossing the midline. In peripheral stimuli pairs, individuals with schizophrenia generally performed worse than controls when there was a smaller degree of separation between the speakers and overall performance was worse in the right than left hemisphere. The results provide insight into the degree of impairment in auditory processing of sound location information in schizophrenia.
ID: 551377

TRANSFER GENERALIZATION IN SCHIZOPHRE-NIA: SPECIFICITY AND CO-FAMILIALITY

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Schizophrenia is associated with hippocampal pathology. Schizophrenia patients show impairments in transitive inference, a component of relational memory organization dependent on an intact hippocampus. Transfer generalization is another component of relational memory organization that is thought to tap hippocampal functioning. In this study we examine whether 1) schizophrenics show deficits on a transfer generalization task, 2) transfer generalization deficits are specific to schizophrenia or also occur in bipolar disorder, and 3) transfer generalization deficits are co-familial (ie, also occur in well relatives of schizophrenia patients). In the transfer generalization task, subjects learn which member of a pair of stimuli hides a smiley face based on one attribute, shape or color. All groups learned to criterion and performed equivalently when tested on the learned pairs. Transfer generalization requires subjects to identify the relevant attribute (shape or color) in new pairs of stimuli based on the relevant attribute of the learned stimuli. There were no group differences in accuracy on the shape pairs. On the color pairs, schizophrenia and bipolar patients performed significantly worse than controls. Relatives of schizophrenics performed equivalently to control subjects and significantly better than schizophrenia patients. The performance of bipolar patients fell between that of schizophrenics and relatives of schizophrenics, and did not differ from either group. The greater salience of the shape stimuli may have facilitated compensation for impairments in hippocampal functioning that became evident when the less salient color stimuli were used. These results indicate that transfer generalization deficits are associated with both schizophrenia and bipolar disorder, but are not co-familial. Transfer generalization paradigms provide a potentially useful behavioral probe of hippocampal function.
ID: 551289

AN ERP STUDY OF "TOP-DOWN" AND"BOTTOM UP" PROCESSES INVOLVED IN VISUAL MASKING DEFICIT IN SCHIZOPHRENIA

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Studies of visual backward masking have frequently revealed an elevated masking threshold in schizophrenia. This finding has frequently been interpreted as indicating a low-level visual deficit. However, more recent models suggest that masking may also involve late and higher-level integrative processes. In a previous behavioural study, we found that access to conscious report of masked stimuli was impaired in schizophrenia, while fast bottom-up processing of the same stimuli, as assessed by subliminal priming, was preserved. [1] These findings suggested a high-level origin of the masking deficit in schizophrenia but left open for further research its exact relation to previously identified bottom-up visual processing abnormalities. In the present work, we tried to investigate the neural mechanisms of this deficit in perceiving visual masked stimuli, based on a previous ERP study in normal subjects. [2] We measured high density event-related-potentials and source localization in a group of 16 patients with schizophrenia compared to a group of 16 normal controls during two different conditions of masking aimed at differentiating top-down from bottom-up processing. We found that abnormal early and late neural events observed in patients during "top down" condition were most normalized for the "bottom up" condition. These results are discussed in the context of previous research in visual masking and cognitive deficits described in schizophrenia.

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SPORTS, HEALTH AND SCHIZOPHRENIA: QUANTIFICATION AND PSYCHO EDUCATION

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Drugs commonly prescribed for schizophrenia and other psychotic illnesses have been shown to increase patients' risk of developing diabetes including increased thirst, frequent urination, appetite and rapid weight gain. Although there are a vast array of studies which have demonstrated the psychological and physical health benefits of regular aerobic exercise for adolescents and adults, studies have not researched in the question of why patients with schizophrenia do not adhere to sporting activities. Understanding the meaning behind a person's posture or body movement comes easily to many people and helps guide how we react to others socially. This understanding is required for team sports but also important in individual sports where learning comes through observing and understanding the moves. But people with schizophrenia, even those who have mild to moderate symptoms and take medications, are not fluent in understanding body language (Paradiso and Andreasen 2006). Motor, cognitive and social deficits may thus be the limiting factor for patients to enjoy and to adhere to regular aerobic exercise. Our project was to use innovating tools—developed and validated in fundamental research protocols—for the quantification of those motor and cognitive deficits observed at an individual level in patients with schizophrenia. From these results, a psycho education program was initiated in order to sensitive patients to their functional deficits and to choose with them that sporting activity that would best fit their capacities but also their taste. A series of motor and cognitive tests were used to quantify motor and cognitive disorders in early onset and chronic patients with schizophrenia. The focus was set on: motor efficiency, motor coordination, motor synchrony; focused, divided and sustained attention; understanding; mental imagery; motivation. A selection of personality tests was also used to better orient the patients toward sports that would suit them best. The experimental session lasted 60 min. The most relevant tests that provided the means to help guide patients in their choice of sporting activities will be presented. We will also present the first results obtained for the psycho education program that seemed to help over half the patients to better understand the importance of sports for their health. This program may also provide the means to help the patients' family to feel more involved in the social rehabilitation of their sibling.
ID: 551256

SPORTS, HEALTH AND SCHIZOPHRENIA: QUANTIFICATION AND PSYCHO EDUCATION

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Drugs commonly prescribed for schizophrenia and other psychotic illnesses have been shown to increase patients' risk of developing diabetes including increased thirst, frequent urination, appetite and rapid weight gain. Although there are a vast array of studies which have demonstrated the psychological and physical health benefits of regular aerobic exercise for adolescents and adults, studies have not researched in the question of why patients with schizophrenia do not adhere to sporting activities. Understanding the meaning behind a person's posture or body movement comes easily to many people and helps guide how we react to others socially. This understanding is required for team sports but also important in individual sports where learning comes through observing and understanding the moves. But people with schizophrenia, even those who have mild to moderate symptoms and take medications, are not fluent in understanding body language (Paradiso and Andreasen 2006). Motor, cognitive and social deficits may thus be the limiting factor for patients to enjoy and to adhere to regular aerobic exercise. Our project was to use innovating tools—developed and validated in fundamental research protocols—for the quantification of those motor and cognitive deficits observed at an individual level in patients with schizophrenia. From these results, a psycho education program was initiated in order to sensitive patients to their functional deficits and to choose with them that sporting activity that would best fit their capacities but also their taste. A series of motor and cognitive tests were used to quantify motor and cognitive disorders in early onset and chronic patients with schizophrenia. The focus was set on: motor efficiency, motor coordination, motor synchrony; focused, divided and sustained attention; understanding; mental imagery; motivation. A selection of personality tests was also used to better orient the patients toward sports that would suit them best. The experimental session lasted 60 min. The most relevant tests that provided the means to help guide patients in their choice of sporting activities will be presented. We will also present the first results obtained for the psycho education program that seemed to help over half the patients to better understand the importance of sports for their health. This program may also provide the means to help the patients' family to feel more involved in the social rehabilitation of their sibling.
ID: 551256

PREPULSE INHIBITION DEFICITS IN SCHIZOPHRENIA ARE MODIFIED BY SMOKING STATUS

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Background: Schizophrenia is associated with high rates of cigarette smoking and deficits in sensorimotor gating, as measured by prepulse inhibition (PPI) of the startle response. However, the relationship between PPI deficits and smoking status is not clear. The goal of this study was to identify how smoking status modifies PPI deficits in schizophrenia.
Methods: We studied PPI as a function of smoking status and schizophrenia diagnosis in four groups using a cross-sectional design: Smokers with schizophrenia (SS; $n = 14$), non-smokers with schizophrenia (SNS; $n = 15$), control smokers (CS; $n = 11$), and control non-smokers (CNS; $n = 10$). PPI in smokers was recorded under conditions of smoking satiation, and smoking status was verified biochemically using expired breath carbon monoxide and plasma cotinine levels. Results: At all prepulse to pulse intervals (PPTPI's; 30, 60 and 120 msec), SNS had decreased (~40–50%; $P < .01$) PPI compared to CNS. However, when SS were compared to CS under conditions of smoking satiation, SS had comparable levels of PPI to CS, and significantly higher levels of PPI than SNS. We also observed significant Diagnosis x Smoking Status interactions on PPI at all PPTPI conditions (all P's <0.05). Conclusions: Our findings suggest that PPI deficits are present in nonsmokers with schizophrenia and are significantly modified by smoking status. Smoking in schizophrenia is associated with an elevation of PPI to the levels present in non-psychiatric control smokers. These findings have significant implications for understanding vulnerability to tobacco dependence in schizophrenia, which can lead to the development of more effective treatments for PPI deficits in this population.
ID: 551251

NEURAL CORRELATES OF EMPATHIC DYSFUNCTIONS IN SCHIZOPHRENIA PATIENTS

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The ability to empathize, ie, to communicate and understand intentions and feelings, and perceive the emotional states of others as well as in oneself is a vital skill. Empathy has various definitions, however, according to most models three core components can be derived: emotion recognition, 2) affective responsiveness, and 3) emotional perspective taking (Decety and Jackson, 2004). In a preceding behavioral study we showed that patients with schizophrenia demonstrate deficits in all three empathy components, thus suggesting a dysfunctional neural network for empathic behavior. The aim of the study was to gather more information on the neural dysfunctions underlying the observed empathy deficit. Thus, we measured patients suffering from schizophrenia and matched controls with a 3T MRI scanner (36 slices, TR = 2200 ms, TE = 30 ms, slice thickness 3 mm, gap 0.3 mm) and applied three paradigms tapping each core component of empathy separately. Data analysis indicates a significant empathic deficit in patients, reflected in their worse performance in all three domains. This deficit was only partly reflected in the self-report empathy questionnaires. Comparing the different tasks, emotional perspective taking was the most difficult task for all subjects. Preliminary analyses of the functional data reveal task specific as well as general neural dysfunctions in brain regions associated with empathy and emotion processing in schizophrenia patients. The data indicate that the observed deficits in perceiving and processing of emotional stimuli leading to a severe impairment in empathic abilities that is also represented on a neural level. Hence, our data suggest that patients with schizophrenia suffer from a more general dysfunction of emotional competencies that can also be characterized within the underlying neural networks. Moreover, our results implicate the necessity to develop specific training programs to improve empathic abilities in schizophrenia patients addressing each competency independently in behavioral therapies, thereby offering a possibility to improve socio-occupational life. The study was supported by the Interdisciplinary Center for Clinical Research (IZKF TVN 70) of the Medical Faculty RWTH Aachen University. BD was also supported by the International Research and Training Group (IRTG 1328, DFG).
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SPATIAL WORKING MEMORY DEFICITS AMONG UNMEDICATED FIST EPISODE PATIENTS WITH SCHIZOPHRENIA, PSYCHOTIC BIPOLAR DISORDER, AND PSYCHOTIC DEPRESSION

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Impairment in working memory processes, including the maintenance of information to guide future responses, is a commonly reported neurocognitive deficit in schizophrenia that implicates dysfunction of prefrontal cortex circuitry. The diagnostic specificity of this neurocognitive deficit to schizophrenia vs. affective psychoses is not known and is of interest given the common risk genes and neurobiological abnormalities observed across these disorders. We investigated working memory maintenance in schizophrenia and affective psychosis patients using an oculomotor delayed response task—a widely used spatial working memory paradigm translated into the clinic from laboratory studies with nonhuman primates. In this task subjects were required to maintain spatial location information in working memory over a delay period and then execute a saccadic eye movement guided only by the mental representation of that remembered location. Thirty-three patients with schizophrenia, 19 patients with psychotic bipolar disorder, 19 patients with psychotic depression and 42 healthy individuals were studied. Patients were early in their course of illness and untreated at the time of testing. Groups were matched on age and estimated IQ. Schizophrenia and affective psychoses patients demonstrated comparably reduced accuracy of their initial eye movement to remembered locations relative to healthy individuals. After the opportunity to correct for the error of their initial movement, only schizophrenia and psychotic bipolar disorder patients remained impaired in the spatial accuracy of their response. All patient groups demonstrated normal accuracy of eye movements made to visible targets. This indicates that the schizophrenia and psychotic bipolar disorder patients' impairments were attributable to deficient use of maintained mental representations of location information to guide responses and not the execution of precise eye movements. Deficits in maintaining information in working memory to accurately guide future behavioral responses appears to be a common trait in schizophrenia and bipolar disorder, but may be less pronounced in patients with psychotic depression. These working memory maintenance impairments which are suggestive of dysfunction of prefrontal system circuitry appear to be most pronounced in schizophrenia and psychotic bipolar disorder. Supported by R01 MH62134, R01 MH080066, NARSAD.
ID: 551227

THE EFFECTS OF ATYPICAL ANTIPSYCHOTIC MEDICATIONS ON LEARNING AND MEMORY IN FIRST-BREAK PSYCHOTIC PATIENTS

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The purpose of this study was to investigate the effects of atypical antipsychotic medications on implicit memory performance in first-break psychotic patients. Atypical antipsychotic medications, such as risperidone, olanzapine and quetiapine, have become the first-line treatment for schizophrenia. Compared to the typicals, these newer medications have multireceptor profiles and produce fewer extrapyramidal motor symptoms due to their lower affinity for dopamine D2 receptors in the striatum. Probabilistic classification learning measures implicit memory and activates the striatum. A probabilistic classification learning task was administered to 19 controls, 32 first-break psychotic patients being treated with atypical antipsychotics and 15 non-medicated first-break psychotic patients. Participants were placed in front of a computer screen and asked to predict the weather (rain or shine)associated with various shapes. Groups were matched on age and education. Given the low affinity of atypical antipsychotics for striatal dopamine D2 receptors, it was hypothesized that controls would perform better than both patient groups but that performance differences between medicated and non-medicated patients would be neglible. Interestingly, controls performed significantly better than both patient groups, as predicted, but non-medicated patients performed significantly better than medicated patients. Participants were administered 100 trials of the probabilistic classification task and results were analyzed and compared in 5 blocks of 20 trials. All groups showed gradual improvement and demonstrated learning over blocks with the control group means ranging from 13.89– 17.26, non-medicated patient group means ranging from 12.4–14.6 and the medicated patient group means ranging from 10.72–12.38. There was a highly significant group effect, $F_{2,63} = 17.23$, $P = .000$. These results suggest that, although atypical antipsychotics seem to cause fewer extrapyramidal motor symptoms, they still may affect striatal functioning. It will also be important to compare levels of psychopathology between the patient groups.
ID: 551225

SCHIZOPHRENIA PATIENTS SHOW ALTERED PROCESSING OF RISK INFORMATION IN THREE DECISION-MAKING TASKS

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We examined decision-making in schizophrenia patients (SZs) and nonpatient controls (NCs) on three tasks in which subjects could win and lose real money, each with a different risk/reward framework: the Iowa Gambling Task (IGT); a modified gambling task (MGT); and the Balloon Analog Risk Task (BART). We focused on how subjects' choices were influenced by information about the frequency and magnitude of potential wins and losses. In the IGT, subjects choose cards from 4 decks where variable frequency and magnitude of wins and losses creates 2 decks with a net gain and 2 with a net loss. In the MGT, 5 decks have equal expected value but different variances of potential win/loss outcomes (low variance is less risky, high variance is more risky). In the BART, subjects accumulate 2 cents with each pump of a balloon, but if it pops before they stop to collect their winnings, then they win nothing. Thus, each pump increases potential winnings by 2 cents, but also risks losing all of that trial's money. Across the tasks, SZs ($N = 53$) processed risk/reward information differently than NCs ($N = 31$). Patients did not show a normal preference for IGT decks with a net gain over those with a net loss, despite a normal preference for infrequent (vs. frequent) losses in general. In the MGT, SZs were less risk-averse than NCs, as they were less likely to avoid the riskiest deck (40% chance of a win, 60% chance of a loss). Patients were also, however, less likely than NCs to choose the safest deck (100% and 0%). In the BART, SZs made significantly fewer balloon pumps than NCs, reliably opting to collect their winnings earlier and, as a result, consistently experienced fewer pops but also won less money. Patients' conservatism suggests they were less driven than NCs to win more, opting instead to avoid winning nothing. These tasks provide convergent evidence of an altered ability in SZs to integrate multiple pieces of information needed to generate optimal choices. In the IGT, SZs showed a diminished ability to pair loss frequency with magnitude information needed to generate a normal preference for advantageous decks. In the MGT, SZs appeared less sensitive than NCs to the outcome variability underlying the decks' relative riskiness, thus appearing less risk-averse. And in the BART, SZs' apparent risk-aversion and under-appreciation of the magnitude of potential rewards led them to choose small but certain wins over larger, less certain wins, leaving them at a disadvantage.
ID: 551208

LARGER TIME VARIABILITY FOR BASIC DECISION PROCESSES IN SCHIZOPHRENIA

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Slower mean Reaction Time (RT), known as psychomotor slowing and an increased error rate, is well documented in patients with schizophrenia performing the antisaccade task. Fewer studies have shown increased variability of RT in these patients suggesting a basic difference in the distribution of RT. In this study, several antisaccade indices including median RT and its variability were measured for the antisaccade task performed by 45 patients and 2006 control subjects. Then average cumulative RT distributions were derived for each group for both correct antisaccades and error prosaccades and the RT distribution for each group was modeled using a decision signal rising linearly to a threshold signaling the beginning of the eye movement. There was a noticeable increase in the median RT for patients performing correct antisaccades while the median RT did not differ significantly between the two groups when performing error prosaccades. More over the patients RTs were much more variable from trial to trial leading to a difference in the average RT distribution of the patient group both for correct antisaccades and error prosaccades. The model application led to the conclusion that this difference in the distribution of RT for patients could be attributed to a basic difference in information processing leading to the decision to move the eyes. The same conclusion was reached in our previous study for visually triggered saccades performed by these patients and favors the hypothesis that a fundamental deficit of larger time variability in basic decision processes might be present in schizophrenia independent of the specific task used.
ID: 551163

COGNITIVE CORRELATES OF ANHEDONIA IN FIRST-DEGREE RELATIVES OF PATIENTS WITH SCHIZOPHRENIA

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There is growing evidence that anhedonia serves as a useful phenotype with respect to the genetic etiology of schizophrenia. Anhedonia has been associated with increased vulnerability to schizophrenia spectrum disorders and with poor outcome in individuals affected by these disorders. First-degree biological relatives of schizophrenia patients also exhibit increased anhedonia, particularly those relatives who carry the form of the COMT gene posited as related to low levels of dopamine in the prefrontal cortex. Although both anhedonia and cognition seem to be abnormal in first-degree relatives, it is unclear whether these symptoms are related to a common biological substrate. Anhedonic individuals from the general population and college samples have been shown to exhibit impaired visual-spatial working memory. Anhedonia has also been associated with a decrease in left visual-field bias in college students, and reduced right hemisphere white matter in people with schizophrenia. More recently anhedonia in patients with schizophrenia has been associated with aspects of episodic memory that may be lateralized in the brain. To explore the possibility that anhedonia and select cognitive deficits derive from a shared substrate, this study examined whether episodic and working memory functions thought to be lateralized in the brain were associated with anhedonia in individuals with genetic liability for schizophrenia. Biological relatives of schizophrenia patients and nonpsychiatric control subjects completed.verbal and nonverbal working memory and episodic memory tests. Subjects also completed questionnaires assessing physical and social anhedonia as well as interviews that assessed DSM Axis-I diagnoses and cluster A personality characteristics. Analyses will be carried out to determine whether performance on select memory tests correlates with scores on social and physical anhedonia scales in biological relatives. We hypothesize that relatives with higher anhedonia scores will exhibit a more lateralized pattern of performance and may also show decreased performance on nonverbal memory tests compared to controls. Such a pattern of results would support a theory that anhedonia and cognitive endophenotypes may both relate to right hemisphere function in individuals with genetic liability for schizophrenia.
ID: 551136

DIFFICULT COMPARISON OF EVENT ONSETS INDEPENDENT OF INTER-HEMISPHERIC TRANSFER

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Patients with schizophrenia show a disturbed sense of continuity. For Husserl, sense of time continuity is underpinned by integration of past, present and future events. The sense of present time results from the continuous integration of successive events in a time window. Inside this window (30 to 50 ms in controls), all events are considered as simultaneous, and events must be separated by a delay of 30 to 50 ms to be distinguished from each other. In previous studies, we suggested that this time window is enlarged in schizophrenia (Foucher et al. 2007 Schizophrenia Res, Giersch et al. in press Schizophrenia Bull). To test this assumption, two bars had been presented left and right from the centre of the screen and subjects decided if bars appeared simultaneously or asynchronously. Given that synchronization of neurons coding the events may underlie the perception of present time (Elliott et al. 2006, J Cogn Neurosci), and given that inter-hemispheric transfer might be impaired in patients, we checked whether the difficulty of the patients was due to presentation of stimuli in different hemifields. In the present study, continuous eyetracking ensured that stimuli were presented in the same or in different hemifields. SOAs varied between 0 and 96 ms. Our results confirm that patients have a difficulty to consciously detect an asynchrony between stimuli and show an inter-hemispheric cost of similar amplitude in patients and controls. However, patients are very sensitive to the apparition of the first stimulus, even if it precedes the second one by only 8 ms. Analysis based on response-compatibility effects in different conditions (the first and second stimulus in the same or opposite hemifields) shows that patients correctly followed instructions. Sensitivity to short-duration stimulus was correlated with impaired asynchrony detection. Patients would have a difficulty to consider separated stimuli together, and thus to compare them. Given that the effect of inter-hemispheric processing is similar in both groups, impaired mechanisms probably require more indirect pathways than inter-hemispheric connexions, like antero-posterior connexions and top-down mechanisms. Difficulty to code separated events in time may originate impairments in cognitive functions that entail the smooth sequencing of different events, like language to motor action.
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PRESERVED BINDING IN VISUAL PERCEPTION AND ATTENTION NORMALIZES WORKING MEMORY IN PATIENTS WITH SCHIZOPHRENIA

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Patients with schizophrenia are impaired at binding visual elements, but the impact of this impairment on working memory is still discussed. Here we base the work on results showing that patients display impaired top-down control in visual perception, but still benefit from binding by proximity, and are able to focalize on object groups (Giersch and Rhein, J Abn Psychol 2008). Evaluation of both perception and memory performance allows to explore whether preserved abilities help patients to memorize pairs of objects and to which amount impaired top-down control impedes memory. 28 stabilized patients and matched controls were submitted to a memory task after each of three different visual perception blocks run in random order. During these blocks, subjects had to find two identical figures displayed among seven different objects. Proximity was manipulated and targets were located in the same pair or belonged to two different groups. According to the proportion of target types (within the same pair or belonging to different groups), the block incited subjects to focalize on either within or between-group pairs of objects. Each block was followed by a memory task designed with the same figures and the same proximity manipulation. After the encoding phase of 2500 ms and an ISI of 1000 ms, one of the 5 figures presented at encoding was displayed with a question mark on one side of the figure. Subjects had to recognize which figure had been displayed in the location of the question mark. At encoding, the two figures had been within a pair of objects (within-group trials) or in different pairs (between-group trials) in equal proportion. This design allowed to attribute a change in performance across memory blocks to the attentional incentive during the visual perception task. There was no effect of visual perception on memory in controls. In patients however, memory accuracy was correlated with the ability to focus on within-group pairs in visual perception. Memory for within-group trials was normalized for patients able to focus attention, except when the visual perception task incited to prioritize between-group pairs. Preserved grouping coupled with attentional prioritization can thus help memorization in patients. This effect is fragile, however, possibly related with weak binding in memory and high sensitivity to distractors. The results give original indications regarding the kind of mechanisms which should be cared for during cognitive remediation.
ID: 551043

EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON PROBABILISTIC CATEGORY LEARNING IN PATIENTS WITH SCHIZOPHRENIA

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Schizophrenia has been characterized, in part, by debilitating cognitive impairments which, in general, are more informative indicators of the biological basis of the illness than measures of psychotic symptoms. The most reliable cognitive deficits, common to the majority of patients, are those related to prefrontal cortex dysfunction. Probabilistic category learning is one such cognitive process shown to rely on frontal-striatal activation in healthy adults that generally elicits a deficit in patients with schizophrenia relative to healthy adults that is suggestive of prefrontal cortex dysfunc-

tion. Weak anodal transcranial Direct Current Stimulation (tDCS) of the dorsolateral prefrontal cortex has been shown to improve probabilistic category learning in healthy adults. The aim of the current study was to evaluate the therapeutic efficacy of weak anodal tDCS of the dorsolateral prefrontal cortex to reverse probabilistic category learning deficits in patients with schizophrenia. Using a single-blind, cross-over, counter-balanced, within-subject design, anodal tDCS at an intensity of 2.0 mA or sham stimulation was administered continuously for 20 minutes to the left dorsolateral prefrontal cortex of patients with schizophrenia while they performed 150 trials of the "weather prediction" probabilistic category learning test. Each individual participated in three testing sessions on different days over the course of one week, an initial baseline session without stimulation followed by randomized presentation of one active and one sham tDCS session. Preliminary results indicate that the patients showed an increase in percent correct, a reduction of omissions and a reduction in reaction times during active stimulation relative to no stimulation at baseline and sham conditions. These results suggest that tDCS may provide a therapeutic benefit by improving cognitive function in patients with schizophrenia.
ID: 551004

DRUG USE IS NOT ASSOCIATED WITH GREATER COGNITIVE IMPAIRMENT IN FIRST-EPISODE PSYCHOSIS PATIENTS.

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Cognitive impairment is a core feature of schizophrenia. Due to the detrimental effects of drug use on cognitive function in healthy individuals, there is concern that schizophrenia plus the misuse of drugs may result in a more pronounced deficit in cognitive function. The aim of this study is to investigate the association between drug use and cognitive function in those with a first-episode psychotic disorder and community matched controls. A comprehensive battery of neuropsychological tests were administered to four groups of participants; 108 with an ICD-10 diagnosis of a psychotic disorder (Psych), 94 participants with an ICD-10 diagnosis of a psychotic disorder plus drug use (Psych+), 85 community matched controls (Cont) and 27 community matched controls plus drug use (Cont+). Both of the psychosis groups performed worse than Cont group on tests of working memory, visual and verbal memory, executive function and visual attention and psychomotor speed. None of the comparisons between the Cont group and Psych or Psych+ groups were significant. There were no differences between drug users and non-drug users for those with a psychotic disorder. When comparing drug users and non-drug users within the controls, the Cont+ group performed significantly worse than the Cont group on a task of working memory. Analyses were repeated for only those participants with a diagnosis of schizophrenia or schizoaffective disorder, similar results were obtained. Individuals with a diagnosis of a psychotic disorder show a wide spread impairment in cognitive function compared to controls that do not use illicit drugs. However, those with a psychotic disorder tend to perform at an equal level to community matched controls that use drugs. It appears that concurrent drug use in those with a psychotic disorder does not result in greater impairment in cognitive function at the first-episode. Longitudinal studies are required to further investigate the effects of substance use on cognitive function in individuals with a psychotic disorder.
ID: 551003

ANTITHETICAL ASYMMETRY IN SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER: A LINE BISECTION STUDY

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Evolutionary theories link pathogenesis of psychoses with anomalous brain asymmetry (DeLisi et al., 1997). Aberrant lateralization is linked to schizophrenia with elevated rates of lefthandedness and reversal of normal cerebral asymmetries. Moreover, a paternally transmitted imprinted gene-LRRTM1 is associated with handedness and schizophrenia. Line bisection task is a valid test to assess behavioral manifestations of cerebral asymmetry (Morton, 2003). Reports suggest rightward bias in schizophrenia in contrast to normal leftward pseudoneglect. However, lateralization is yet to be explored in bipolar affective disorder (BPAD). We, for first time, report concurrent analyses of asymmetry in schizophrenia and BPAD using line bisection task. Study group consisted of 30 schizophrenia and 31BPAD patients and 103 healthy controls. A 2-hand line bisection task with established methodology was used. Task consisted of 20 horizontal black lines of width 70 to 160 mm randomly placed to the right or left side of paper. Subjects were asked to bisect each line at center first from right hand and then from left, on separate sheets. Raters with good interrater reliability (ICC>0.8) measured deviation from center. Study groups did not differ significantly on age, sex and handedness ($P > 0.06$). Task performance was compared using analysis of covariance (age, sex and education as covariates). Patients (schizophrenia and bipolar) had significantly greater errors in identifying center than controls ($P < .001$). On further analysis between schizophrenia and BPAD, there was a significant rightward deviation in schizophrenia ($P = .04$) and trend towards leftward deviation in BPAD ($P = .10$). There was a significant interaction between diagnosis and direction of deviation ($P = .01$). Our findings suggest the accentuation of normal pseudoneglect in BPAD and attenuation in schizophrenia. That is, schizophrenia patients showed a tendency towards symmetry, supporting impaired laterality and right hemisphere involvement (Mitchell and Crow, 2005). Thus, from an evolutionary perspective, schizophrenia and BPAD may lie along a continuum.

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ID: 550995

NEUROCOGNITIVE DEFICITS ARE ASSOCIATED WITH PSYCHOTIC-LIKE EXPERIENCES AFTER CANNABIS.

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Background: The relationship between cannabis and psychotic disorders is still under debate. It is clear however that in some individuals even recreational use of cannabis can lead to a transient period where some symptoms of psychosis are experienced. There is extensive anecdotal evidence for individual differences in the experiences which people have after smoking cannabis. Previous work has shown that schizotypy may mediate the experiences which people have when smoking cannabis (Barkus et al., 2006; Barkus and Lewis, 2008). Specifically, those who score higher on schizotypy are more likely to experience psychotic-like immediate effects and report more after effects from cannabis use. Given that altered cognitive performance has been associated with both schizotypal trait and cannabis use, it is possible that cognition may have a role in mediating the experiences which people have when they use cannabis. We hypothesised that individuals who reported psychotic-like experiences after cannabis use would have impaired cognitive performance across multiple domains of cognition. Method: We tested fifty participants (mean age 23 years) who had been selected on the basis of their scores on the psychotic-dysphoric subscale on the Cannabis Experiences Questionnaire (Barkus et al., 2006). They were tested on measures of working memory, spatial working memory, executive functioning and learning. Groups were well matched on other recreational drug use and patterns of cannabis use. Results: Those who reported psychotic-like experiences after cannabis reported higher scores on neuroticism and emotional reactivity ($t = 2.479$, $P < 0.05$ and $t = 2.739$, $P < .05$ respectively), these effects were independent of gender. Those who had psychotic-like experiences had more between search errors on the spatial working memory task and longer latencies on a working memory task; while there were no differences on attention and Trails A and B. Conclusion: In the absence of differences in patterns of cannabis use, individuals who have psychotic-like experiences after cannabis do demonstrate some cognitive deficits, particular in working memory. These cognitive deficits occur in the absence of differences in patterns of cannabis use.
ID: 550982

THEORY OF MIND AND NEUROCOGNITION IN FIRST-EPISODE SCHIZOPHRENIA

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This study aims to investigate the extent, impact and specificity of 'theory of mind' (ToM) impairment in first-episode schizophrenia. Numerous studies have demonstrated that people with chronic schizophrenia are impaired in their abilities to accurately infer other people's thoughts and hence to take appropriate account of other people's mental states in social interactions. Such impairments are significant and impact upon the patients' real-world social functioning. In order to examine whether such impairments represent a trait marker of schizophrenia, 22 first-episode schizophrenia patients were recruited from two early psychosis intervention services in New South Wales, Australia. Fourteen patients were diagnosed with schizophrenia, two with schizoaffective disorder, and six with schizophreniform disorder. Nineteen age and gender-matched healthy controls were also recruited from the general community. All participants completed a battery of three ToM tasks, as well as neurocognitive tests of IQ, attention, memory, and executive function (planning, set-shifting and semantic fluency). Symptom severity, socio-occupational functioning and quality of life were also assessed in the patients. Significant group differences were found for most tasks. A composite ToM score, semantic fluency and verbal memory showed the largest effect sizes (d's = −2.32, −2.39, −2.03). While neurocognitive measures correlated with ToM scores, logistic regression analysis revealed that the best (independent) predictors of group membership were the ToM and semantic fluency scores. Both of these measures correlated significantly with levels of negative, but not positive, symptoms, while it was the semantic fluency score which better predicted socio-occupational functioning and quality of life in the patients. In conclusion, the study findings indicate that selective ToM impairments are evident in first-episode schizophrenia, consistent with the proposal that such impairments are domain-specific and represent a trait marker of schizophrenia.
ID: 550979

ACUTE AND CHRONIC PCP-INDUCED COGNITIVE PERFORMANCE DEFICITS IN THE 5-CHOICE SERIAL REACTION TEST: INFLUENCE OF CLOZAPINE

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Cognitive deficits are a core feature of schizophrenia that respond minimally to existing drugs. Improved translational models with greater predictive validity are required to identify treatments that are most likely to be clinically effective. We have shown that repeated PCP treatment to rats reproduces dysfunctional prefrontal cortex activity (hypofrontality) (Cochran et. al. 2003 Neuropsychopharmacology 28: 265–75; Pratt et al. 2008 Brit. J. Pharmacol, 153 Suppl 1:S465–70.). Since hypofrontality correlates with cognitive performance in schizophrenia, the aim of this study was to determine if PCP elicits deficits in a cognitive task that recruits the prefrontal cortex. We selected the 5-choice serial reaction time task (5-CSRTT) since this test measures aspects of attentional function related to the Continuous Performance Task in humans. To increase the translational validity of this approach we employed analysis taken from signal detection theory (SDT). Long Evans rats were trained to criteria in the 5-CSRTT. PCP (2.6 mg/kg i.p.) was administered according to our chronic intermittent treatment regime (Cochran et. al. 2003) in the presence or absence of clozapine (20mg/kg/day). A range of attentional performance and inhibitory control measures were recorded. In addition, SDT analysis of perceptual sensitivity and discriminability measures were employed. Measurements were made in the presence and absence of PCP intermittently over the treatment period. There was a marked increase in anticipatory responding 30min following PCP injections ($F1,34 = 5.34$ $P < .05$) that was maintained throughout the four-week treatment protocol. Clozapine did not reduce the PCP-induced increases in anticipatory responding although there was a modest ability to restore sustained PCP-induced deficits in perceptual sensitivity; a measure of discriminative accuracy impaired in schizophrenia. Taken together, these results support the view that performance deficits in the 5-CSRTT induced by PCP may be of relevance to schizophrenia. The modest ability of clozapine to restore these deficits is in line with the minimal effects of the drug in restoring cognitive processes in the clinic and its inability to restore hypofrontality. In conclusion, PCP-induced deficits in the 5-CSRTT may be a useful model for identifying new agents that may be clinically effective in schizophrenia.

ID: 550975

EMOTIONAL-SOCIAL INTELLIGENCE IN PATIENTS WITH SCHIZOPHRENIA AND THEIR HEALTHY SIBLINGS

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Background: Emotional intelligence is concerned with understanding oneself and others, relating to people, and adapting to and coping with the immediate surroundings to be more successful in dealing with environmental demands. Higher scores on emotional intelligence tests have been associated with various indicators of social adaptation. Aims: The aim of this study is to investigate emotional intelligence in patients suffering from a first psychotic episode in order to identify social cognitive markers for developing a non-affective psychosis. Method: 32 patients, 32 siblings and 32 healthy volunteers completed the Bar-On Emotional Quotient Inventory (EQ-i. The EQ-i is a self-report measure of emotionally and socially intelligent behavior, which provides an estimate of one's underlying emotional and social intelligence. The Hinting Task(a theory of mind task) and a short version of the Wechsler Adult Intelligence Scale were also measured. Results: The groups differ significantly on total EQ-I scores ($F = 35.8$, $P < .001$) and all of the subscales. Post hoc tests revealed that the patients had lower scores than both other groups. The siblings had significantly lower scores than the control subjects. The difference remains significant when the EQ-I scores are corrected for IQ and theory of mind ($F = 13.9$, $P < .001$). Discussion: The differences in emotional intelligence between the groups may provide an explanation for the deficits in social functioning of patients with schizophrenia.
ID: 550968

REVERSAL OF COGNITIVE DEFICITS BY AN AMPAKINE (CX516) AND SERTINDOLE IN TWO ANIMAL MODELS OF SCHIZOPHRENIA—SUB-CHRONIC AND EARLY POSTNATAL PCP TREATMENT IN ATTENTIONAL SET-SHIFTING.

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In schizophrenia, cognitive impairment is believed to be one of the overall decisive factors for a patients' community functioning. Healthy subjects receiving the NMDA antagonist phencyclidine (PCP) have been reported to experience a schizophrenia-like psychotic state. Concordantly, injection of PCP in laboratory animals has been shown to induce abnormalities similar to those observed in patients with schizophrenia.

The purpose of this study was to evaluate sub-chronic and early postnatal treatment of PCP in rats as preclinical models of schizophrenia. Briefly, for the sub-chronic paradigm Lister Hooded rats were treated with PCP, 5 mg/kg, BID for 7 days and tested 8 days after the last dose. For the early postnatal treatment regime, PCP (20 mg/kg) was administered on postnatal days (PNDs) 7, 9, and 11 and rats were tested in adulthood (ie, after PND 56). Rats were tested in an attentional set-shifting task addressing cognitive deficits, specifically deficits in executive functioning. The test requires subjects to respond to various extra dimensional-intra dimensional (EDID) shifts in accordance with changing rules. Data analyses were performed using a general linear model followed by Tukey post-hoc analyses.

The data showed that rats treated with PCP, ie, both models, were selectively impaired in performing the extra dimensional shift compared to a control groups ($P < .05$). In order to further validate the preclinical models, we tried to reverse the PCP induced deficits with two drugs, which were chosen due to their potential as clinically relevant drugs in the treatment of cognitive deficits associated with schizophrenia. Sertindole, a 2nd generation antipsychotic, which has shown to reverse cognitive deficits significantly more than haloperidol and the AMPAkine (ie, potentiator of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor function) CX516. Both sertindole and CX516 showed significant ($P < .05$) effects in their ability to reverse the PCP induced deficits to the levels of the control group. Taken together, these data suggest that sub-chronic and early

postnatal treatment of PCP, demonstrates a phenotypes, which in some aspects resembles the symptoms observed in patients with schizophrenia. Both models also seem to have some predictive value. However, this cannot be fully concluded until the effect of the tested drugs on the cognitive domain has been firmly established in clinical trials.
ID: 550956

COGNITIVE EFFECTS OF 6-MONTH QUETIAPINE TREATMENT IN ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE SCHIZOPHRENIC PATIENTS

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Studies have found that atypical antipsychotics improve some cognitive deficits in schizophrenia, although it is unclear whether improvements are due to ameliorated cognitive functions, placebo effects, or retest-effects. Very few treatment studies have included both first-episode antipsychotic-naïve schizophrenic and matched healthy controls, and may therefore be confounded by prior medication and retest effects on neuropsychological tasks. Effects of quetiapine on cognition were investigated in a group of first-episode antipsychotic- naïve patients with schizophrenia ($n = 24$). A comprehensive battery of neuropsychological tests was administered at baseline and after 6 months of treatment with quetiapine (mean dose 519.6 mg/day; S.D. = 297.4). In order to control for retest effects, a matched and untreated healthy control group was also tested at baseline and after 6 months. At baseline, patients performed significantly worse than controls on measures of intelligence, attentional set shifting, sustained attention, spatial working memory, spatial memory span, processing- and psychomotor speed, verbal and figural fluency, and verbal memory. While patients seemed to improve at follow-up on a number of these measures (within-group tests), they were found to improve significantly only on measures of attentional set shifting and speed of processing when controlled for retest effects (between group tests). The results suggest that cognitive changes after treatment with quetiapine may mainly be due to retest effects. However, certain cognitive measures are also improved beyond retest effects, which supports some efficacy of quetiapine on cognition. The results emphasize the importance of controlling for retest effects, by including baseline-and follow-up assessments of healthy controls, in order to distinguish retest effects from cognitive amelioration.
ID: 550949

PRENATAL STRESS DIFFERENTIALLY IMPACTS THE SOCIAL AND ANXIETY-RELATED BEHAVIORS OF ADULT MALES AND FEMALES

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Schizophrenia is a disease with etiological links to the prenatal period. In particular, stress during the second trimester of pregnancy is associated with increased incidence of schizophrenia in offspring. The current study sought to better characterize the effects of prenatal stress on behaviors associated with the negative symptoms of schizophrenia such as social withdrawal. In addition, given that anxiety disorders are common in schizophrenia, we sought to characterize the effects of prenatal stress on adult anxiety-related behavior. Both the severity of negative symptoms and comorbidity with anxiety disorders differ between male and female schizophrenia patients. The negative symptoms tend to be more severe in men than women, but women are more likely to exhibit an anxiety disorder, suggesting that the neurodevelopmental underpinnings of this disease differentially effect the expression of symptoms across gender. Given these gender differences found in schizophrenia, we tested the hypothesis that prenatal stress will cause sex-specific changes in adult social interactions and anxiety-related behaviors. This hypothesis predicts that prenatal stress will impair social interactions of adult males more so than adult females, and will increase anxiety behavior in adult females more so than in males. Sprague-Dawley rats experienced random stress 2–3 times daily during the last week of gestation (P14–21). At weaning, the offspring of the stressed and nonstressed dams were assigned to same-sex treatment groups (male vs. female, stressed vs. nonstressed; $n = 10$; overall $N = 40$). In adulthood, animals were tested for anxiety-related behavior in an elevated zero maze and social behavior in an open field with a same-sex same-treatment partner. Prenatal stress significantly decreased the amount of time spent in the open areas of the zero maze in females [$F_{1,18} = 4.45$, $P < .05$], but not males [$F_{1,18} = 0.32$, $P > 0.05$], indicating that prenatal stress increased anxiety only in females. In contrast, prenatal stress decreased the amount of time males sniffed partners, and slightly increased the duration of sniffing in females [sex x treatment interaction $F_{1,36} = 4.32$, $P < .05$], indicating that prenatal stress decreased social interactions in males but not females. These data suggest that prenatal stress differentially impacts males and females to bring forth sex-specific adult behaviors similar to those observed in schizophrenia.
ID: 550934

COGNITIVE REMEDIATION THERAPY FOR SCHIZOPHRENIA IN MALAYSIA

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Cognitive Remediation Therapy (CRT) was introduced in Malaysia in 2006. The effectiveness of computerised cognitive remediation using the principles of Neuropsychological Educational Approach to Remediation (NEAR) was studied in a randomized controlled trial involving five treatment centres throughout Malaysia. The main difference in this treatment model was the use of a web-based assessment for neurocognition and minor adjustments that had to be done to accommodate for lack of resources in a developing country. This study investigated whether a 20 session intervention with CRT was more efficacious than wait list in reducing cognitive deficits and improving psychosocial functioning. It was also designed to investigate whether or not there would be any additional benefit of adding four booster sessions following completion of CRT. In the first phase, schizophrenia patients with cognitive deficits were recruited and randomly allocated into either CRT group ($n = 30$) or Waitlist ($n = 30$). They were assessed at baseline and post-treatment using measures of cognitive functioning, psychosocial functioning and psychopathology. In the second phase, patients including those from the waitlist were randomly allocated into standard treatment ($n = 20$) or booster group ($n = 20$). In the booster group, after receiving 20 sessions of CRT an additional four sessions were given after a two weeks gap. The same measurements were repeated 5 weeks post standard treatment. Patients receiving CRT demonstrated significant improvements in both verbal and visual memory and a trend towards improvement in processing speed and attention. There was also significant improvement in psychosocial functioning and a positive trend in psychopathology. However, booster sessions did not contribute to any additional benefit. In conclusion, CRT is effective for Malaysian patients with schizophrenia, although adding booster sessions did not give additional

advantage to patients. This may reflect the brief period between CRT and booster sessions. Thus, CRT is a promising treatment option for schizophrenia patients with cognitive deficits in Malaysia. This further supports the role of CRT in the treatment of schizophrenia.
ID: 550930

RESPONSE INHIBITION AND RESPONSE MONITORING OF SACCADES IN A STOP SIGNAL TASK IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Objective: The goal of this study was to investigate response inhibition and response monitoring in individuals with schizophrenia (SZ) and bipolar disorder (BP) using a saccadic stop signal task, which assesses the ability to stop a planned action. Research from nonhuman primates have identified specific neural correlates of both the stopping and monitoring of behavior during this task. Methods: SZ patients, BP patients and demographically-matched control participants performed a saccadic stop signal task. On no-stop signal (NSS) trials, a peripheral target appeared, and subjects were instructed to look towards it. On stop signal (SS) trials, the fixation point was re-illuminated after a variable delay (stop signal delay; SSD) following the initial target, and subjects were instructed to withhold the saccade. Successfully inhibited trials were labeled as cancelled, and trials in which they failed to inhibit were labeled noncancelled. As SSD increases, successful inhibition becomes more difficult. The probability of failing to cancel at each SSD describes the inhibition function. The duration of the inhibitory process (stop signal reaction time; SSRT) was determined according to a race model. Response monitoring was indexed by the magnitude and direction of RT adjustments as a function of performance in the prior trial. Results: Preliminary results suggest that SSRT is increased in SZ, but not in BP, compared to healthy controls. Longer SSRT was associated with increased positive symptoms. Across groups, the greatest RT slowing followed cancelled trials, with less slowing following noncancelled trials. SZ patients showed enhanced RT adjustments based on trial history. Compared to both BP patients and healthy controls, SZ patients showed greater RT slowing after successfully cancelled stop-signal trials. Conclusions: Results suggest that SZ but not BP, patients require more time to inhibit a planned response, compared to controls, and the time needed to cancel a response is associated with increased positive symptoms. This deficit exists despite greater RT adjustments, which were enhanced compared to both healthy and BP participants. Results speak to the nature of inhibitory deficits in SZ, and provide evidence for potentially enhanced response monitoring, compared to healthy controls and a psychiatric control group. (Supported by F32-EY016679, P30-EY08126, Ingram Chair in Neuroscience, MH073028).
ID: 550914

NEUROPLASTICITY-BASED COGNITIVE TRAINING IMPROVES REALITY MONITORING IN SCHIZOPHRENIA PATIENTS: BEHAVIORAL AND FMRI ASSESSMENTS

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Prior research indicates that schizophrenia patients (SCZs) are impaired at identifying themselves as the source of self-generated information (reality monitoring). They also show relatively decreased activation within the dorsal medial prefrontal cortex (dMPFC) compared to healthy comparison subjects (HCs) when engaged in this process (Vinogradov et al., 1997; 2006). In the present study, we investigated whether this deficit is amenable to a behavioral intervention. Twenty four SCZs and 12 HCs underwent an fMRI source-memory task at baseline. Twelve SCZs were then randomly assigned to 80 hours of computerized targeted cognitive training (TCT) that focused on auditory and visual processing, facial affect recognition, and mentalizing tasks. The other twelve SCZs were assigned to a control condition of 80 hours of computer games (CGs). All subjects repeated the task after the 16-week intervention. Prior to scanning, subjects were presented with sentences, where the final target word was either supplied by the experimenter, or left blank for subjects to generate themselves. During scanning, subjects were presented with target words, and decided whether they were experimenter-presented or self-generated. BOLD fMRI activity was measured on a 3T GE scanner (EPI; TR = 1sec, 14 slices) before and after the intervention. Images were analyzed using SPM2. At baseline, patients were significantly more impaired on each category within the source-memory task, relative to controls. Whole-brain analyses focused on brain regions showing greater activation for correctly remembered self-generated versus externally presented items (a self-referential effect). Across 12 HCs at baseline, the largest region that demonstrated this self-referential effect was dMPFC. In contrast, at baseline, all SCZs showed deactivation in bilateral frontal regions. Paired t-tests indicate that after 16 weeks of computer games compared to baseline, CG subjects showed increased activation in bilateral occipital gyri during self-referential processing. In contrast, after 16 weeks of TCT exercises compared to baseline, TCT subjects showed increased activation in dMPFC during self-referential processing. These fMRI results indicate a possible "restorative" effect of targeted training in schizophrenia subjects, not observed in computer games control subjects, whereby behavioral performance on a self-referential source memory task is improved and brain activation patterns are "normalized."
ID: 550910

RELIABILITY OF REPEATED ASSESSMENT OF ATTENTIONAL PERFORMANCE IN INDIVIDUALS AT RISK FOR PSYCHOSIS AND IN THE FIRST EPISODE OF SCHIZOPHRENIA

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As attentional deficits, particularly the CPT-IP paradigm, have been implicated as an endophenotypic marker suggesting predisposition towards psychosis, this study aims to examine the reliability of repeated CPT-IP assessment in young adults at risk for schizophrenia. Subjects at risk for psychosis (AR $N = 51$), patients in their first episode of schizophrenia (FE $N = 21$), and normal comparison subjects (NC $N = 36$) were assessed for attentional performance on the d' measure of the CPT-IP at baseline and follow-up ranging from six months to one year. The reliability of CPT-IP over the subjects' initial and follow up visit was examined to assess whether the paradigm is a stable measure of attentional deficits. A repeated measures ANOVA displayed a significant overall group effect ($F_{2,105} = 7.2$, $P = .001$) with post hoc tests revealing that first episode subjects displayed significant attentional impairments in comparison to the AR and NC samples. However, the AR sample did not differ significantly from the NC sample. While all groups improved in performance over time ($F_{1,105} = 19.4$, $P < .000$), there were no group by time interaction effects. Paired samples t-test correlations revealed all CPT conditions were stable across groups in the

AR and NC samples, while only the Numbers Slow condition and Shapes Fast condition were stable in the FE sample. On longitudinal assessment, the CPT-IP appears stable within control and at risk populations on all measures of d', however some variability is observed in the first episode sample, perhaps indicative of the neurodevelopmental processes and dynamic changes in the early stages of illness. The reliability of particular measures of the CPT-IP across all groups confirms the validity of the CPT-IP paradigm as an endophenotypic marker for schizophrenia which, combined with clinical and genetic risk factors, may improve our ability to predict which individuals are at greatest risk for developing psychosis.

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ID: 550831

FUNCTIONAL ASSOCIATIONS OF DECLARATIVE MEMORY DEFICITS IN SCHIZOPHRENIA

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Schizophrenia (SCZ) is broadly defined by psychosis and diverse cognitive abnormalities, with declarative memory deficits among the most noted. In healthy persons, declarative memory reliably encapsulates representations of facts and events which subsequently enable novel inferences and generalizations about the world and self. This study employs the acquired equivalence task (AE) and conjunctive memory task (CM) to analyze declarative memory in schizophrenic subjects on- or off-antipsychotic drugs (APDs) (SZ-on vs. SZ-off) and healthy volunteers (NV). The AE was used as a performance measure and fMRI paradigm to localize BOLD-activations associated with deficits in 'generalization'; likewise, we are using the CM to dissociate mnemonic processes required for 'inference-making' from simple declarative recall. Results (NV $N = 20$, SZ-on $N = 40$, SZ-off $N = 16$) from the AE are nearly complete, showing SZ-on and SZ-off to have intact memory for trained-item recall (NV 98±3%; SZ-on 99±3%; SZ-off 97±3%; $P = .82$). However, there is a selective medication effect on 'generalization' performance (t-test, SZ-off 59±3%, NV 91±3%, $P = .001$); in contrast to SZ-off, when tested on-medication, 'generalization' performance improved significantly (t-test, SZ-on 75±4% vs. SZ-off 59±3%, $P = .04$). A preliminary SPM group analysis shows that NV ($N = 7$) activated hippocampus proper during the 'generalization' trials as contrasted with the trained-item trials, whereas SZ-on ($N = 10$) failed to show any activation in hippocampus. Voxel-level subtraction of the SZ-on from the NV shows a significant activation decrement in SZ-on within the hippocampus, albeit analyzed at a $P = .05$ level. A complementary trend is emerging from preliminary CM data (NV $N = 11$, SZ-on $N = 13$, SZ-off $N = 2$) showing that SZ-on performs similarly to NV on trained sets of face-house pairs but worse than NV on unlearned (related via 'inference' only) face-face pairs ($P = .056$, d' = .81). We hypothesize that whole-brain group analysis of the CM will also reveal task-related hypofunction in the medial temporal lobe (MTL) in SZ , with further alterations in the basal ganglia and prefrontal cortex. Results already demonstrate MTL-hypofunction to be associated with selective impairment of declarative memory in schizophrenia, specifically during trials requiring generalization or inference-making. APD treatment may partially remediate, but not fully repair, memory performance in these contexts.
ID: 551929

SCHIZOPHRENIA: MEASURING BRAIN PLASTICITY

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The brain is plastic and can respond to interventions. The data in this presentation demonstrates that specific interventions change (improve) brain function and ecologically valid/functional behaviors. Brain function was measured via on-line EEG during a series of cognitive training interventions. These interventions included the Orientation Remediation Module (ORM) (NYU Rusk Institute), auditory stimulation, and relaxation training. A computer software program, the ORM, measured reduction in the high variability of reaction time scores and in decreased attention/concentration scores, as well as improved reasoning and planning scores. High variability is indicative of brain states that are not stable, synchronized and functioning coherently. Ecologically valid/functional behavior was measured on behavioral observation scales. The behavior was rated as present or absent (1 = present and 0 = absent). Treatment staff and observers measured the behavior pretreatment and at intervals during treatment. The results of a pilot study using on-line EEG demonstrated that subjects who are actively hallucinating were able to move their brain activity from a slow wave state to a normal alpha rhythm. This study showed that working on the ORM changes brain function to a normal alpha rhythm; which is reflected in lower reactions time in general and reduced variability in responding. Training subjects on the ORM and other interventions leads to improved ecologically valid behaviors as measured by rating of functional behaviors. In conclusion the brain functions as a homeostatic system with activating and inhibiting networks. Change (improvement) in brain function and ecologically valid behaviors occur through a process. The process can use a variety of interventions. This change in reciprocal activating and inhibiting systems produced a change from slow wave to alpha rhythms on EEG, reduce errors and variability on reaction time and reasoning cognitive tasks, and improved ecologically valid/functional behaviors. Networks of the brain that are involved with hallucinatory activity were inhibited by the intervention, while networks of the brain that are involved in a normal alpha state and frontal lobe activity were activated.
ID: 563719

A UNITARY MODEL FOR THE MOTOR ORIGIN OF SCHIZOPHRENIA AND BIPOLAR DISORDER

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The core problem in brain research of schizophrenia and bipolar disorders is the lack of an adequate physiological model. An attempt was made to bridge the gap between biological and psychological phenomenon's (van Hoof, 2003). In this model, it is assumed that the relevant problems are the manifestation of an imbalance between two mechanisms in the brain: the first is motor power or drive and the second is steering or guidance. Both mechanisms are used to control movements. The core of this model's thesis is that during the normal phylo- and ontogenesis of the human brain both of these mechanisms are implemented in a repetitive way from the "how to do" motor domain into the "what to do" intentional (limbic) domain through cortical- subcortical circuits. The first, striatal mechanism (parallel information processing) is necessary to initiate and calibrate movements and intentions, such as intimidation or affiliation. This intentional drive mechanism is organized primarily by a circuit located in the ventral part of the brain. The second, cerebellar (serial information processing) mechanism is necessary for guidance. The intentional variant of the representational guidance mechanism is organized primarily in a circuit located in the dorsal part of the brain. The repetitive application of both mechanisms

during brain development allow the creation of unique human capacities; viz. the ability to create (meta) representations, language and consciousness, but also an increased capacity to deal with conflicting demands and emotions. This development is the neuronal correlate for the process called mentalization. Evidence is accumulating that the principally genetically based reliance on one or both types of mechanisms has a bimodal distribution. A genetically based insufficient development of one of both mechanisms and an exaggerated reliance on the other mechanism cause an imbalance. The repetitive implementation of these mechanisms will increase this imbalance and create a situation where comparatively small stressors produce a tipping of the scale manifesting itself as schizophrenia or a bipolar disorder. This model has a greater explanatory power than current alternatives and therefore it will provide a useful framework for further research.
ID: 555590

MYRIADS OF SEX HORMONAL EFFECTS ON BRAIN, PERSONALITY AND THEIR MODULATING EFFECTS ON SCHIZOPTYPY.

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Sheldon believed that the masculine and feminine components of the physique are two "most important constitutional factors in determining personality." Rees wrote, "the work of [several authors-six cited] suggests that schizophrenics with [frail] body build tend to have [an early onset, more withdrawn], apathy and scattered thinking, whereas, schizophrenics of [sturdier] built tend to have [later onset and better] preservation of personality and better affective responses." This implies that testosterone deficiency worsens the psychopathology in (only male) schizophrenics. More recently, five studies in a total of 145 male schizophrenics in Delhi (2000, 2004), Japan (2002), Iran (2006), South Korea (2007) and Kerala, India (2007), all essentially showing a negative correlation between negative symptoms and testosterone levels, and none so far refuting it. Contrariwise, Manfred Bleuler and coworkers found that women with signs of virilism tended to have poor prognosis, with severe deterioration. And Jayashree Kulkarni's group demonstrated effective adjuvant role for estradiol in female schizophrenics. Further, more recently, as well as over 50 years ago dehydroepiandrosterone has been shown to cause modest reversal of negative symptoms. 5alpha-reduced androgen and progesterone metabolites have neuroprotective, and probably cognitive enhancing effects, whereas, testosterone, but not its 5alpha-reduced dihydrotestosterone enhanced "spatial working memory" in another animal model. Further, in Alzheimer's disease brain, the level of allopregnanolone, an eventual 5alpha-reduced progesterone metabolite, is decreased proportionately to neuropathological changes. And allopregnanolone can reverse transgenic mouse model of Alzheimer's disease. Thus, sex hormones can at least modulate the course and severity of schizophrenia.
ID: 555063

DIFFERENTIAL EFFECTS OF DIFFICULTY ON LEARNING STRATEGY AND ON MONITORING OF KNOWLEDGE IN PATIENTS WITH SCHIZOPHRENIA

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This study was aimed at further investigating the strategic control of study time and the metamemory processes and accuracy of schizophrenia patients during the encoding of episodic information. Metamemory refers to the ability to monitor and control how well information is processed depending on the loads and needs of the task at hand. Metamemory functions are impaired in schizophrenia at both the times of memory acquisition and retrieval (Danion and al., 2001; Bacon and al., 2007). The difficulty of to-be-learned material was varied (associated versus non associated word pairs). The participants controlled themselves their learning time allocation and had to judge how efficient they were. 23 patients and 23 control subjects participated in the study. Both memory control and memory monitoring were assessed using study time allocation and Judgments Of Learning (JOL), respectively. Patients used the same strategies as normal participants with respect to difficulty, and they spent more time to learn the difficult than the easy pairs. However, their learning strategy was less adapted and their memory performance was worse. In the meantime, Their Judgments Of Learning about their future performances in an eventual cued recall task, expressed question by question, remained sensitive to the difficulty of the material. The patients' JOL did not differ from the controls for the easy items, but they were lower for the difficult items, for both the eventual correct and the incorrect recalls. Moreover, the global patients' predictive accuracy of their JOLs (the Gamma correlation) was accurate and not different from the controls. This reveals that in some circumstances, even if their cognitive behavior and awareness differs in some respects from healthy subjects, schizophrenia patients may display intact ability to take into account the intrinsic characteristics of the to-be-learned material to adapt their learning strategies so as to improve performance, and may have a relatively preserved awareness of their own efficiency in a learning task.

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ID: 553883

INVESTIGATING THOUGHT DISORDER IN SCHIZOPHRENIA: EVIDENCE FOR PATHOLOGICAL SPREADING OF ACTIVATION

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Background: Previous research has yielded evidence for enhanced semantic priming in formal thought-disordered schizophrenia patients, a result that fits well with the hypothesis of disinhibited processes of spreading activation in this population. Methods: The present study tested this hypothesis by using semantic and identical priming in two different experiments and manipulating the SOA (Stimulus Onset Asynchrony, 240ms vs. 740ms) within block. Assuming that performance in this paradigm relies on a balance between activation and inhibition processes in healthy participants, we compared formal thought-disordered schizophrenia patients, $n = 33$ non-thought disordered schizophrenia patients, $n = 35$ and healthy controls $n = 34$. Results: For thought-disordered schizophrenia patients, we found a large positive semantic and identical priming effect (129 ms and 154 ms respectively) only in short SOA. SOA and type of priming did not modulate the priming effects in the control groups. Conclusions: This result yields further evidence for the lack of inhibitory processes in thought-disordered patients. Hyper priming in the Thought Disorder group may be an outcome

of withdrawing of activation from the initially activated prime stimuli after a short time.
ID: 552006

DO CURRENT PRECLINICAL MODELS ACCURATELY ASSESS THE CONSTRUCTS OF CONTROL OF ATTENTION AND RULE GENERATION AND SELECTION IDENTIFIED BY CNTRICS?

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The need for comparable animal models was an important consideration to CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) during the identification and development of the cognitive systems and tasks to be used to drive the discovery of novel treatments cognitive impairment associated with for impaired cognition in schizophrenia. In order to determine if animal models are indeed comparable to those tasks being used and/or developed by CNTRICS it is essential to understand the relationship between the underlying cognitive constructs of the preclinical and clinical tasks. Similar to what has been done for the tests used in humans, the animal models need to be individually deconstructed and the underlying cognitive constructs be compared with the higher cognitive functions delineated by CENTRICS to determine the degree of congruence. This presentation will focus on constructs established by CNTRICS for attention and executive control addressing specifically control of attention and rule generation and selection. There are a variety of preclinical models used to study attention and executive function/control in rodents and this presentation will include the Sarter Sustained Attention Task, the 5-choice serial reaction time test and the attention set-shift (ID/ED) test. Our own data from these tasks along with literature data will be used deconstruct these tasks to identify similarities and critical differences between these preclinical tasks and between tasks identified by CNTRICS for assessing control of attention and rule generation and selection.
ID: 551976

19. 19. Clinical Neuropsychology

RELATIONSHIP OF COGNITIVE TRAINING ACHIEVEMENT TO NEUROCOGNITIVE IMPROVEMENT IN SCHIZOPHRENIA

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Cognitive training has been shown to improve neurocognition in a number of studies using a variety of training methods. Neurocognitive Enhancement Therapy (NET) has been found to improve working memory and executive function in two published RCT's. It is a "bottom-up" approach that relies on intensive practice and a hierarchy of training tasks. In the RCT's it was imbedded in a rehabilitation program that included skills groups and work activity. The current study attempted to determine the link between achievement in the cognitive training and neuropsychological outcomes in order to isolate the effects of the cognitive training and to directly associate cognitive performance during training to improvements in neurocognition. Method: 72 stable outpatients with schizophrenia or schizoaffective disorder recruited from an urban CMHC were randomly assigned to a 12 month vocational program (VOC, $n = 34$) or NET + VOC ($n = 38$). NET included 26 computer-based cognitive training exercises, a social skills group and a work feedback group. Participants completed a comprehensive neuropsychological test battery before and after treatment. Subjects either graduated from a task (met a criterion of performance), reached a plateau and moved to another task, or never attempted the task. Number of graduations was used as the sole measure of achievement and entered as a mediator to explain previously reported differences between conditions in a MANCOVA of working memory tasks and a MANCOVA of executive function tasks. Results: The mean number of graduations was 8.66 (sd = 7.7) and the median was 8 with a range of 0 to 26. A significant difference on Working Memory was found for condition ($F = 3.16$, $P < .05$) with NET+VOC showing greater improvement over 12 months than VOC only. However, when Total Graduations was used as a mediator, there was no longer a difference between condition ($F = .383$, $P < .68$). Similarly, conditions differed significantly on improvement in Executive Function ($F = 3.49$, $P < .02$) with NET+VOC showing greater improvement than VOC only. When Total Graduations was used as a mediator, the difference was no longer significant ($F = 2.45$, $P < .07$). Conclusions: Findings support the direct contribution that achievement in cognitive training makes to improving neurocognitive outcomes. It suggests that whatever other non-specific features may be involved, mastering cognitive tasks in NET has meaningful cognitive benefits.
ID: 538046

THE NEGATIVE SUBSYMPTOM APATHY AND ITS RELATION TO EXECUTIVE FUNCTIONING IN FIRST EPISODE PSYCHOSIS

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Background: Investigation of the relationship between the different negative sub symptoms and neurocognition is one approach in the effort to understand more of the underlying nature of the negative symptom complex in psychosis. Apathy, one of the negative sub symptoms, is also common in other brain disorders such as Alzheimer- and Parkinson disease, where the association with neurocognition is well studied. Here apathy has been found to be repeatedly associated with executive dysfunction. The only study of apathy and its relationship to neurocognitive function in patients with psychosis also found the same specific relationship, but the study was of small sample size and in a chronic patient population. Objective: The aim of the present study was to investigate the association between apathy and neurocognitive functioning in patients with first episode psychosis (FEP) and compare this with a group of healthy controls (HC). Material and Method Seventy-one FEP patients and 62 HC were assessed with an extensive neuropsychological test battery. Level of apathy was assessed with the abridged Apathy Evaluation Scale (AES-C-Apathy). Results: The FEP patients were significantly more apathetic than the HC (mean 27.2 (SD +6.8) vs. 18.0 (SD +4.4); $t = −9.04$; $P < .01$). The FEP group performed worse than HC on all neuropsychological tests, with an effect size ranging from moderate to large. For FEP; apathy was only found to be significantly correlated with Semantic fluency ($r = .37$, $P < .01$), Phonetic fluency ($r = .25$, $P < .05$) and Letter Number Span ($r = .26$, $P = < .05$); the first two are verbal fluency tests and represent the initiation part of executive functioning, whereas the latter test represent working memory, another aspect of executive functioning. Confounding variables such as co-occuring depression, positive symptoms or use of antipsychotic medication did not significantly influence the results. For the HC there was a trend toward a statistical significant relationship only between Semantic fluency ($r = .18$, $P = .16$) and apathy, and no other neuropsychological tests. Conclusion: Apathy in FEP was found to have the same relationship to executive functioning, and specifically Semantic fluency, as that reported in patients with other brain disorders. This points to a common underlying nature of apathy across disorders that can add to the understanding of the puzzle of the underlying nature of the negative symptom complex.
ID: 550767

DOES MORNING CORTISOL INFLUENCE COGNITIVE FUNCTION IN FIRST EPISODE PSYCHOSIS?

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Background: Hyperactivity of the HPA axis can be found in a variety of psychiatric disorders, including first episode psychosis. High level of morning cortisol indicates a stable long-lasting HPA axis hyperactivity. Furthermore, general cognitive decline, executive and memory abnormalities have been observed in animals given glucocorticoids and in stress related disorders. Method: We recruited 15 patients with first episode psychosis and 21 controls as part of the Genetic and Psychosis study carried out in South London. Patients and controls underwent neuropsychological assessment to measure general cognitive performance from WAIS-III (Information, Block Design, Digit Symbol Coding and Matrix Reasoning) executive function from the Trails (Trail A and Trail B) and immediate and delayed memory from WMS-III (Logical Memory and Visual Reproduction). Salivary cortisol was collected on two consecutive days, just after awakening. The saliva was centrifuged at 3000 rev/min for 5 minutes and frozen at $−20°C$. The patients and controls were divided in two groups based on the cortisol median of the controls (9.40 nmol/l). 8 patients and 10 controls were in low range cortisol group and 7 patients and 11 controls were in the high range cortisol group. Results: The mean age of the patient group was $28 ± 8$ yrs,

and 35% of these subjects were females. The mean age of the controls was of 27 ± 5 yrs, and 28% of these subjects were females. For all tests presented the patients scored significantly worse than the controls ($P < .05$). For executive and memory tasks patients with high cortisol did worse than the patients with low cortisol, while the opposite or no effect was found in the controls. Specifically, the P values for the statistical interaction, covariate for age, were: Trail A, $P = .005$; Trail B, $P = .014$; Logical Memory Delayed Recall, $P = .020$; Logical Memory Immediate Thematic Score, $P = .020$; Logical Memory Delayed Thematic Score, $P = .031$; Visual Reproduction Percentage Retention, $P = .005$; Visual Reproduction Immediate Recall, $P = .046$; and Visual Reproduction Delayed Recall, $P = .010$. No effect of stress was found for general cognition from the WAIS-III. Conclusions: The present data show that patients with first episode psychosis may be particular vulnerable to an increased HPA axis, shown by significant stress effect on performance on executive tasks, such the Trails and immediate and delayed memory from WMS-III Logical Memory and Visual Reproduction.
ID: 550735

A DATA-DRIVEN METHOD TO ILLUSTRATE MECHANISMS UNDERLYING VERBAL RECALL AND ITS APPLICATION TO SCHIZOPHRENIA RESEARCH

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The California Verbal Learning Test (CVLT) is a widely used neuropsychological tool for evaluating verbal memory recall strategies. A list of 16 words comprised of four semantic categories is presented orally and freely recalled. Performance metrics include number of words recalled in the initial trial and final trial, improvement between the initial and final trials, and overall recall in all five trials. In general people who recall the most words employ a semantic clustering technique, whereas those with poor recall tend to rely on serial techniques. Limitations to previous analysis approaches include the rigidity of the predetermined serial and semantic divisions and the assumption that the two strategies have an inverse relationship. In order to be agnostic about the possible orthogonalization of recall mechanisms and strategies, we adopted a data-driven approach of computing transition probabilities (the probability that one item on a list will follow another during recall) across all learning trials as a function of word presentation order and recall. Out of approximately 450 patients with schizophrenia and 700 healthy unrelated volunteers, we selected the 50 highest and 50 lowest performers in each group and applied the probability measures. Performance was defined as total words recalled over the 5 trials in the CVLT. Parsing CVLT with respect to learning trial revealed that strategies interact and change over time, with serial-based strategy the first step for high and low performers. The high performing healthy volunteers utilized serial strategies in trial one, but adopted semantic strategies for the remaining trials. The pattern of healthy low performers did not change across trials, suggesting that it is the combination of strategies more than use of a semantic strategy that leads to good performance in verbal recall. High performing patients changed strategies after relying on serial order in trial one, while low performing patients recalled only the words for which they employed serial strategies. This agnostic approach may aid in examination of verbal memory recall strategy in people suffering from memory disorders and may be especially useful in patients with schizophrenia for whom episodic memory deficits are a hallmark feature. Greater knowledge of how cognitive deficits and strategy choice interact may help identify the neural mechanisms underlying these specific strategies.
ID: 550732

COGNITIVE DYSFUNCTION IN EARLY PSYCHOSIS OF SCHIZOPHRENIA, BIPOLAR DISORDER, AND PSYCHOTIC DEPRESSION BEFORE AND AFTER ANTIPSYCHOTIC TREATMENT

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Neuropsychological dysfunction is associated with affective and nonaffective psychosis, but the potential for distinct profiles of cognitive dysfunction and differential rates of improvement with treatment are not well studied. This study was designed to compare the severity and profile of cognitive dysfunction in first episode affective and nonaffective psychotic disorder patients before and after antipsychotic treatment. Untreated first-episode psychotic patients (30 schizophrenia, 22 bipolar with psychosis, and 21 psychotic depression) completed tests of reasoning and flexibility, attention, verbal memory, face memory, working memory, and processing speed. Patients completing 6-weeks of antipsychotic treatment were retested at that time. A group of healthy individuals ($n = 41$) matched on age, education, and parental SES were studied in parallel. At baseline, schizophrenia patients displayed significant deficits relative to controls in all cognitive domains. The two psychotic affective groups were also impaired overall relative to controls, but generally performed intermediate between the schizophrenia patients and controls. There was no difference in the profile of neuropsychological deficits across the three psychotic patient groups. Following 6-weeks of treatment, no patient group improved more than practice effects seen in healthy individuals, and improvement in the affective psychosis groups was no greater than that observed in schizophrenia. These findings with first episode psychosis patients document generalized neuropsychological deficits in psychotic affective disorders that were similar in profile but less severe than the deficits observed in schizophrenia. Recovery of cognitive function after clinical stabilization was no greater in mood disorder patients than in schizophrenia, suggesting that, as in schizophrenia, neuropsychological deficits may be trait-like deficits with persistent functional implications.
ID: 550687

ABNORMAL MODULATION OF PROSODY PRODUCTION IN SCHIZOPHRENIA

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Abnormal perception of prosody has been shown reliably in schizophrenia patients but the production of prosodic speech in schizophrenia has not been extensively studied. Production of appropriate prosody in speech is central to effective verbal communication and social interactions. Emotional prosody in speech can be evaluated by examining the range of fundamental frequency (Fo), which corresponds to pitch. The goal of this study was to investigate prosody regulation during a structured interview in individuals with schizophrenia and healthy controls. All participants were interviewed with the same set of neutral and emotional questions. The interviews were recorded and digitized for acoustic analyses using Praat software. Minimum and maximum Fo were extracted from two neutral and two emotional speech samples to derive pitch ranges. Results indicate that there was no significant difference between the two groups in the minimum Fo but schizophrenic patients have significantly reduced range of pitch compared with healthy participants. Moreover there was an

interaction between diagnosis and pitch range such that healthy participants, but not schizophrenic patients, increased range during emotional speech compared with neutral speech. Thus, healthy participants modulate their tone of voice appropriately in affective context. In contrast, schizophrenia patients seem unable to connect the content of their speech (semantics) with prosody. Negative symptoms score was inversely correlated with pitch range in the patients. These results suggest that in addition to prosody perception, prosody production is also impaired in schizophrenia and this deficit is associated with negative symptoms. Impairment in prosody production may be due to deficits in emotion expression. On the other hand, it is also possible that difficulties in modulating the tone of voice in affective context is due to an inability to coordinate the left and the right hemisphere language systems in real time in everyday interactions. These possibilities remain to be tested.
ID: 550541

INTELLECTUAL AND COGNITIVE DYSFUNCTIONS IN CHILDREN WHO PRESENT PSYCHOTIC-LIKE EXPERIENCES AND OTHER ANTECEDENTS OF SCHIZOPHRENIA

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We have proposed that children who present psychotic-like experiences as part of a triad of antecedents of schizophrenia (including also a speech and/or motor developmental delay or abnormality, and a social, emotional, or behavioural problem) may experience elevated risk for the development of schizophrenia (Laurens et al. 2007). While only longitudinal follow-up will establish the degree to which the triad of antecedents predicts later schizophrenia, the present study examined whether children experiencing the triad also present intellectual and cognitive deficits that characterise first-episode patients with schizophrenia and "high-risk" (prodromal) youth. Questionnaire data from 5 158 children aged 9–12 years and 1 133 of their primary caregivers demonstrated that 9% of children (12% of boys, 6% of girls) present the triad of antecedents. Fifty-eight children (21 presenting the antecedent triad and 37 control children without the antecedents) subsequently completed standardised assessments of IQ (WASI), scholastic achievement (reading, spelling, numerical operations; WIAT), memory (verbal, visual, and working memory; WRAML2) and executive function (verbal fluency, and inhibition; D-KEFS). Children presenting the antecedent triad experienced moderate deficits in cognitive function (mean effect size −0.65, range −0.56 to −0.77) relative to control children, with significant performance decrements observed in all domains (excepting a non-significant trend in visual memory performance). Children who present antecedents of schizophrenia demonstrate moderate intellectual and cognitive impairments that are comparable to those observed in prodromal youth (mean effect size ~0.8), but less marked than deficits apparent in first-episode patients (mean effect sizes ~1.1–1.8). Children experiencing the antecedents of schizophrenia might represent a "high-risk" population who may benefit from preventive interventions for schizophrenia. Acknowledgements: NIHR Career Development Fellowship, NARSAD Young Investigator Award, BMA Margaret Temple Award, BIAL Foundation.

Reference
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A VERBAL MEMORY-BASED APPROACH TO REDUCING THE HETEROGENEITY OF SCHIZOPHRENIA

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Schizophrenia is a heterogeneous condition involving widespread variability in symptoms, neurocognitive function, and functional outcome. It has been argued that verbal memory performance is a valuable dimension along which to organize patients. Verbal memory impairment constitutes a significant cognitive defect in many, but not all, patients with the illness. Research has shown that patients with verbal memory impairment experience more psychotic symptoms and a poorer quality of life than unimpaired patients. However, a major limitation of this research is that it does not address the question of whether verbal memory impairment reflects a broadly based impairment or whether it occurs disproportionately to other cognitive impairments. Accordingly, this study aimed to: 1) identify patients with specific verbal memory impairment that is disproportionate to their general cognitive abilities, and 2) assess the cognitive, clinical and functional status profiles of this specifically impaired group. The California Verbal Learning Test (CVLT-II) provided an index of verbal memory acquisition, whereas the Wechsler Adult Intelligence Scale (WAIS-III) Vocabulary subtest provided an estimate of general verbal abilities. Disproportionate impairment was defined as a Z-score CVLT-WAIS differential of at least 1.0. On the basis of these two measures, patients were partitioned into three groups: patients with a verbal memory impairment that is disproportionate to their general verbal abilities, patients with a verbal memory impairment that is proportionate to their general verbal abilities, and patients with intact verbal memory and average verbal cognitive abilities. Demographic, clinical, cognitive, and functional data were obtained from 157 patients with schizophrenia or schizoaffective disorder and from 74 healthy adults. Results show that when general verbal abilities are held constant, the clinical and functional profiles of memory-impaired patients are indistinguishable from their memory-unimpaired counterparts. Although specific verbal memory impairment distinguishes a subgroup of patients with schizophrenia, they do not have distinct clinical or functional profiles when compared to other patients. These findings suggest that key indicators of clinical severity and functional status are premorbid, illness-resistant abilities; and thus have implications for the development of treatments aimed at improving functional outcome via cognitively-enhancing medications.
ID: 550484

COGNITIVE CONTROL DEFICITS IN PRODROMAL PSYCHOSIS

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Although impairment in cognition related to DLPFC functioning is consistently documented in schizophrenia, it remains unclear how such frontally-mediated deficits in cognitive control manifest during the developmental period prior to psychosis onset. This study investigates the profile of performance on a measure of cognitive control in individuals identified as ultra-high-risk (UHR) for psychosis, first-episode schizophrenia individuals, and demographically matched controls. It was hypothesized that UHR individuals would show impairment in accuracy on the AX-CPT, a computerized measure of cognitive control, that is intermediate between healthy control (HC) and first episode (FE) participants. Specifically, it was predicted that UHR and FE participants would demonstrate a pattern of impaired context processing, as indicated by increased rates of BX errors relative to AY errors. Eighteen UHR, 22 FE, and 22 HC

participants were identified from referrals to the UC Davis Early Detection and Preventive Treatment (EDAPT) clinic, using the Structured Interview for Prodromal Syndromes (SIPS) and Structured Clinical Interview for DSM-IV (SCID-I/P). Participants completed a cognitive test battery including the AX-CPT. While no differences in accuracy were observed across groups on the AY condition, UHR and FE participants demonstrated equivalent impairment in accuracy on BX trials when compared to controls, suggesting that both groups demonstrate a generalized deficit in cognitive control. Consistent with previous findings in UHR samples, current results suggest that UHR individuals show deficits in sustained attention and response inhibition when compared to demographically matched controls, in a manner that is similar to individuals in the first episode of schizophrenia.
ID: 550477

SIMULATING FUTURE EVENTS IN PSYCHOSIS

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Mental simulation is an effective means of predicting events and planning future behaviour. The ability to generate detailed simulations of future events facilitates effective coping. Simulation is also likely to utilise executive functioning, which is a neuropsychological domain known to be impaired in psychosis. We sought to firstly establish the integrity of simulation processes in psychosis, secondly to establish how simulation was affected by a threat theme and thirdly to determine how the ability to simulate future events might relate to other established measures of reasoning. There were two groups of participants: people with psychosis ($N = 21$) and healthy comparison participants ($N = 21$). All participants completed a simulation task, which required participants to give a step-by-step account of how various scenarios might come about. The scenarios either had threat or neutral themes. Following simulation, participants rated each scenario on how likely and worrying it appeared. Analysis included independent ratings of the quality of the responses, yielding a goodness of simulation (GOS) score. In addition, a cognitive measure of data gathering and a self-rated measure of thinking style were applied. People with psychosis showed lower GOS overall, less data gathering and reduced self-rated rational thinking. GOS scores were also lower in threat themed scenarios—an effect that was equivalent in both groups. In addition, GOS was negatively correlated with worry about the threat themed scenarios. Furthermore, in both groups GOS scores were positively associated with both data gathering and a rational thinking style. These data indicate that the simulation task can be used to successfully index simulation processes in psychosis. More specifically, it suggests that improved simulation of threatening events promotes successful coping, as higher quality simulations of threat scenarios were associated with less worry. Taken together, these findings suggest that simulation might provide a useful way of understanding how basic cognitive processes relate to functional measures of outcome in psychosis.
ID: 550433

ATTENTIONAL SET-SHIFTING ABILITY AND REVERSAL LEARNING OVER THE FIRST THREE YEARS OF PSYCHOTIC ILLNESS: CHANGES OVER TIME AND RELATIONSHIP WITH IQ AND CLINICAL MEASURES

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The Intradimensional/Extradimensional (ID/ED) task offers a differentiated assessment of the processes involved in the Wisconsin Card Sort Task. Studies of patients with schizophrenia have consistently revealed deficits at the set-shifting, extra-dimensional shift (EDS) stage with some also reporting difficulties at earlier stages. Cross sectional studies examining length of illness and a one-year follow up study additionally suggest that performance on this task may deteriorate over the course of illness. Two-hundred and sixty-two first-episode psychosis patients and 76 healthy controls, matched for age and premorbid IQ, were assessed using the ID/ED task and the Wechsler Adult Intelligence Scale. Significantly more patients failed at the EDS stage suggesting that shifting attention from a previously reinforced dimension presented the greatest difficulty. However, patients additionally made more errors prior to successful rule acquisition at all stages indicative of more subtle difficulties in rule acquisition and reversal learning. As passing the EDS stage predicted WAIS IQ, a subgroup of patients and controls with equivalent current IQ were compared. The difference in pass rate was no longer significant but patients showed selectively greater errors at all reversal stages indicating that, whereas set shifting is inextricably linked with IQ, inhibition of a prepotent response may be independent. Further, errors on reversal learning were correlated with disorganisation symptoms, particularly positive formal thought disorder. A subset of 104 patients and 25 controls were followed up on two further occasions over three years and a small improvement was observed in patients by third assessment, although they continued to substantially underperform compared to controls. There was consistency in terms of passing the test over the three assessments, with passing the previous assessment predicting passing the next. Examining the three-year follow-up data, significantly more patients who failed at the EDS stage had residual negative symptoms. In conclusion, rule acquisition, set shifting and reversal learning are impaired from first presentation to services in patients with psychosis. However, contrary to what has been previously suggested, we did not find evidence of further deterioration over the first three years of illness.
ID: 550378

GENDER DIFFERENCES IN NEUROPSYCHOLOGICAL PERFORMANCE IN PATIENTS WITH FIRST EPISODE OF PSYCHOSIS

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Although there are several studies examining neuropsychological performance in first episode of psychosis, the issue of gender differences in neurocognitive function among psychotic patients has been addressed by few studies, and the results are inconsistent. We examined gender differences in neuropsychological performance in an epidemiological sample of first episode psychosis patients: schizophrenia (M = 42, F = 23), bipolar/manic (M = 15, F = 22), and depressive psychosis (M = 16, F = 23), and compared performance with a representative sample of healthy

controls (M = 77, F = 98). Data was collected on 18 neuropsychological measures assessing six cognitive domains: (1) memory (verbal and visual), (2) WAIS-R academic verbal abilities, (3) attention, concentration and mental speed, (4) executive functions and working memory, (5) language, and (6) visual constructual/perceptual abilities. Premorbid intelligence (NART), current full-scale IQ, performance IQ and verbal IQ were also assessed. There was strong evidence for disorder-specific gender differences in neuropsychological functioning. In the schizophrenia group, women performed better than men on the majority of neuropsychological measures. By contrast, women with psychotic depressive disorder performed worse than men. Differences in neuropsychological performance between men and women with bipolar/manic disorder were restricted to verbal memory and language. In our epidemiological study, gender appeared to modify the characteristics of cognitive impairment of patients with first episode psychosis.
ID: 550321

AWARENESS OF NEURO-COGNITIVE ABILITY IN PEOPLE WITH SCHIZOPHRENIA VERSUS HEALTHY CONTROLS

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Objective: The objective of this study was to compare self-report of cognitive deficit in neuropsychologically impaired schizophrenia patients with self report of cognitive deficit in normal controls who do not have neuropsychological deficit. Method: Seventy-one patients with schizophrenia were administered the MIC-SR along with the PANSS, BACS, and ILS. The MIC-SR is a scale that measures self reported frequencies of cognitive problems in everyday life. Forty-six healthy controls were also administered the MIC-SR as well as a cognitive battery. All healthy controls obtained z scores above −1.35 on neuropsychological measures and therefore were considered cognitively intact. Results: Patients with schizophrenia reported significantly more cognitive problems as occurring "Almost Daily" than did healthy controls. Subsequent analysis showed that those schizophrenia patients who evidenced more depression, but not those with more objective neuropsychological deficit, were more likely to endorse cognitive problems as occurring "Almost Daily". All the schizophrenia patients had cognitive impairment yet they were most likely to respond that a cognitive problem "Never" occurred, whereas the healthy controls who were not cognitively impaired most often responded that they experienced cognitive problems "Once a Week or Less." Schizophrenia patients who reported that cognitive problems "Never" occurred had less depression, but not less objective neuropsychological performance than other schizophrenia patients. About one quarter of the cognitively impaired patients with schizophrenia showed no awareness of cognitive deficit on the MIC-SR. The Total Score on the MIC-SR did not prove useful in differentiating healthy controls from patients. Conclusions: These findings suggest that clinicians must use self report judiciously as an indicator of actual cognitive impairment. Many cognitively impaired schizophrenia patients reported having no cognitive problems, and as a group they reported having no more cognitive problems than did the cognitively intact healthy controls. However, the response patterns of schizophrenia patients and healthy controls differed significantly. The MIC-SR captures a range of awareness of cognitive difficulty in schizophrenia patients, and those with depression were most likely to report cognitive problems. The data indicates that many patients would benefit from psycho-education about the impact of schizophrenia on neuro-cognition.
ID: 550299

THE ROLE OF IMPULSIVITY IN SUICIDAL AND NON-SUICIDAL SELF-HARM AMONG PEOPLE WITH SCHIZOPHRENIA

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High rates of self-harm, including suicide are well known to be associated with schizophrenia. Previous research has identified trait impulsivity, such as that measured by the Barrat Impulsivity Scale (BIS-11) as being linked to self-harm in a range of psychiatric disorders. In addition, raised levels of cognitive-motor impulsivity, such as measured with the Go/No-Go reaction time task appear to be linked to past self-harm. We wished to examine the association of both trait and cognitive-motor impulsivity to past self-harm behaviour among people with schizophrenia. We hypothesized that impulsivity, measured either as a trait or as cognitive-motor performance, would be related to self-report of past suicidal and non-suicidal self-harm behaviour. To test these hypotheses, a sample of 88 patients with a DSMIV diagnosis of schizophrenia was recruited. The mean age of the sample was 39.8 (SD = 11.4, range 18–63) and 74 (84%) were male. Patients were asked to complete the self-report BIS-11 and the Deliberate Self-harm Inventory, which assesses lifetime frequency of a range of self-injurious, but non-suicidal behaviours. In addition, details of the lifetime history of suicide attempts were recorded. The patients also performed a computerized Go/No-Go task to asses cognitive-motor impulsivity. The sample were divided into groups on the presence or absence of past self-harm to compare levels of trait and cognitive motor impulsivity using independent groups t-tests. Forty seven of the 88 patients (53.4%) reported at least one suicide attempt in the past, and 41 (46.6%) reported at least one occasion when they had deliberately self-harmed without suicidal intent. Comparing patients with or without an attempted suicide history, there was a trend for higher trait impulsivity scores in the attempted suicide group, though this did not reach significance ($P = .058$). There was no relationship between impulsive errors on the Go/No-Go task ($P = .58$) between the two groups. However, those with a history of non-suicidal self-harm produced significantly more impulsive errors on the Go/No-Go task ($P = .018$) and reported significantly higher trait impulsivity scores on the BIS-11 ($P = .001$), than those without a non-suicidal self-harm history. Our findings provide evidence to support the conclusion that impulsivity in schizophrenia is primarily a risk for self-harm behaviour which is not motivated by intent to die.
ID: 550255

SELF MONITORING DEFICITS AND AUDITORY VERBAL HALLUCINATIONS: IS THERE ANY EVIDENCE?

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A range of psychological theories have been proposed to account for the experience of auditory hallucinations in patients with psychosis One of the most influential cognitive models proposes that auditory verbal hallucinations (AVH) result from an impairment in the ability to monitor one's own inner speech leading to the misidentification of verbal thoughts or memories as alien voices. However, data from tasks used to examine verbal self monitoring (VSM) has provided mixed results. Evidence from studies of patients with schizophrenia, individuals in the prodromal phase of the illness and non-clinical will de presented and discussed. Overall the available data suggest that cognitive impairments other than self-monitoring, such as difficulties with appraising degraded stimuli may contributed to the observed

misidentification bias. The specificity of such a bias to AVH is also questionable as most studies report that patients with delusions tend to make external misidentification errors when listening to their own distorted speech.
ID: 550253

SUICIDE ATTEMPTS AND NEUROCOGNITIVE FUNCTIONING IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Studies of the relationship between schizophrenia, suicidality and neurocognition are few and have yielded inconsistent results. This study aimed to investigate whether patients with schizophrenia spectrum disorder who had attempted suicide showed better general neurocognitive functioning, better executive functioning and were more impulsive compared to non-attempters. The study included 174 patients, 58% men, mean age 32 years (SD = 10). Diagnoses were set according to SCID-I for DSM-IV (79% schizophrenia, 15% schizoaffective disorder and 6% schizophreniform disorder). Patients were classified as suicide-attempters (31%) if they reported one or more suicide attempts. Age at illness onset, duration of illness, number of psychotic- and depressive episodes, use of medication, years of education, and drug- and alcohol use the last 6 months was recorded. The Positive and Negative syndrome scale (PANSS) was used to rate psychotic symptoms and depression. Premorbid functioning was assessed with the Premorbid Adjustment Scale (PAS). The neurocognitive test battery comprised measures of motor functioning (Grooved Pegboard), psychomotoric tempo (Digit Symbol), attention (Digit Span), verbal memory (CVLT-II), and intelligence (WASI). Executive functioning and impulsivity was measured by subtests from the D-KEFS. There were no statistically significant differences between suicide attempters and non-attempters on neurocognitive variables. Significantly more suicide attempters were found amongst female patients (42%) compared to male patients (22%) ($P = .008$, χ^2), and amongst patients with schizoaffective disorder (54%) compared to the patients with schizophrenia/schizophreniform disorder (26%) ($P = .01$, χ^2). Suicide attempters had significantly lower age at illness onset ($P = .032$), more depressive episodes ($P < .000$) (both Mann-Whitney U Test), longer duration of illness ($P = .014$, Independent-Samples T-Test), and had a significantly smaller decline in premorbid social functioning ($P = .011$, Independent-Samples T-Test). A series of multiple hierarchical regression analyses showed no confounding effects of clinical and demographical variables. There were no differences in general neurocognitive functioning, executive functioning or impulsivity between suicide-attempters and non-attempters with schizophrenia spectrum disorders.
ID: 550228

COGNITIVE IMPAIRMENT IN DUAL DIAGNOSIS: THE ADDITIVE EFFECT OF ALCOHOLISM AND SCHIZOPHRENIA

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Patients with dual diagnosis constitute one of the biggest challenges faced by mental health services. Their 'revolving-door' pattern of service use and poor clinical outcomes incur a considerable economic burden. Cognitive impairment is common among patients with schizophrenia and patients with alcohol use disorders. Outcomes may therefore be further compromised if cognitive impairment is compounded by the co-occurrence of the two disorders. However, little is known about the severity and nature of cognitive impairment and the possible 'additive effect' among patients with both disorders. A detailed neuropsychological battery including tests of pre-morbid, current IQ, motor speed, attention, verbal and visual memory and executive functioning was administered to 30 inpatients with schizophrenia and 30 inpatients with schizophrenia and alcohol use disorder. The mean age was 36.4 (± 8.5) years and participants averaged 11.5 years education. Patient population profiles of cognitive impairment were examined using Z-scores based on the performance of 30 matched controls. Both clinical populations exhibited generalised impairment across the battery. Greater impairment was observed on almost all measures among the dually diagnosed, with significant differences in mental flexibility (working memory and cognitive set-shifting), delayed verbal memory and planning (all $P < .01$). Logistic regression with diagnosis (schizophrenia or dual diagnosis) as the dependent variable, and executive functioning score, memory score, pre-morbid IQ, age of onset of schizophrenia, and severity of psychiatric symptoms (HADS and BPRS) as co-variates revealed the finding that executive functioning and psychiatric severity (BPRS) were the best predictors of dual diagnosis status ($\chi = 11.0$, $P < .01$). The current findings provide support for an 'additive effect' of the two disorders on cognitive impairment. The implication of this finding is that greater (positive) symptom severity and cognitive deficits may affect response to treatment and subsequent outcomes. Patients may benefit from learning compensatory techniques or from CRT as executive deficits may increase risk of relapse. An understanding of the cognitive profiles of the dually diagnosed can inform the adaptation of treatment delivery. Psychological interventions can then be tailored to enhance cognitive strengths, accommodate deficits, promote further recovery and ultimately improve clinical outcome.
ID: 550197

DISTURBANCES IN OBSERVABLE BEHAVIOURS IN PATIENTS WITH FIRST-RANK (PASSIVITY) SYMPTOMS

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First-rank (passivity) symptoms (FRS) refer to experiences where there is a subjective disturbance in the voluntary control of actions and mental acts. Theoretical models propose that FRS result from deficits in internal motor representations and from a failure in representing the self. One question that arises is whether these cognitive disturbances are associated with impairments in observable behaviours linked to interactive and communicative skills. In this study, we examined the relationship between FRS and observable behaviours in a large sample of patients with first-episode psychosis. We also examined the stability of this performance after 2-years. A secondary aim of the study was to observe the course of symptom profiles relating to FRS over a 2-year period. As part of the WHO study on the Determinants of Outcome of Severe Mental Disorders, a large prospective cohort of non-medicated patients with first-episode psychosis was assessed with the Psychological Impairment Rating Schedule (WHO-PIRS), a validated instrument which allows detailed recording of patients' behaviours. 227

patients, in whom the presence/absence of FRS could be evaluated with certainty, completed the PIRS. Results show that patients with FRS had significant impairments in behaviours linked to interactive and communicative skills compared to patients without these symptoms; furthermore, these impairments persisted 2 years after the initial assessment. The results also showed that the symptom profile of patients relating to FRS was remarkably stable over time. In conclusion, deficits in behavioural interactive skills were found in patients with FRS, consistent with theoretical accounts proposing that FRS represent disturbances in internal cognitive motor representations and in processes underlying self/other differentiations. The results also suggest that the presence of FRS may have enduring consequences on the quality of patients' interpersonal communications, and interactions with the social environment. These findings have implications for interventions in FRS, which need to target behavioural impairments and social skills training. Flavie Waters is recipient of an Australian National Health and Medical Research Council (NHMRC) Research Fellowship (nu 404117).
ID: 550051

SELECTIVE ENHANCEMENT OF VISUOSPATIAL IMAGERY AND ITS DISSOCIATION FROM WORKING MEMORY IN SCHIZOPHRENIA

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Working memory (WM) deficit in schizophrenia (SZ) is a fundamental characteristic of the disorder and may be a result of difficulty generating and manipulating internal representations. However, previous research has shown that SZ patients have more vivid mental imagery (MI). WM and MI both rely on generation and manipulation of internal representations. WM and MI are associated in healthy populations, but very little is known about the relationship between WM and MI in SZ. Schizophrenic (SZ), bipolar (BP), and demographically matched healthy (CO) participants performed a spatial delayed response WM task and a letter MI task. In the WM task, a target was presented briefly, and after a 10 s delay the participant selected the remembered location of the target. In the MI task, participants were asked to imagine the position of a series of block letters on a grid and decide whether a marker on the grid overlapped with the imagined letter. In the perceptual control task, the same task was performed with the letter shown on the grid. SZ were less accurate and slower compared to CO on the WM task, but they were faster than CO on the MI task. Importantly, within the MI task the RT advantage for SZ was only observed for the imagery and not for the perceptual control condition, suggesting a selective advantage for the MI component. BP and CO did not differ on the WM task, but BP were faster than CO on both the MI and the perceptual control task. Thus, BP participants showed intact WM and enhanced MI. These results indicate that the generation and manipulation of MI is intact or enhanced in SZ even though they show WM deficits. The selective MI enhancement may be unique to SZ and not characteristic of other psychiatric conditions such as BP. In SZ there is dissociation between MI and WM whereas the two cognitive processes appear to be linked in CO and BP. A comprehensive theory of WM should account for this dissociation in SZ between manipulation of internal representations required for performance on WM and MI tasks. This work was supported by MH073028.
ID: 549911

NEUROCOGNITION IN EARLY PSYCHOSIS: FROM PRODROME TO FIRST EPISODE AND BEYOND

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Background: Compromised neurocognition is a core feature of schizophrenia and well characterized. However, it is still unclear when most of the neurocognitive impairment occurs and when deterioration occurs. In order to answer this question, we carried out two meta-analyses, on premorbid IQ and on neuropsychological functioning in first episode (FE) schizophrenia and compared these with existing meta-analyses. Methods: In the meta-analysis of IQ in the premorbid phase in persons who later develop schizophrenia, we analyzed 18 studies meeting study criteria (Woodberry, Giuliano, Seidman, 2008, Am J Psychiatry). In a subsequent meta-analysis (submitted), we analyzed 43 separate samples of 2204 FE patients with a mean age of 25.3 (3.5) and 2775 largely age- and gender-matched control subjects across ten neurocognitive domains. Results: Overall, schizophrenia samples demonstrated a reliable medium-sized impairment in premorbid IQ ($d = -0.54$) in Woodberry et al. (2008). The IQ effect size in FE schizophrenia was $d = -0.91$, which was virtually comparable to that observed in Heinrichs and Zakzanis, 1998 ($d = -0.96$) in chronic schizophrenia. Moreover, the effect sizes of most neuropsychological domains were just as impaired as in chronic patients with schizophrenia with a mean effect size deficit of about 1.0. Conclusion: Substantially larger impairments in IQ at the FE compared to the premorbid period strongly suggest maximal deterioration occurs between those phases. Moreover, neuropsychological impairment, at least in group samples, suggests that impairment is roughly as severe in the first episode as in chronic phases. Further research during the premorbid, prodromal and very early stages of psychosis is required to detect when the decline specifically occurs. Research designed to categorize heterogeneity of courses is important to address which patients decline and which improve over the long term. Data linking brain structure, function and cognition is essential to understand the neural bases of neurocognitive impairment.

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ID: 549881

OLFACTORY IDENTIFICATION AND PREFERENCE IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Brain regions reported to be abnormal in schizophrenia (SZ) overlap with the neural circuits that support olfactory functioning including the orbitofrontal and entorhinal areas. Olfactory identification deficits have been reported in individuals with SZ regardless of medication status. This deficit has also been reported in healthy schizotypal individuals and relatives of individuals with schizophrenia. However, it is unclear whether the olfactory identification deficit is specific to SZ or present in psychotic disorders in general. The major aim of this study was to compare olfactory identification and preference in SZ and bipolar disorder (BPD). In addition, we examined the relationships among olfactory functioning, clinical symptoms and social functioning. Individuals with SZ or BPD and demographically matched healthy participants (CO) were given the University of Pennsylvania Smell Identification Test (UPSIT). After identifying each odor, participants were asked to indicate how much they liked or disliked the odor on a 5-point

rating scale. The severity of symptoms, social functioning and general intellectual functioning were also assessed. SZ patients made significantly more errors on the UPSIT than did CO. The error rates of BP patients were in the intermediate range between those of SZ and CO. SZ and BPD did not differ from CO on ratings of olfactory preference. Across participants there was a significant correlation between olfactory identification performance and social functioning. There were no significant correlations between clinical symptoms ratings and olfactory errors or preference scores. These results support previous evidence of an olfactory identification deficit in SZ and further provide evidence that this ability may also be impaired in BPD, although to a lesser degree. This finding suggests that olfactory identification deficit may not be specific to schizophrenia. Instead, such deficit may also be present albeit in a milder form in bipolar disorder. Regardless of diagnosis, olfactory identification deficits may be linked to a decrease in social functioning. This study was supported by the MH073028 and NARSAD.
ID: 549764

POOR INSIGHT IN PSYCHOSIS: COGNITIVE DEFICIT OR BIAS?

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Introduction: A recurrent theme in cognitive neuropsychiatry is whether psychopathological symptoms are best explained as deficits (following the neurological model) or biases (a social-psychological model). Taking lack of insight as a phenomenon which may be studied in this way, evidence for a deficit account comes from studies correlating neuropsychological impairments on standard tests with lack of insight in schizophrenia patients. An alternative view is that patients choose certain explanations over others to explain unusual experiences or their predicament. Such explanations may seem implausible or may betray the lack of acknowledgement of information—ie, they are biased—but are not evidence of a fixed disability or a limitation to cognitive processes. Methods: We conducted a meta-analysis of neuropsychological studies in relation to insight and psychosis and also conducted a number of novel cognitive studies in a group of schizophrenia patients selected on the basis of good or poor insight. These included semi-qualitative methods to explore the acceptance of traits (including those associated with mental illness) and the use of vignettes to explore attitudes to self- disclosure of evidence of mental disorder. Results: In favour of the deficit account, we showed that though there are reliable effects in relation to IQ, executive functioning and insight, effect sizes are modest. We postulated that trait acceptance would be biased towards individual judgement of the desirability of such traits but this was not found to be influential in the poor insight group. Second, using vignettes we found that self-disclosure of mental illness traits in both sets of patients was influenced by pragmatic factors and preservation of the participants 'image'. Discussion: Our results suggest that both deficits and biases may contribute to poor insight in schizophrenia and that assessment of both is necessary for a full account of psychopathology.
ID: 549753

EXECUTIVE FUNCTION AND NEGATIVE SYMPTOMS IN EARLY-ONSET SCHIZOPHRENIA-SPECTRUM DISORDERS.

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The literature on adult schizophrenia show that one of the most severe neuropsychological impairments are apparent in executive functioning, evident also on a background of a generalized cognitive deficit. This executive function deficit has in some studies been associated with more negative symptoms, adding to the risk of a poor functional outcome. Accordingly, cognitive deficits have been found prevalent in early-onset schizophrenia, but are investigated to a much lesser extent. We wanted to examine the relationship between executive functions and negative symptoms in the adolescent group. 31 adolescents (12–18 years) with schizophrenia spectrum disorders are included at the time of their first contact with the mental health service. Diagnoses are based on the DSM-IV criteria. Symptom level is assessed using the PANSS and the Global Assessment Scale. Neuropsychological functioning is assessed with the MATRICS battery, WSCT and Stroop. Eighty-three healthy adolescent controls have also been included in the study. Results show that adolescents with schizophrenia performed poorer than healthy controls on executive functioning ($P = .005$). We found, however, no significant correlation between the patients' negative symptoms and executive functioning, suggesting that executive dysfunction is more independent of negative symptomatology in early-onset schizophrenia.
ID: 549712

DIFFERENTIAL EFFECTS OF EMOTION ON EPISODIC MEMORY SYSTEMS AS A BASIS FOR MOOD CONGRUENT VS. MOOD INCONGRUENT DELUSION FORMATION

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A phenomenological distinction has been made between delusions that arise out of underlying affective disturbance (mood congruent delusions) and delusions arising in the absence of affective disturbance (mood incongruent delusions) (1). Yet the role of emotion in delusion formation and maintenance has only recently begun to be investigated. Emotional arousal may contribute to memory errors and distortions that may play a role in the formation and maintenance of delusional beliefs. We hypothesised that this would be more likely to be the case in mood congruent (MC) versus mood incongruent delusions (MI). We used the Deese-Roediger-McDermott (DRM) (2) paradigm to investigate the effect of emotional arousal on false memory formation in 24 patients with delusions (13 MI, 11 MC) and 31 healthy volunteers. Participants studied 15 DRM word lists (5 positive, 5 negative and 5 neutral) followed by an old/new recognition memory test comprising 30 presented target words, 30 non presented "lures" and 60 novel words. We calculated recognition rates and signal detection measures (discrimination d' and response bias C) The MC patient group demonstrated higher false recognition rates for negative words (lures and novel) and poorer discrimination for negative words than the MI group. There were no effects in relation to positive items. The results indicate differential effects of emotional arousal on memory errors in patients with MC versus MI delusions, in support of our hypothesis. This provides further insight into emotional memory and constructive memory processes in psychosis and is relevant for potential therapeutic approaches.

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ID: 549700

THE PROCESS OF BINDING IN SCHIZOPHRENIA: EXAMINATION OF ASSOCIATIONS WITH TEMPORAL AND SPATIAL CONTEXT IN WORKING MEMORY

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It is well established that schizophrenic (SZ) patients have difficulties in binding target information with their contextual features in order to create a unified episodic representation in memory but the nature of this deficit remains unclear. The present study proposes a systematic examination of memory for target information and its association with either spatial or temporal context in working memory. Performance of SZ patients ($n = 25$) was compared to that of matched healthy controls on a probe-recall task modified to capture both target information and associations. We observed a memory deficit in SZ patients compared with healthy controls that encompassed the capacity to remember items per se and the association with their temporal as well as spatial context. Our results confirm the patient's difficulty to bind items and locations in WM, and extend this binding deficit to the capacity to associate items to their temporal context. Consequently, the binding deficit observed in previous studies using tasks with a spatial component cannot be exclusively attributed to an impairment in dealing with spatial information.
ID: 549633

PSYCHOMETRIC PROPERTIES OF A NORWEGIAN VERSION OF THE MATRICS CONSENSUS COGNITIVE BATTERY (MCCB)

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Introduction: In the making of MCCB, tests rated high on (a) test-retest reliability, (b) utility as repeated measures, (c) sensitivity to functional outcome, and (d) tolerability and practicality, were chosen. The battery seeks to be the preferred method for assessing neurocognition in research on psychosis patients, especially when treatment issues are in question. The MCCB has recently been translated into Norwegian and is being used in several ongoing research projects, paralleling studies initiated by the Thematic Organized Psychosis (TOP) group using another set of neuropsychological tests within largely the same cognitive domains. In this paper we question reliability and validity issues of the Norwegian MCCB in comparison to the TOP battery. Method: Healthy subjects ($n = 66$, age: 35, IQ: 114) and outpatients with a psychotic spectrum disorder ($n = 20$, age: 28, IQ: 114) from the TOP study were recruited for retesting with the MCCB. The TOP battery consists of measures of speed (Grooved Pegboard, Digit Symbol, Semantic Fluency, Color-Word Interference), attention (Digit Span), learning and memory (CVLT-II, LM I and II, RCFT), reasoning and problem solving (WASI), and social function (SFS). Predefined correlations between

tests from the MCCB and the TOP batteries within the same cognitive domains were computed, and test profiles for patients and controls within each test battery were compared. Results: Correlations between a priori defined same-function tests were generally high ($r > .50$, $P < .001$) indicating high test-retest stability. Patients scored systematically below controls on each battery irrespective of using published norms or control group means as reference, indicating diagnostic validity for each battery. On one test (Animal naming) Norwegian subjects outperformed the US normative sample. Otherwise the US norms suited the Norwegian group well. Correlations and group differences were generally smaller than expected due to high IQ-level in both groups. Conclusion: The Norwegian version of the MCCB documents adequate psychometric properties. Further research is needed to confirm the conclusion also for subjects with less cognitive reserve.
ID: 549578

DECONSTRUCTING EXECUTIVE FUNCTIONS IN SCHIZOPHRENIA

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Deficits in executive functions may be among the strongest predictors of everyday functioning difficulties among people with schizophrenia. Yet, there is considerable debate over whether executive functions comprise a unitary construct or multiple constructs, and whether they are uniquely impaired above and beyond general cognitive deficits. The aim of the current study was to clarify the construct of executive functions in schizophrenia, and to examine the performances on ten executive functioning tasks as measured by the Delis-Kaplan Executive Functioning System (D-KEFS) among 81 adults with schizophrenia or schizoaffective disorder (SCs) relative to 81 demographically-matched neuropsychiatrically healthy comparison subjects (HCs). SCs, on average, had consistently worse performance than did HCs on all executive functioning tasks. Overall differences between performances on multi-level executive tasks, ie, those demanding two or more cognitive processes at the same time (eg, switching), and basic cognitive tasks (eg, motor speed) were greater among SCs than among HCs. Exploratory factor analysis of the ten D-KEFS tasks among the SCs revealed a two-factor solution, ie, abstraction and cognitive flexibility. A latent profile analysis of the D-KEFS performances among the SCs yielded three distinct executive functioning profiles, with most patients being characterized as mildly impaired or average, and about 10% being classified as high-average-to-superior. Within-group ipsative comparisons indicated that SCs in the mildly-impaired group did worse on abstraction tasks and better on switching, while those in the high average group, while generally doing better on all tasks, showed the opposite pattern of results, ie, they did relatively worse on switching tasks and better on abstraction tasks. Findings from the current study support the idea that executive functions are not a single, unitary construct in schizophrenia, but may comprise at least two distinct, but related constructs, ie, abstraction and cognitive flexibility. While in general, patients with schizophrenia did worse than demographically-matched healthy comparison subjects, similar to deficits in other cognitive domains, the presence and degree of executive functioning impairments varied considerably. Among the executive functions, abstraction seemed to be more impaired than cognitive flexibility in schizophrenia; if replicated, this distinction may be relevant to treatment planning.
ID: 549560

A 10-WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED, CROSS-OVER TRIAL OF ADJUNCTIVE MODAFINIL FOR NEUROCOGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA

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Although some open-label studies suggest that modafinil could be an effective cognitive enhancer in schizophrenia, results from controlled studies are contradictory and the scope of the cognitive domains that they assessed was limited. Therefore, the aim of the present study is to assess the effects of modafinil on neurocognition in participants suffering from a schizophrenia spectrum disorder. Twenty subjects treated with a second-generation antipsychotic and showing attentional impairments completed this 10 week double-blind, placebo-controlled cross-over study. The participants were assessed on four occasions with neuropsychological tests typically assessing information processing speed, visual selective attention, sustained attention, inhibition, cognitive flexibility, verbal and visual short term memory, as well as lexical and semantic verbal fluency. Clinical scales were also used to characterise changes on psychotic symptoms, side effects, clinical global improvement, and global functioning. Tirthy-one participants took part to the initial assessment, 28 were randomized in the two experimental conditions, and 20 out of them completed the entire assessments. In regard to the neuropsychological respects, modafinil, in comparison to the placebo, significantly improved the semantic verbal fluency, verbal short term memory, and the ability to detect visual targets among non-verbal distractors. However, modafinil increased the commission errors in a task typically used to assess sustained attention. Clinically, modafinil significantly improved subjective memory, as well as fatigue. In conclusion, modafinil do not seems to lead to specific improvements in processing speed, but rather, to facilitate response initiation in various neurocognitive domains. Furthermore, it improves some side effects which are frequently reported by patients and constitute challenge for clinicians. Therefore, modafinil remains an alternative as a potential neurocognitive enhancer in schizophrenia spectrum disorders although further neurocognitive and clinical studies are needed.
ID: 549474

PATTERNS OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA: RESULTS FROM THE MATRICS PSYCHOMETRIC AND STANDARDIZATION STUDY (PASS)

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An aim of the MATRICS initiative was to address an obstacle to drug development in the treatment of cognitive deficits in schizophrenia, namely the absence of a consensus-based measurement of cognition for clinical trials. Following a careful process of evaluation, the MATRICS Consensus Cognitive Battery (MCCB) became available in April, 2006. The MATRICS Psychometric and Standardization Study (PASS) collected data on the MCCB from 176 persons with schizophrenia or schizoaffective disorder from five participating sites (Duke University, Harvard University, University of Kansas, Maryland Psychiatric Research Center, and UCLA). To obtain norms on the MCCB, 300 community residents stratified by age, sex, and education, were tested at the same sites. This symposium will be the first to present findings on: (a) the profile pattern of patients vs. community residents on the seven neurocognitive domains assessed by the MCCB, and (b) the neurocognitive domains which best discriminate patients vs. community residents. For profile pattern, the data were analyzed using MANOVA with two groups (patients vs. community residents) and seven neurocognitive domains (attention/vigilance, working memory, verbal learning, visual learning, speed of processing, reasoning and problem-solving ability, and social cognition). Discriminant function analyses were used to evaluate how well each neurocognitive domain discriminated patients vs. community residents. Patients performed significantly worse than community residents on all seven neurocognitive domains with level of impairment ranging from 0.9 sds (reasoning and problem-solving ability) to 1.5 sds (speed of processing). The combination of speed of processing, social cognition, and verbal learning best discriminated patients from community residents, correctly classifying 74.1% of patients, 88.1% of community residents, and 83.0% of the overall sample. These findings provide support that the MCCB is sensitive at detecting patient vs. healthy adult differences across multiple domains of neurocognition.
ID: 549398

CLINICAL APPLICATIONS OF THE NEUROLOGICAL EXAMINATION IN SCHIZOPHRENIA

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Many neurologic signs are readily elicited and prevalent in schizophrenia, so they may have potential for routine clinical use. This presentation will cover research pertaining to several applications of "soft signs" in the management of schizophrenia: (1) screening for conditions causing a secondary (organic) psychosis, (2) enhancing differential diagnosis among primary (functional) psychotic disorders, (3) predicting onset and outcome, (4) selecting among treatment options; and increasing the yield of special diagnostic measures, including (5) neuroimaging and (6) neuropsychological testing. Some of these applications (screening for relevant neuropathology, selecting among treatment options, and clinically relevant relationships with neuroimaging) have received very little direct investigation in schizophrenia. Results in other areas are inconsistent, probably due to differences in item selection, differences in the ways that individual neurological signs are grouped for statistical analysis, differences among groups in the administration of these tests and rating of performance, and inter-rater reliability. These issues of methodology will also be reviewed.
ID: 549121

AGE AND GENDER EFFECTS ON SCHIZOTYPY AND COGNITIVE FUNCTION

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Deficits in neurocognition are one of the hallmarks of schizophrenia, a finding present prior to the onset of illness, in those with psychosis and psychosis prone individuals. Initial symptoms of psychotic disorders emerge during adolescence when adult levels of neurocognition come online. Investigating neurocognition and psychosis proneness at different stages of development may help to determine which cognitive alterations are indicative of the emergence of symptoms. Adolescents and young adults in the age range 16–25 took part in an online survey where they completed the SPQ (Raine, 1991) and three cognitive tasks examining spatial working memory, sustained attention and spatial cognition. From an initial sample of 1178 participants, 98 were invited back for follow up questionnaires and a battery of cognitive tasks measuring executive function, verbal fluency, working memory, attention and IQ. In the initial sample, age was associated with a decline in levels of schizotypy in females only ($P < .001$). Cognitive performance was influenced in an age and gender dependent manner. High levels of negative schizotypy were associated with impaired performance on the spatial working memory task in young females only ($P < .05$). Higher levels of positive schizotypy were associated with impaired performance on the sustained attention task in older males only ($P < .05$). Preliminary analysis of the sub-sample of 98 participants indicates high levels of schizotypy were associated with cognitive biases in a variety of other domains. During the critical risk period of late adolescence and early adulthood, levels of schizotypy decrease in females only. Gender differences are also noted in the relationship between schizotypy and neurocognitive performance. These findings may be indicative of different developmental trajectories in males and females. The results may also raise issues with the measurement of schizotypy in younger samples, as well as the inclusion of mixed samples which are used extensively in the literature. Further testing on a subset of participants is being carried out to investigate other effects of schizotypy on cognition in the age range 16–25.

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ID: 549043

HOW TO ENHANCE INTRINSIC MOTIVATION WITHIN THE SETTING OF A COGNITIVE REMEDIATION PROGRAM

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Amotivation is a telling hallmark of negative symptomatology and it impacts nearly every facet of behavior, including inclination to attempt the difficult cognitive tasks involved in cognitive remediation (Medalia and Freilich, 2008). Experiences of external reward and reinforcement are diminished in schizophrenia (Gold et al. 2008), so therapeutics which target intrinsic motivation for cognitive tasks may enhance task engagement, and subsequently, remediation outcome. We examined whether outpatients could attain benefits from an intrinsic motivation approach which (a) presents materials in a meaningful game-like context, (b) personalizes elements of the learning materials into themes of high interest value, and (c) offers

choices so patients can increase their control over the learning process. We directly compared one method that incorporated the motivational paradigm into an arithmetic learning program against another method that carefully manipulated out the motivational variables in the same learning program. Subjects were randomly assigned to one of the two conditions for 10 thirty-minute sessions. Outcome measures were attention, motivation, self competency, arithmetic, and symptom severity. Results showed the motivational group (a) acquired more arithmetic skill, (b) possessed greater intrinsic motivation for the task, (c) reported greater feelings of self competency post-treatment, and (d) demonstrated better attentional resource allocation. Also, baseline perceptions of self competency accounted for 43% of the variance on post-test arithmetic scores. Results demonstrate that incorporating intrinsic motivation techniques into a difficult cognitive task promotes greater learning of the material, higher levels of intrinsic motivation to attempt the demanding task, and greater feelings of self efficacy and achievement. Research supported by NIMH grant 1 R03 MH071733-01A2.

Table.

Measures	Treatment (n = 20)	Control (n = 22)	ANOVA
Intrinsic Motivation Inventory (0–147) Pre Post	57.60 (17.47) 97.32 (15.45) *	61.14 (16.83) 72.06 (14.02)	.03
Perceived Competency Scale (4–28) Pre Post	10.21 (3.02) 18.43 (3.89) *	11.29 (4.92) 14.02 (3.93)	.05
Arithmetic Test Total Correct (0–60) Pre Post	31.32 (7.27) 52.31 (6.34) *	34.92 (9.05) 44.88 (8.56)	.04
CPT-IP False Positives Pre Post	9.95 (3.43) 6.01 (4.37) *	8.47 (4.38) 9.97 (5.55)	.05

ID: 548962

SEARCHING FOR ANHEDONIA IN SCHIZOPHRENIA

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Evocative studies have shown that subjects with schizophrenia (SCH) report the same level of pleasure from positive stimuli as non-patient control subjects (NCS): they do not show a global anhedonia. However, two questions remain: do SCH show a domain-specific pleasure deficit, and are SCH with negative symptoms anhedonic? Seventy-two patients with a SCID diagnosis of schizophrenia (including 23 SCH with primary negative symptoms) and 36 NCS participated in the study. The stimuli were 48 photographs of low or high intensity from the International Affective Pictures System, and 48 sounds from the International Affective Digitized Sounds. After each stimulus, participants rated the degree of pleasantness, unpleasantness and arousal that they experienced. From this battery, specific stimuli were identified to measure three hedonic domains: 1) food (three pictures), 2) erotica (one picture, two sounds), and 3) social pleasure (12 pictures). Compared to NCS, SCH with or without negative symptoms gave similar pleasantness and arousal ratings, and higher unpleasantness ratings for each hedonic domain. Pleasantness ratings were not significantly correlated with SANS scores. For positive pictures, a significant interaction was found for group by intensity by sociality; SCH without negative symptoms rated social positive stimuli of moderate intensity as more pleasant than NCS did, whereas SCH with negative symptoms did not differ from NCS. To conclude, SCH with or without negative symptoms were not anhedonic when representations of food, sex and social interaction were used. However, they

reported a higher degree of unpleasantness to these positive stimuli, leading to more affective ambivalence. SCH with negative symptoms did not show impaired reactivity to positive social stimuli of moderate intensity, which are the stimuli that people encounter most often in their daily life, suggesting that lack of social motivation is not secondary to affective deficits in schizophrenia.
ID: 548853

WHAT DIFFERENCES AND SIMILARITIES BETWEEN SCHIZOPHRENIA AND BIPOLAR DISORDER ARE SHOWN IN NEUROCOGNITIVE FUNCTIONS?

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Introductions: Considering recent progresses of genetics, neuroimaging and psychopharmacologic studies for schizophrenia and bipolar disorders (BPD), Kraepelinian dichotomy needs to be taken into account. We examined neurocognitive functions tests for patients with schizophrenia, BPD and normal controls. Methods: We compared the neurocognitive functions of 19 patients with schizophrenia and 22 patients with euthymic BPD to those of 17 healthy controls. The following domains of the neurocognitive functions were tested in 3 groups: auditory attention (digit span), sustained attention (Degraded Stimulus Continuous Performance Test), verbal memory (Korean-California Verbal Memory Learning Test: K-CVLT), working memory (N-Back Working Memory Task) and executive function (Wisconsin Card Sorting Test: WCST and Chicago Word Fluency Test: CWFT). Multivariate of analyses of variance (MANOVAs) was performed for statistical comparisons of neuropsychological functioning among three groups. Results: There were significant overall differences among the three groups for the cognitive domains in the statistical comparisons. Bonferroni-adjusted post hoc comparisons showed that the neurocognitive functions of schizophrenia group were significantly ($P < .01$) worse than normal controls groups and BPD group also were significantly ($P < .01$) worse than normal controls on almost every cognitive domains except 0-back task and CPT False Alarm. In the comparison of performance of digit span and K-CVLT, the order was schizophrenia<BPD<normal controls. Both patient groups performed significantly worse than normal controls especially on the N-back working memory task and CWFT. Conclusions: Attention and memory are thought to differentiate schizophrenia from BPD. Both similarities and differences were present in neurocognitive functions of both schizophrenia and BPD. It might mean that schizophrenia and BPD are neither wholly mutually exclusive nor wholly continuous.
ID: 548558

THE ENDURING INFLUENCE OF D. SHAKOW'S NEUROPSYCHOLOGICAL INVESTIGATIONS ON SCHIZOPHRENIA RESEARCH

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David Shakow (1901–1981) investigated a range of cognitive and performance measures of schizophrenia patients at Worcester State Hospital and later at the NIMH, initially focusing on reaction time and efforts to precisely characterize the deficits (and capabilities) of schizophrenia patients. The variables that he delineated in his schizophrenia research have in recent decades proven fruitful in family and developmental studies of schizophrenia. Contemporary schizophrenia research literature bears witness to his enduring influence. While the term he coined for schizophrenia-related deficit, segmental set, is not frequently used in contemporary publications, Shakow's papers describing his empirical work with schizophrenia patients remain frequently cited. The consortium on the genetics of schizophrenia describing neurocognitive endophenotypes for use in investigations of the genetics of schizophrenia cited Shakow's 1962 Archives paper on segmental set as support for inclusion of attentional measures; in the last decade there have been eighteen journal citations to that single paper. The phenomenon of reaction time crossover that Shakow explored continues to engage researchers, and has been expanded to the investigation of crossover effects in schizotypy, reflecting contemporary interest in schizophrenia spectrum conditions. Perhaps one of the most counterintuitive of Shakow's empirical findings is his description of normalizing trends observed in schizophrenia, such that individuals with schizophrenia can at times perform in the normal range on neuropsychological tests. The investigation of the correlates of normal neuropsychological function in schizophrenia is an active research area, with some reports replicating Shakow's findings of normal neuropsychological functioning among some schizophrenia patients. More broadly influential in schizophrenia research than any specific variable or domain was Shakow's insistence on methodological rigor and the importance of reliability and validity in measurement. In a 1966 paper, Shakow summed up his approach thus: (Bull. Men. Clinic, (1966) 30:15–60) "Above all I want to stress the guiding principle I learned from the Worcester studies…It can be summed up in just three words: Standards, standards, standards."
ID: 547645

TEMPORAL EXPERIENCE OF PLEASURE IN INDIVIDUALS WITH SCHIZOTYPAL PERSONALITY FEATURES

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Background: Hedonic experience is one of the core features being studied in schizophrenia research. The Temporal Experience of Pleasure Scale (TEPS) has recently been devised to capture two distinct constructs of anticipatory and consummatory pleasure. Aim: The current study aimed to evaluate the feasibility of administering the Chinese version of the TEPS using a rigorous 2-stage factor analysis approach to validate the Chinese version, ie, performing the exploratory factor analysis and confirmatory factor analysis in two independent samples to examine the latent structure of the TEPS. Method: 2275 healthy college students were recruited from local universities in mainland China. They were randomly split into two subsamples. The first subsample was submitted to an exploratory factor analysis in order to identify a factor structure for the TEPS in a Chinese sample. The second subsample was used as a validation sample for the identified structure from the EFA and CFA was adopted. All the data preparation and EFA analyses were performed using SPSS 15.0 and the CFAs were performed with LISREL 8.70. The Beran-Stine-Bentler bootstrapping procedure was performed with EQS6.1. Results: The EFA suggested a four-factor model instead of Kring's two-factor model. However, the constructs of the four-factor models were highly correlated in such a way that

two consummatory factors (abstract and concrete) contributed to a second order latent factor (known as consummatory factor). Similarly, the two anticipatory factors (abstract and concrete) also contributed to a second order latent factor (known as anticipatory factor). Therefore, the CFA was performed with a four-factor model and a four-factor 2nd order model, in parallel with the original two-factor model of the TEPS. Conclusions: The 2nd order model showed a better fit to the subsample and this finding was confirmed in the second subsample based on the validation CFA in the Chinese non-clinical sample.
ID: 546392

SOCIAL FUNCTIONING SCALE FOR PSYCHOSIS IN THE CHINESE SETTING: A PRELIMINARY PSYCHOMETRIC STUDY

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Background: Impaired social functioning is one of the most crucial features of schizophrenia. However, most of the current clinical ratings maybe too brief to capture this complex construct. Aims: The current study aimed to report the preliminary psychometric properties of a Chinese version of a new questionnaire capturing different domains of social functioning in psychosis. Methods: The Social Functioning Scale for Psychosis Scale (SFSPS) was administered to 220 university students, 69 university students with schizotypal personality features, and 43 patients with schizophrenia. All the participants also completed the validated Chinese versions of the Schizotypal Personality Questionnaire, Beck Depression Scale, Beck Anxiety Scale, General Health Questionnaire, and Dysexecutive Questionnaire. Results: Principal component analysis of the university students with and without schizotypal personality features yielded a 5-factor model comprising Interacting, School, Family, Living Skills and Intimacy. These factors also demonstrated adequate internal consistency (Cronbach alpha ranges from 0.6 to 0.76) and test-retest reliability (r ranges from 0.4 to 0.75) supporting the construct validity and reliability of the assessment. Significant differences were found in Family ($P < .05$), Living Skills ($P < .0005$), and Intimacy ($P < .0005$) factor scores between participants with and without schizotypal personality features, and patients with schizophrenia. Trends of significance were also demonstrated in Interacting ($P = .064$ and School ($P = .061$). Conclusions: The results provide the preliminary psychometric adequacy of the translated SFSPS in the Chinese setting.
ID: 546389

ARE PSYCHOTIC PSYCHOPATHOLOGY AND NEUROCOGNITION ORTHOGONAL? A SYSTEMATIC REVIEW OF THEIR ASSOCIATIONS

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Objective: A systematic review (58 studies, 5009 individuals) is presented of associations between psychopathological dimensions of psychosis and measures of neurocognitive impairment in subjects with a lifetime history of non-affective psychosis. Results: Results showed that negative and disorganized dimensions were significantly but modestly associated with cognitive deficits (correlations ranging from -0.29 to -0.12). In contrast, positive and depressive dimensions of psychopathology were not associated with neurocognitive measures. The patterns of association for the four psychosis dimensions were stable across neurocognitive domains and independent of age, gender and chronicity of illness. In addition, significantly higher correlations were found for the negative dimension in relation to verbal fluency (P-value: .005), and for the disorganized dimension in relation to reasoning and problem solving (P-value: .004) and attention/vigilance (P-value: .03). Conclusions: Psychotic psychopathology and neurocognition are not entirely orthogonal, as heterogeneity in non-affective psychosis is weakly but meaningfully associated with measures of neurocognition, suggesting differential latent cerebral mechanisms underlying the cluster of disorganized and negative symptoms versus positive and affective ones.
ID: 546121

LACK OF INSIGHT AND COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

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Lack of insight represents a core symptom of schizophrenia and accounts to a large degree for the lack of adherence to treatment, frequently encountered in this group of patients. Previous studies in chronic schizophrenia found either deficits of executive function or of declarative memory to be related to lack of insight. In the present study, 27 patients with predominantly positive symptoms were administered a battery of neuropsychological tests and the SUMD (Scale to Assess Unawareness of Mental Disorder). Symptom ratings and scores of test performance were entered into regression analysis with insight scores as dependent variable. Results revealed deficits in declarative memory to be significantly related to lack of insight. The results are consistent with findings of lack of insight in amnestic disorders.
ID: 542335

COGNITIVE ASSESSMENT IN PATIENTS WITH FIRST EPISODE PSYCHOSIS USING SPANISH BACS (BRIEF ASSESSMENT IN COGNITION IN SCHIZOPHRENIA)

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Neurocognitive impairment is a core feature of schizophrenia and is closely associated with functional outcome. The importance of the cognitive assessment nowadays is broadly accepted, and it is becoming increasingly necessary to have available a cognitive tool that is easy to use and validated internationality. In first psychosis episode patients the cognitive assessment it would be a predictor of daily life functioning. We evaluate 14 first episode psychosis with 36 healthy controls with the Spanish BACS. Spanish BACS cognitive measures discriminated between patients and controls in almost all the BACS domains. These preliminary results indicate that Spanish BACS is a good neuropsychological tool in patients with first episode psychosis.
ID: 541809

FURTHER CLARIFICATION OF THE NATURE OF PROSPECTIVE MEMORY IMPAIRMENT IN SCHIZOPHRENIA

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Memory impairment is a core deficit in schizophrenia, previous studies have focused on retrospective memory, and several studies have found prospective memory deficit in schizophrenia, the nature of this deficit is yet to be fully known. Prospective memory refers to the ability to execute a delayed intention, and it includes the following stages: intention formation; intention maintenance; cue detection and intention retrieval; intention execution. The present study aimed to further clarify the nature of prospective memory impairment in schizophrenia. Fifty-four patients with schizophrenia and 54 age, education, IQ and executive function matched healthy controls participated the study, they completed time-, event-, and activity-based prospective memory tasks and a set of neurocognitive tests, ie, working memory tests (Chinese Letter-Number Span, N-back), verbal and visual memory tests. Patients with schizophrenia performed worse in all time- ($P < .001$), event- ($P < .01$) and activity-based ($P < .001$) prospective memory tasks than healthy controls. Correlation analysis found that prospective memory correlated significantly with other cognitive functions. Patients still performed poorer even after controlling other cognitive functions (working memory, verbal memory, visual memory and executive functions). Results also found patients with schizophrenia did not perform poorer in recalling task requirements after finishing the prospective memory tasks, so the intention formation and intention maintenance stages maybe relatively intact in schizophrenia, and patients were mainly impaired in cue detection and intention retrieval stage. Prospective memory is a primary not secondary deficit in schizophrenia. Prospective memory deficit mainly occur in cue detection and intention retrieval stage.
ID: 541548

EARLY STIMULANT EXPOSURE IS RELATED TO THE SEVERITY OF PSYCHOSIS

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Stimulant abuse has been a growing concern and increased use of potent drugs like methamphetamine over the last decade have lead to a host of social problems, including increased presentations of drug-induced psychiatric disorders. Stimulants like methamphetamine can lead to a persistent psychotic disorder not unlike schizophrenia, however there has been a paucity of research investigating why some users develop these symptoms and others do not. As part of a larger study examining biological correlates in drug-induced psychosis, 35 abstinent stimulant users aged 18–35 were recruited from the community and subjected to a semi-structured interview to assess prior drug exposure and to quantify psychiatric symptoms with Positive and Negative Syndromes Scale (PANSS). Age at first use of the stimulant drug was inversely related to the PANSS Positive Syndrome Score (Pearson correlation = -0.300; $P = .040$). Also, subjects with more than five years duration of chronic use exhibited greater severity of symptoms on the PANSS Positive Syndrome Score ($t = -2.469$, $P = .019$) and the PANSS General Syndrome Score ($t = -3.029$, $P = .005$). The method of drug administration, duration of abstinence, latency from first use to regular use, and prior solicitation of treatment were not related to PANSS Positive, Negative, or General Syndrome Scores. Severity of psychosis appears to be related to earlier and longer exposure to stimulants, consistent with a "threshold" effect of stimulant use on the development of psychotic symptoms. The association may also suggest a critical developmental period that is most susceptible to the deleterious effects of stimulant exposure. The identification of a biological correlate to this vulnerability may offer insight into pathogenesis while also offering an important tool for the differential diagnosis of substance induced psychosis. These biological factors, including those that are purported to be contributory to schizophrenia are being examined in this cohort and will be reported on at a later date.
ID: 541124

IDENTIFICATION OF PLEASANT, NEUTRAL, AND UNPLEASANT ODORS IN SCHIZOPHRENIA

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Recent work on odor hedonics in schizophrenia has indicated that patients display abnormalities in hedonic judgments of odors in comparison to healthy comparison participants. In the current study, identification accuracy for pleasant, neutral, and unpleasant odors in individuals with schizophrenia and healthy controls was examined. Thirty-three schizophrenia patients (63% male) and thirty-one healthy volunteers (65% male) were recruited. The groups were well-matched on age, sex, and smoking status. Participants were administered the University of Pennsylvania Smell Identification Test, which was subsequently divided into 16 pleasant, 15 neutral, and 9 unpleasant items. Raw scores were rescaled to standard equivalents based on means and standard deviations of the control group to ensure comparability across valence types. Analysis of identification z-scores for pleasant, neutral, and unpleasant odors revealed a significant diagnosis

by valence interaction. Post-hoc contrasts revealed that the schizophrenia participants made significantly more identification errors on pleasant and neutral odors compared to the control group. Conversely, accuracy did not differ significantly between the schizophrenia and control groups for unpleasant odors. No effect was seen for sex. Analysis of odor identification performance by valence category within patients revealed that significantly more identification errors were made in response to both pleasant and neutral odors relative to unpleasant odors. No differences between identification of pleasant and neutral odors was observed. The findings from the current investigation suggest that odor identification accuracy in patients is influenced by odor valence. Specifically, males and females with schizophrenia displayed significantly reduced identification accuracy for pleasant and neutral smells while showing intact identification for unpleasant smells. This pattern of results parallels a growing body of literature indicating that patients display aberrant pleasantness ratings for pleasant smells with ratings for unpleasant smells comparable to healthy controls. These findings highlight the need for additional research on the influence of odor valence on olfactory identification performance in individuals with schizophrenia. This study was funded in part by NIH Grants MH-63381 to PJM, MH-59852 to BIT, and an Independent Investigator Award from NARSAD to PJM. The authors thank the Hofmann Trust for their support.
ID: 550839

COMPARISON OF CURRENT AND ESTIMATED PREMORBID IQ AT FIRST-EPISODE: UTILITY IN PREDICTING CLINICAL AND COGNITIVE FUNCTIONING DURING THE FIRST THREE YEARS OF PSYCHOTIC ILLNESS

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Longitudinal studies suggest that IQ is attenuated and may also decline premorbidly in individuals who later go on to develop schizophrenia. Comparison of concurrently obtained measures of current IQ and estimated premorbid IQ, derived from irregular word reading tasks, have also shown this pattern and suggest that patients can be subgrouped into those with consistently low, deteriorated or preserved IQ. Previous studies have demonstrated these subgroups to have differing neuropsychological profiles, although none to date have followed-up these subgroups longitudinally to establish whether they demonstrated differing cognitive or clinical trajectories. One hundred and twenty-nine individuals with first episode psychosis were subgrouped based on comparison of current and estimated premorbid IQ scores, with 44% demonstrating evidence of a ten point or greater deterioration, 23% showing consistently low IQ, 23% of preserved IQ with a further 8% demonstrating current full scale IQ that was greater than reading IQ by at least ten points. Comparison of these patient groups and 120 healthy controls revealed equivalent patterns in the low and deteriorated groups, namely impairment compared to controls on all neuropsychological tests and greater negative and disorganisation symptoms than the other patient groups. The preserved IQ group underperformed compared to controls on WAIS-III digit symbol and working memory suggesting that processing speed difficulties are present even in those without evidence of attenuated or deteriorated IQ and may underpin working memory dysfunction. The small subgroup with higher current IQ were unique in that they did not evince poorer digit symbol performance than controls although they were impaired on learning and memory measures; a deficit observed in all four patient groups. Fifty-one patients and 27 controls were assessed on two further occasions and the subgroups derived from baseline scores were compared. Analyses revealed that the patient groups did not differ in terms of cognitive or clinical trajectory over the first three year of illness. Indeed, controls and patients showed a very similar pattern of change in performance on neuropsychological tasks, despite differences in overall level of achievement. The results suggest that grouping patients based on premorbid-current IQ differences has limited utility and that current IQ measures may be more informative.
ID: 551902

THE NATURE AND FRACTIONATION OF INSIGHT IN SCHIZOPHRENIA: A CORE SET OF PREDICTIVE FACTORS

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Patients with schizophrenia commonly lack insight into their psychotic symptoms, and cognitive and behavioural impairments. In turn, low insight has been shown to be associated with poor adherence to treatment, clinical outcome, mood and also increase the level carer-burden. It is, therefore, of clinical interest to delineate the nature of insight and in so doing reveal therapeutic targets for reducing low insight, and improve patient quality of life. As insight has been shown to fractionate by domain, such as insight into cognition, behavioural functioning and symptomatology, the present study aimed to contrast awareness into these different dimensions and examine whether there was a common constellation of factors which predicted awareness irrespective of domain or alternatively whether each domain of awareness was associated with specific predictors. Thirty-one schizophrenia patients with low levels of insight underwent clinical interview, assessment on standard insight scales and a battery of psychological tests. Results suggested that there existed a core set of variables which together were associated with insight per se. Thus greater insight across all domains of interest was associated with lower positive, and manic-excitement symptomatology factor scores (Brief Psychiatric Rating Scale; Lukoff et al. 1986), better memory, and greater self-reflectivity and lower self-certainty scores (Beck Cognitive Insight Scale; Beck et al. 2004). Over and above these core factors, correct attribution of symptoms to mental disorder was additionally predicted by executive test performance; while awareness of mental disorder was associated with capacity to 'set-shift'; and higher awareness of behavioural impairments was associated with low mood. Post-hoc analyses suggest that a key mechanism in poor insight may be that deficits in attention and working memory impact negatively on the capacity for awareness via their effects on reducing the capacity for self-reflectivity. In conclusion, the cognitive capacities of attention and memory are suggested to underpin the ability to reflect on changes to mental and functional status. If this is impaired, low self-reflectivity and high self-certainty could develop which, when coupled with the presence of psychiatric symptoms, precludes good insight. Reducing positive symptoms, improving attention, increasing the capacity to self-reflect, and lowering self-certainty are therefore key targets for improving awareness.
ID: 551817

PREDICTORS OF REMISSION IN SCHIZOPHRENIA

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Background: Development of remission criteria for schizophrenia has been hindered by the heterogeneity of the disorder and limitations of currently available treatments. The first consensus-based definition of remission proposed by the Remission Working Group in Schizophrenia (Andreasen et al. 2005) provided a conceptual model incorporating criteria that were easy to assess in different phases of the disorder. This new definition linked remission to symptoms as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and used established rating scales to measure these symptoms. The objective of these analyses was to

determine whether remission could be predicted by improvement defined by rating scales such as the PANSS or BPRS at early time points during treatment. Methods: A search of the ziprasidone clinical trials database identified10 ziprasidone studies, all ≥ 1 year, including acute core studies and their open-label extensions, as well as 1 year trials. As many as 600 subjects were included in analyses that identified potential symptomatic, syndromal, functional predictors of functional remission in schizophrenia. Several criteria for response were examined as predictors of remission, and PANSS and BPRS scores at weeks 1, 3, and 4 were used to predict remission at end point. Remission was also defined using the working group definition: PANSS (P1, P2, P3, N1, N4, N6, G5, and G9) ≤ 3 for ≥ 6 consecutive months and BPRS (items 4, 7, 8, 11, 12, 15, and 16) ≤ 3 for ≥ 6 consecutive months. ROC curves were generated for each of these predictors (at each time point) for each of these definitions at end point, and area under the ROC curve (AUC) was calculated. Results: In the combined ziprasidone arms, BPRS scores at weeks 1, 3, and 4 successfully predicted PANSS remission ($P < .01$); and BPRS remission ($P < .0001$) at study end point (44–196 weeks). PANSS scores (at weeks 1, 3, and 4) successfully predicted PANSS remission ($P < .01$); and BPRS remission ($P = .02$ at week 3 only) at study end point. AUC ranged from 0.59 to 0.93. Conclusion: BPRS and PANSS remission criteria at study end points were accurately predicted by BPRS or PANSS total scores at weeks 1, 3, and 4.

Reference

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ID: 551815

COGNITIVE GAINS FROM NEUROCOGNITIVE ENHANCEMENT THERAPY SUSTAINED AT 2-YEAR FOLLOW-UP

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Background: Previous work from our lab evaluated outcomes of a 1-year program of Neurocognitive Enhancement Therapy(NET) for persons with schizophrenia or schizoaffective disorder. In a component control design, NET plus a supported employment program, modified with transitional funds (NET+VOC) was compared with VOC alone. At the conclusion of 1 year of treatment, participants randomly assigned to NET+VOC had significantly greater improvement on measures of executive functioning and working memory than those in the VOC only condition (Greig et al. 2007). We now report results of follow-up assessments at 2 years, 12 months after the end of active treatment. Methods: $N = 72$ participants were administered neurocognitive assessments at baseline and again at 1 and 2 years post-baseline. Measures include tests of executive function, working memory, visual and verbal memory, and social cognition. Intent to treat analyses were conducted by the longitudinal method of Generalized Estimating Equations. Each cognitive measure served as an outcome, regressed on Group, Time and Group x Time: all models were evaluated by omnibus Wald χ^2 test (3df) with Bonferroni-corrected criterion alpha = .0038 for 13 outcomes. Subsequent tests of significance for each regression coefficient β are considered protected. Secondary analyses focused on the degree of achievement in NET treatment and its relation to outcome. Results: With no differences by condition at baseline, participants in both conditions improved over time on story telling (WMS-LMI: $\beta = 1.01$, $P < .001$; WMS-LMII: $\beta = 0.66$, $P < .005$) and executive functioning (WCST errors: $\beta = 1.90$, $P < .10$) [All Wald χ^2 s > 20.95, P's < .0001]. Further, NET participants showed significantly greater improvements on measures of executive functioning (WCST-CL: $\beta = 2.59$, $P < .10$); visual memory (WMS-VR1: $\beta = 0.87$, $P < .05$; WMS-VRII: $\beta = .52$, $P < .10$) and social

cognition (Hinting: $\beta = 1.03$, $P < .005$) [All Wald χ^2 s > 17.40, P's < .001]. A moderator effect of achievement in NET training was found to predict condition effects for WCST, WMS-VRI, WMS-VRII, and Hinting Task. For example, with each"graduation" from one task to another, experimental participants increase their subsequent performance on WMS-VR1 by $\beta = .18$ scale score points (z = 3.17, $P < .002$). Discussion: Some neurocognitive gains seen immediately following a 1-year program of NET are sustained at 2-year follow-up in the context of ongoing vocational placement and coaching.

ID: 551805

FUNCTIONAL DISABILITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER: CLINICAL AND NEUROCOGNITIVE CORRELATES

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Schizophrenia is a debilitating illness, characterized by positive and negative symptoms, as well as significant cognitive impairment. Converging data suggest that persistent low-level psychosis, negative symptoms, and neurocognitive impairment during remission are directly related to poor functional outcome in schizophrenia (SZ). Less is known about the relationship between these illness features and everyday functioning in patients with bipolar disorder (BPD). The relative impact of persisting symptoms and neurocognitive impairment upon functional capacity is of extreme clinical importance and critical to our efforts toward improving psychosocial outcome in both SZ and BPD. We evaluated a large cohort of remitted SZ patients ($n = 69$) and a sample of euthymic BPD patients with a history of psychosis during mania ($n = 31$) on a comprehensive neurocognitive battery and on several measures of functional capacity (social, occupational, and independent living) and compared their performance with a demographically-matched healthy control sample. We further assessed the contributions of subsyndromal symptoms and cognitive performance on functional outcome in each group using logistic regression. Results indicate that SZ patients were significantly impaired on nearly all major cognitive domains, including premorbid IQ, attention, processing speed, verbal memory, and executive functions as compared with healthy controls (−0.41 to −1.53 SDs below average). BPD patients were comparably impaired on measures of processing speed (−0.56 SDs below average) and verbal memory (−0.52 SDs below average) but otherwise demonstrated intact cognition in all other domains. The pattern of the influence of cognitive impairment and symptomatology on functional assessments differed by diagnostic group; however, cognition was a significant predictor of functional outcome in both patient groups. These data support previous reports that cognitive impairment is a strong correlate of functional disability in stable SZ patients and extends these findings to demonstrate a similar relationship in euthymic BPD patients. Furthermore, while some clinical symptoms overlap between these major psychiatric disorders, the relative contribution of affective symptoms and psychosis to functional capacity differs by diagnostic categorization. These results are derived from an ongoing study; thus, a larger sample will be available for presentation by ICOSR 2009.

ID: 551800

EXECUTIVE FUNCTIONING AND FUNCTIONAL CAPACITY IN SCHIZOPHRENIA

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Executive dysfunction is common in schizophrenia and adversely affects everyday functioning. The relationship between different aspects of executive function and functional capacity, however, remains unclear. This study aimed to examine multiple types of executive functioning in a schizophrenia sample. We used the Delis-Kaplan Executive Functioning System (D-KEFS), a comprehensive battery measuring set-switching abilities (Trail-Making, Verbal Fluency, Design Fluency, and Color-Word Interference) and abstraction abilities (Sorting, Twenty Questions, Word Context, Tower, and Proverbs). No published studies have yet characterized D-KEFS performance in individuals with schizophrenia. It was hypothesized that executive functioning would be associated with functional capacity. 73 outpatients diagnosed with schizophrenia or schizoaffective disorder participated in the study. Participants completed a baseline neuropsychological, functional, and clinical battery that included the D-KEFS, the UCSD Performance-Based Skills Assessment (UPSA), the Positive and Negative Syndrome Scale (PANSS), and the Hamilton Depression Rating Scale (HAM-D). Less than a third of participants were impaired on set-switching tasks (age-corrected scale score ≤ 6 on contrast scores comparing switching to the same task without the switching component); 32% were impaired on Trails, 11% on Verbal Fluency, 7% on Design Fluency, and 4% on Color-Word. On subtests of abstraction, 19% were impaired on Sorting, 23% on Twenty Questions, 36% on Word Context, 33% on Tower, and 29% on Proverbs. Overall, more participants were impaired on a mean switching score (40%) than were impaired on a mean abstraction score (32%). Functional capacity, as measured by the UPSA, was significantly correlated with positive symptoms ($r = -.377$; $P = .002$), negative symptoms ($r = -.244$; $P = .045$), and the mean abstraction score ($r = .428$; $P < .001$). Using partial correlations to control for positive symptoms, functional capacity was still significantly related to abstraction ability ($r = .437$; $P < .001$). Similar results were observed when controlling for negative symptoms ($r = .408$; $P = .001$). UPSA performance was not related to the mean switching score ($r = .067$; $P = .586$). These results indicate that although a minority of schizophrenia outpatients are impaired on various D-KEFS tests of executive function, abstraction ability is related to everyday functioning ability beyond what can be explained by positive or negative symptomatology.
ID: 551788

NEUROCOGNITIVE AND COPING CORRELATES OF SPEECH DISORDER IN SCHIZOTYPY

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Speech disorder is a cardinal symptom of schizophrenia. There is evidence to suggest that difficulties in basic neurocognitive abilities are related to SD in patients with schizophrenia. Moreover, increases in SD are associated with impairments in 'real world' functioning. There is reason to believe that speech disturbances (SD) are also important in understanding schizotypy, defined in terms of a putative genetic risk for schizophrenia without full phenotypic expression. The aim of this project was to investigate the relationship between speech disorder, neurocognition, and coping style, a 'real world' measure of functioning, in individuals with schizotypy. We also wanted to examine whether specific schizotypal symptoms were associated with neurocognition and coping. In this study, data from 83 psychometrically-identified individuals with schizotypy and 22 healthy controls was examined. Speech samples were produced by all participants during separate laboratory controlled pleasant and stressful conditions. SD was rated using a validated measure of assessing speech disorder. Comparing groups, we found a significant increase in the use of avoidant coping and a trend level increase in SD for the schizotypy group. There were no significant differences when comparing these groups on overall cognitive functioning; however, the schizotypy group had significantly higher scores on

the immediate memory scale. Within the schizotypy group, avoidant coping was correlated with a significant increase in SD in the stressful, but not pleasant, condition. Surprisingly, increased SD rates were associated with better performance on immediate and delayed memory. When investigating specific schizotypy symptoms, overall cognitive performance and attention scores were correlated with increased negative symptoms, and avoidant coping was correlated with increased positive and disorganized symptoms. In sum, we found that avoidant coping strategies are significantly related to increases in SD when stress was induced, and that cognitive functioning was not, as we predicted, inversely correlated with speech disorder. These findings demonstrate that individuals with schizotypy who produce high levels of SD in stressful situations also tend to implement more unhealthy coping strategies. However, we were unable to find a link between cognitive performance and SD, which may suggest that the neurocognitive underpinnings of speech disorder may differ in schizotypy and schizophrenia.
ID: 551785

BASELINE CHARACTERISTICS ASSOCIATED WITH SUICIDE AMONG 18 154 PATIENTS WITH SCHIZOPHRENIA IN A LARGE SIMPLE TRIAL OF ZIPRASIDONE AND OLANZAPINE

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Background: Patients with schizophrenia are at increased suicide risk relative to the general population. Understanding characteristics of patients with schizophrenia who have committed suicide is of critical importance to the identification of patients at risk and the development of preventive interventions. Objective: To determine baseline factors associated with completed suicide among patients with schizophrenia in routine clinical treatment enrolled in a randomized, open-label, post-approval large simple trial across 18 countries. Methods: 18 154 subjects were randomized to ziprasidone or olanzapine and followed for 1 year. A baseline questionnaire collected demographic data, medical/psychiatric history, and concomitant medication use; follow-up questionnaires elicited data on hospitalization, vital status, randomized study medication status, and concomitant antipsychotic medication(s). Completed suicide was a secondary end point adjudicated by a blinded end point committee according to a prespecified algorithm Results: 35 completed suicides were observed over the 1 year study period, yielding an incidence of 1.9 per 1000 patients. Subjects who committed suicide had a similar demographic profile to those who did not. Patients who committed suicide had a shorter duration of illness and were more likely to be older adults. In univariate analyses, clinical impression score, frequency of psychiatric hospitalizations, and history of suicide attempts was greater for patients committing suicide, as was frequency of baseline use of concomitant antipsychotics, antidepressants, and hypnotics, sedatives, or anxiolytics. Multivariate logistic regression modeling yielded 2 variables associated with risk of completed suicide: history of suicide attempts and baseline use of hypnotics, sedatives, or anxiolytics. Due to their clinical importance, age, sex, age at diagnosis, and prior psychiatric hospitalization were also kept in the final model. Conclusions: In this real-world cohort of 18 154 people with schizophrenia, 1-year incidence of completed suicide was 1.9 per 1000 patients. Completed suicide was associated with older age at the time of diagnosis, history of psychiatric hospitalization, prior suicide attempts, and baseline use of hypnotics, sedatives, or anxiolytics. These findings suggest that patients with a shorter duration of illness, history of suicide attempts, and comorbid mood/anxiety symptoms are at increased risk for suicide.
ID: 551743

EXECUTIVE FUNCTIONS AND RETRIEVAL CONTEXT SPECIFICITY IN HABITUAL PROSPECTIVE MEMORY PERFORMANCE IN SCHIZOPHRENIA

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Habitual prospective memory (PM) is the mechanism by which one is able to remember to perform some intended future action on a regular interval (eg, taking medication). Such tasks are hypothesized to have heavy reliance on executive functions (EF). Previous research with non-impaired populations indicates that retrieval context specificity benefits task performance. The present study examined the role of retrieval context specificity and EF in a habitual PM task in schizophrenia. Participants and Methods: Forty-four outpatients diagnosed with schizophrenia were administered the Wisconsin Card Sorting Test and received instructions to complete a 5-day habitual PM task with either a general or specific retrieval context. Group effects for specificity of retrieval context and level of EF on habitual PM task performance were examined. Results: One-way between subjects ANOVAs were calculated to examine the effects of instruction set (general vs. specific) and level of EF (fair vs. poor) on task performance. Analyses yielded no significant main effect for instruction set ($F_{1,42} = .009$; $P = .923$), but a significant main effect for level of EF ($F_{1,39} = 5.213$; $P = .028$). Specifically, participants with fair EF outperformed those with poor EF. The sample was divided to explore the effect of task specificity on performance by level of EF. There continued to be no benefit of context specificity for participants with poor EF ($F_{1,24} = .000$; $P = 1.00$); however, there was a trend for participants with fair EF to demonstrate a benefit in performance when provided with a specific retrieval context ($F_{1,13} = 4.129$; $P = .063$). Conclusions: Findings indicate that participants with better EF completed more days of the task compared to participants with poorer EF regardless of retrieval context specificity. However, further analyses indicated a trend for patients with better EF to demonstrate improved performance with increased task specificity as has been shown with non-impaired populations. Findings support the hypothesis that EF is an important aspect in the performance of habitual PM tasks. However, a minimum level of EF may be necessary for individuals to benefit from additional information which further specify the retrieval context.
ID: 551724

TREATMENT DELAY AND COURSE OF ILLNESS IN AFRICAN AMERICAN PATIENTS WITH FIRST EPISODE PSYCHOSIS DURING A TWO-YEAR FOLLOW-UP

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Delays in treatment of psychotic illnesses adversely impact their prognoses. Cross cultural studies on duration of untreated psychosis (DUP) have indicated ethnic differences in the length of delay. However, the findings are inconsistent. Few studies have examined course of illness over time in African American patients. The purpose of this study was to examine DUP in African American (AA) and White patients and the course of illness in the two groups of patients during two years of time. Two hundred thirty seven patients with a first episode of psychosis, recruited at the Western Psychiatric Institute and Clinic, Pittsburgh, were included in this study at baseline. There were 159 White and 78 AA patients, 153 males and 84 females, with a mean age of 24. ANCOVA was used to examine DUP with gender and patient years of education as covariates. Similarly, separate race by time ANCOVAs with positive and negative symptoms were conducted to examine longitudi-

nal clinical outcome. The AA patients had significantly longer DUP than that of White patients ($P = .001$). No significant differences in positive and negative symptoms between the two groups were observed at baseline. However, there was significant race by time interaction effects for positive ($P = .002$) and negative symptoms ($P = .001$) respectively during follow-ups up to two years. AA patients showed significantly more persistent positive and negative symptoms than White patients. African American patients had significantly longer DUP. African Americans may interpret the illness differently, influencing their help-seeking behavior. The longitudinal outcome of AA patients was also not as promising as White patients. Negative experiences with mental health services, lack of insurance and family support, lack of compliance to treatment, and lack of culturally sensitive professionals may account for the poor outcome of AA patients. The clinical implications of the findings and directions for future research will be presented. This study was supported by a Center for Neuroscience in Mental Disorders grant: MH 45156 (David Lewis, MD, PI).
ID: 551714

USING ACOUSTIC ANALYSIS OF NATURAL SPEECH TO UNDERSTAND THE NEUROCOGNITIVE, CLINICAL AND FUNCTIONAL CORRELATES OF DIMINISHED EXPRESSIVITY IN SCHIZOTYPY

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Diminished expressivity is a cardinal negative symptom of schizophrenia-spectrum disorders, but surprisingly little is known about its underlying neuropathology and clinical and functional concomitants. The present study employed acoustic-analysis of natural speech during a laboratory condition to understand diminished expressivity in individuals with schizotypy—individuals with the putative genetic loading for schizophrenia pathology that do not meet full diagnostic threshold. We examined a) the severity of diminished expressivity across the heterogeneous manifestations of schizotypy b) whether schizotypic individuals with diminished expressivity show a distinct neurocognitive profile, and c) the extent to which diminished expressivity is associated with real world impairments in coping and quality of life. Data for a relatively large group of individuals with psychometrically-identified schizotypy and controls were examined here. As a group, individuals with schizoypy and controls did not differ in overall expressivity, although expressivity was dramatically reduced in individuals with negative schizotypy. Interestingly, individuals with more pronounced positive and disorganization symptoms showed abnormally high levels of expressivity. Within the schizotypy group, diminished expressivity was significantly associated with dysfunctions on tests tapping right hemispheric functions. There was virtually no association between left-hemispheric tests and diminished expressivity suggesting that the neurocognitive dysfunction is not generalized in nature. Finally, diminished expressivity was associated with poorer quality of life, notably in social domains, and greater use of unhealthy coping strategies. These findings highlight the deleterious effects of diminished expressivity in schizotypy and raise questions about the specificity of the right hemisphere in this symptom. The use of acoustic analysis of speech as a sensitive means of measuring diminished expressivity is also supported here.
ID: 551693

LACK OF EARLY IMPROVEMENT DEMONSTRATES STRONG NEGATIVE PREDICTIVE VALUE FOR LATER TREATMENT RESPONSE WITH ATYPICAL ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Prediction of antipsychotic treatment response based on patient outcomes within the first 2 weeks of treatment would facilitate the decision to continue treatment or switch to an alternative agent. Methods: Data were pooled from 2 similarly designed, flexible-dose, randomized, comparative trials of inpatients with an acute exacerbation of schizophrenia or schizoaffective disorder. In the 8-week study (ziprasidone vs risperidone), patients were required to have a PANSS total score ≥ 60, and a score of ≥ 4 on ≥ 2 core items of the PANSS. In the 6-week study (ziprasidone vs olanzapine), patients were required to have a CGI-S score ≥ 4, and a score of ≥ 4 on ≥ 1 item of the PANSS positive symptom items. Ziprasidone and risperidone were titrated to a flexible dose range of 80–160 mg/d (mean dose: 114.2 mg/d) and 6–10 mg/d (mean dose: 7.4 mg/d), respectively. In the 6-week trial, ziprasidone and olanzapine were titrated to a flexible dose range of 80–160 mg/d (mean dose: 129 mg/d) and 5–15 mg/d (mean dose: 11.3 mg/d), respectively. Week 1 improvement, week 2 improvement, and week 6 response based on the PANSS or BPRS total score were defined as $\geq 10\%$, $\geq 20\%$, and $\geq 40\%$ reductions from baseline, respectively. Baseline characteristics for week 1 and week 2 improvers and nonimprovers were compared descriptively. Sensitivity and specificity, positive predictive value (PPV), negative predictive value (NPV), and predictive power (PP) were calculated. Results: Early improvers and early nonimprovers were comparable with regard to their baseline characteristics. Improvement at week 1 correctly identified 71 of 107 (66.36%, sensitivity) week 6 responders, while nonimprovement at week 1 correctly identified 159 of 262 (60.69%, specificity) week 6 nonresponders. Of the 174 week 1 improvers, 71 (40.80%, PPV), were week 6 responders. Of the 195 week 1 nonimprovers, 159 (81.54%, NPV) were week 6 nonresponders. The PP of the week 1 result was 65.4%. Similar results were obtained using week 1 and week 6 PANSS scores (sensitivity 66.35%, specificity 65.03%, PPV 42.59%, NPV 83.17%, PP 65.4%). The use of week 2 and week 6 BPRS scores yielded: sensitivity 80.43%, specificity 69.16%, PPV 52.86%, NPV 89.16%, and PP 72.5%. Conclusion: These results indicate that early assessment of symptom change is predictive of later treatment outcome, which may have important clinical implications in the treatment of patients with schizophrenia.
ID: 551681

PROPERTIES OF THE DOT PATTERN EXPECTANCY TASK FOR CLINICAL USE

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The Dot Pattern Expectancy (DPX) task was created to efficiently assess context processing deficits in patients with schizophrenia. Three studies together investigated the characteristics of the DPX that may qualify it for clinical use in assessing cognition in schizophrenia. To answer questions regarding the psychometric properties of the task, performance on this task was studied in samples of healthy undergraduates ($n = 214$), healthy community adults (n's = 38 and 48), and schizophrenia patients ($n = 47$). Acceptable internal consistency and retest reliability, as evidenced by significant similarity in performance across runs (d'-context intra-class correlation = .77) and lack of practice effects ($F_{46,1} = .03$, $P = .88$, $\eta 2 = .001$), were found for both longer versions of the DPX and a suggested brief version (DPX-brf), which may be practical for clinical purposes. Alpha values ranged from .81–.97 for AX trials and from .81–.90 for BX trials. Performance on the DPX was studied in the sample of schizophrenia patients to address the task's ability to detect specific deficits. The DPX task revealed a deficit in context processing in patients with schizophrenia (d'-context $\eta 2 = .249$); the DPXbrf was also sensitive to this deficit (d'-context $\eta 2 = .251$). The combination of adequate psychometric properties, shorter duration and ability to elucidate a specific deficit in context processing suggested this task may be useful for assessing this construct in both clinical and research settings.
ID: 551619

NEUROCOGNITIVE PREDICTORS OF FUTURE RECOVERY IN SCHIZOPHRENIA: A 20-YEAR FOLLOW-UP

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Objective: Previous research has indicated that patients with schizophrenia demonstrate deficits in cognition, though little is known about whether or how these deficits change across the lifespan. Furthermore, the question remains as to whether cognitive deficits in schizophrenia are related to global outcome and recovery. The current prospective longitudinal research is unique in that it affords comparison of potential changes in cognitive functioning over time and the relationship between cognitive deficits and outcome, for patients with schizophrenia as well as other psychotic disorders. Method: As part of The Chicago Follow-up Study, we prospectively assessed 187 patients seven times (once at index hospitalization, and then 6 times over 20 years) to provide longitudinal data about cognitive deficits and recovery. Patients were assessed on standardized research instruments evaluating cognitive functioning, symptoms, work disability, psychosocial functioning, treatment, and recovery. Results: 1) At all 7 assessments, patients with schizophrenia showed poorer processing speed than patients with other psychotic disorders or nonpsychotic disorders. 2) All patient groups showed improvement in cognitive functioning between index hospitalization and the first follow-up 2 years later (P's < .001). 3) Contrary to previous hypotheses, schizophrenia patients did not show cognitive declines as they grew older ($P > .60$). 4) There was a strong association between better cognitive function and recovery for patients with schizophrenia, as well as for patients with other psychotic disorders and non-psychotic depression. 5) Schizophrenia patients demonstrated significant associations between better cognition at 2-year follow-up and recovery at each successive follow-up (P's < .005), whereas these relationships were also present, but not as robust, in other patient groups. Conclusions: Current data support the presence of cognitive impairment in schizophrenia, as well as the association between cognitive impairment and global recovery in all patient groups. Our findings suggest that cognition in schizophrenia is related to current level of recovery and may be predictive of likelihood of future recovery.
ID: 551556

THE CONSISTENCY BETWEEN CLINICALLY RATED ANHEDONIA AND OLFACTORY VALENCE JUDGMENT IN PATIENTS WITH DEFICIT SYNDROME SCHIZOPHRENIA

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Previous research on emotion and schizophrenia reveals a consistent pattern of contradictory findings, whereby individuals with schizophrenia report experiencing significantly less pleasure than non-patients when emotional experience is measured using self-report questionnaires and clinical interviews (ie, anhedonia), yet appear surprisingly normal when rating evocative stimuli in laboratory-based paradigms. Few studies, however, have examined whether this discrepancy holds when patients with the most severe affective deficits, such as those with primary and enduring negative symptoms (ie, deficit syndrome schizophrenia), are compared to patients with less pronounced affective disturbance. The current study examined the consistency of affective disturbance as evaluated by clinical rating and a laboratory-based measure of olfactory valence judgment in 22 healthy controls (CN) and 41 patients with schizophrenia. Patients were sub-grouped into deficit (DS: $n = 15$) and non-deficit (ND: $n = 26$) syndrome subtypes using the Schedule for the Deficit Syndrome. Valence ratings for pleasant and unpleasant odors were assessed for items on the Brief Smell Identification Test (B-SIT). Results indicated that DS patients received significantly higher anhedonia ratings than ND patients, and that although schizophrenia patients as a whole did not differ from CN in their subjective valence ratings of pleasant odors, differences did exist among DS and ND sub-types. Specifically, DS patients rated pleasant odors as being significantly less pleasant than ND patients and CN, who did not significantly differ from each other. No differences were found between DS and ND groups when rating unpleasant odors. Furthermore, DS patients rated a significantly higher proportion of pleasant smells as falling within the unpleasant range of the valence scale than ND patients and CN, indicating that they may experience some pleasant stimuli as aversive. Findings suggest that among individuals with schizophrenia, patients meeting criteria for the DS uniquely rated olfactory valence in a way that was consistent with their self-reported positive mood as measured by clinical rating scales.
ID: 551542

SEX SPECIFIC ASSOCIATIONS BETWEEN OLFACTORY PROCESSING AND SCHIZOTYPY IN HEALTHY VOLUNTEERS

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A number of studies have shown that people with schizophrenia and their relatives have impaired olfactory identification. This suggests that it may prove to be a useful vulnerability marker for schizophrenia. The evidence for olfactory abnormalities in schizotypy is less clear, with some studies indicating deficits in olfactory threshold in males and some indicating no abnormalities. Variability in findings may be attributable to variations in the sensitivity of psychometric measures of schizotypy and the specific aspect of olfactory function being tested, identification, threshold or discrimination. We examined olfactory ability in healthy volunteers using an olfactory test that addresses different aspects of olfactory ability and a schizoptypy measure that measures distinct schizotypal subscales. The "sniffin sticks" test of nasal chemosensory performance based on pen-like odour dispensing devices was used. It includes three tests of olfactory function, 1) odour threshold (using n-butanol concentrations), 2) odour discrimination (16 pairs of odours, triple forced choice) and 3) odour identification (16 common odours, multiple forced choice from 4 verbal items per odour). Schizotypy was measured using the O-LIFE which provides measures relevant to positive (unusual experiences, UNEX) negative (introvertive anhedonia, INTAN) and cognitive (cognitive disorganisation, COGDIS) symptoms. Healthy Volunteers (26 M, 50 F, mean age 21yrs) were used. The results indicate that UNEX is positively associated with odour identification in females but negatively in males. COGDIS is positively associated with odour identification and discrimination in females only. No association with INTAN was found for any olfactory measure. There were no sex differences in identification, threshold or discrimination ability. These data support the suggestion of a negative association between olfactory ability and schizotypy in males. They further suggest that these associations are specific to positive aspects of schizotypy, males and the odour identification aspect of olfactory ability.

Table. Association between olfactory scales and O-LIFE

OLFACTORY/ O-LIFE SCALE	THRESHOLD	DISCRIMINATION	IDENTIFICATION
FEMALE UNEX	−0.12	0.08	0.28*
FEMALE COGDIS	−0.16	0.32*	0.25
MALE UNEX	−0.15	−0.18	−0.29*
MALE COGDIS	−0.01	−0.04	−0.09

*$P < .05$, spearman's rho
ID: 551538

RANKING NEUROCOGNITIVE DOMAINS BY LEVEL OF IMPAIRMENT IN FIRST-EPISODE PSYCHOSIS: DOES PREMORBID ADJUSTMENT MATTER?

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Background: There is evidence that impairments in a simple processing speed test, the Digit Symbol Coding Test (DST), are larger than the ones in other cognitive domains in schizophrenia. It is not clear whether these differences between domains can be identified during the first episode and if poor premorbid adjustment is associated differentially with severity of impairments in cognitive domains. Method: Patients ($N = 129$) with first-episode schizophrenia-spectrum psychosis completed a full neuropsychological battery at baseline. All test scores were converted into z-scores based on a sample of 52 healthy controls. Five cognitive domains were computed using the mean z-scores for relevant tasks (ie, Verbal Memory, Processing Speed, Working Memory, Attention, Executive Functions). Performance on the DST was examined independently. To test for group differences on all cognitive domains and the DST, ANCOVA models were conducted with group (patient vs.control) as the between-group factor and gender and education as covariates. Based on the Premorbid adjustment scale, patients were classified into three groups (ie, deteriorating, stable-good and stable-poor). Results: The patient sample (mean age 22.9; 72% male; education 11 years; median DUP 18.7 weeks) was significantly more impaired compared to healthy controls on all domains and on the DST after adjusting for gender and education. Impairments were most pronounced in the Verbal Memory domain (ES = −1.54) followed closely by the DST task (ES = −1.45) and the processing speed domain (ES = −1.25). All three premorbid groups were impaired on all domains. Patients in the stable-poor group showed the largest impairment across most cognitive domains, followed by the deteriorating and stable-good groups. Conclusion: As early as the first episode, generalized cognitive impairments are present with more pronounced deficits in verbal memory and processing speed. Although significantly impaired in first-episode psychosis, impairment on the DST task was not much higher than impairment in other processing speed tasks. We found that the more neurodevelopmentally impaired sub-group (ie, stable poor) may be distinguishable from other sub-groups on the basis of severity and not type of cognitive impairments.
ID: 551519

STRIATAL AND EXTRASTRIATAL DOPAMINE D2/3 RECEPTOR BINDING POTENTIALS AND OCCUPANCY IN FIRST-EPISODE SCHIZOPHRENIA: CORRELATIONS WITH COGNITIVE DEFICITS

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Introduction: Studies of *in vivo* dopamine receptor activity and density in schizophrenia have mostly focused on high-density striatal areas. The purpose of the current study was to examine D2/3 dopamine receptor binding potentials (BP) and occupancy (OCC) in both striatal and extrastriatal ROIs. The primary objective was to examine whether BP when drug-naïve predicted the effects of antipsychotics on cognition. The secondary objective was to examine whether OCC was related to the change in cognition after treatment with antipsychotics. Methods: Twenty-one drug-naive schizophrenic patients were scanned with Single-Photon Emission Computerized Tomography (SPECT) using the D2/3-receptor ligand [123I] epidepride. The regions of interest (ROIs) were the frontal cortex, the temporal cortex, the thalamus, caudate nucleus, and putamen. BPs were assessed when patients were drug-naïve, and OCC after 12 weeks of antipsychotic treatment. Cognitive functions including verbal memory, attention, executive functions, processing speed and pre-morbid intelligence were assessed within days of the SPECT scans. The level of significance (0.05) was divided by the number of regions, and significant results considered according to this level (0.01). Results: Baseline BP did not predict the efficacy of antipsychotics on most measures of cognition, except for one measure of verbal learning, where faster learning was positively correlated with baseline BP in the temporal cortex. Frontal and temporal D2/3 occupancy after 12 weeks of antipsychotic treatment was significantly positively correlated with improved measures of planning efficiency but also negatively correlated with improved measures of attention. Discussion: The results suggest involvement of extrastriatal D2/3 BP and OCC in aspects of cognitive functions, and suggest differential levels of optimal D2/3 occupancy for attention and planning.
ID: 551453

PLANNING SKILLS, COGNITIVE REMEDIATION THERAPY AND WORK PERFORMANCE AMONG PEOPLE WITH SCHIZOPHRENIA

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Introduction: Cognitive problems are commonly observed in people having schizophrenia. A growing body of evidence indicates that such problems are linked to poor social functioning, including poor work performance. The aim of this study is to investigate these relationships and to explore the potential impact that receiving cognitive remediation therapy may have on work performance. This investigation expanded on previous findings by exploring the influence of metacognition. Metacognition allows the person to reflect upon and regulate their own thinking. This may be important, for example, when generating and implementing strategies, problem solving, evaluating plans, etc. Methods: 57 participants aged 18 to 65 who satisfied DSM-IV criteria for schizophrenia or schizoaffective disorder. They were in sheltered, voluntary or open/competitive employment and receiving dedicated employment support. Participants were excluded if they had a history of brain injury, organic brain disorder, learning difficulty or current primary substances abuse. Work performance was assessed using the Work Behaviour Inventory (WBI). Cognitive assessments encompassing executive functions, working memory, memory, IQ and metacognition were also administered. Positive and negative symptoms were also rated. Path analysis was employed to explore relationships between differing domains of cognition, metacognition, symptoms and work performance before receiving cognitive remediation therapy and three months after therapy completion. Metacognition and symptoms were included in all our models as hypothesised predictors of work behaviour. Results: At baseline planning skills predicted work performance, $\chi^2 = 10.3$, $df = 8$, $P = .25$. The same model also predicted work performance 3 months after therapy completion, $\chi^2 = 6.7$, $df = 8$, $P = .57$. Both models have good goodness of fit ($P > .20$). The data will be further analysed to assess the relationship between change in planning skills and work performance. Discussion: Poor planning skills appear to impact on work performance and are potentially a target for remediation in this regard. One possible explanation could be that the two tests that fed in to the latent variable of planning captured cognitive processes critical for dealing with real-life scenarios at work. Both tests (the Key Search Test and the Zoo Map Test) are designed to have ecological validity, being part of the Behavioural Assessment of the Dysexecutive Syndrome (BADS) battery.
ID: 551445

THE AFFECTIVE PATHWAY TO PSYCHOSIS: EVIDENCE FROM A LARGE, EPIDEMIOLOGICAL SAMPLE

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Objectives: It has been argued that an affective pathway is underlying the development of positive symptoms of psychosis (Myin-Germeys et al. 2007). This affective pathway is characterized by an increased sensitivity to stress, possibly resulting from a sensitization process from previous exposures to life events or childhood trauma. This affective pathway model has mainly been developed in smaller samples using momentary assessment technology. The current paper aims to validate this model in a large, epidemiological sample. Method A large sample of 312 patients diagnosed with a non-affective psychotic disorder, partly pertaining to the same families, was assessed with the Positive and Negative Syndrome Scale (PANSS) and the Youth Trauma Questionnaire. Stress-reactivity was assessed using the Eysenck Neuroticism scale. Results Multilevel regression analyses revealed that neuroticism was significantly associated with positive symptoms (B = 0.36, $P = .00$), whereas no significant association with negative symptoms was found (B = 0.07, $P = .44$). In addition, a history of childhood trauma was significantly associated with positive (B = 0.10, $P = .00$), but not negative symptoms of psychosis (B = −0.00, $P = .87$). The association between childhood trauma and the positive symptoms of psychosis was partially mediated by levels of neuroticism. Conclusion: The current results provide further evidence for an affective pathway to psychosis, characterized by increased levels of neuroticism or stress-reactivity and higher levels of childhood trauma, which is specifically associated with the positive symptoms of psychosis.

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ID: 551431

EXPLORING THE DYNAMIC ASSESSMENT PARADIGM AND ITS USEFULNESS AT ASSESSING LEARNING POTENTIAL OF SCHIZOPHRENIA PATIENTS

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Clinicians hoping to improve the quality of life of schizophrenia patients constantly face the situation of scarce rehabilitation resources. Dynamic assessment (DA) proponents suggest using DA to measure patients' learning potential to prioritize the allocation of rehabilitation resources to patients. DA measures cognitive functions through an active teaching process aimed at quantifying and also qualifying learning potential of a person during the acquisition of new cognitive skills. A general DA paradigm consists of a pretest—training—posttest scenario. The training is the quintessential part of DA whereby it allows examiners to evaluate the examinee's learning potential, specific deficient functions, and possible mediational strategies that may be utilized by the examinee. While proponents of DA argue that the training in the assessment paradigm is the reason that brings about the improved performance, critics suggest that practice effect may be the reason behind the improvement. Validation of the training paradigm in DA is needed before it can be utilized to measure learning potential in clinical settings. This study examines whether the improvement in performance detected in DA sessions is due to the training or practice effect. Patients diagnosed with schizophrenia are recruited and divided into four groups. All four groups are administered the Wisconsin Card Sorting Test (WCST) twice. One group is taught how to perform on the WCST in between the two test sessions while other groups of patients either undergo a control task intervention or is administered WCST without training. The last group of patients acts as a control group. Preliminary result suggests the efficacy of DA on the assessment of learning potential has implications on the utility of rehabilitation resources. The assessment of learning potential by DA means can streamline the referral process of admitting patients into rehabilitation programs, making the programs more cost effective by pre-selecting patients based on their readiness for rehabilitation.
ID: 551403

AUTOBIOGRAPHICAL MEMORY DEFICITS IN CHRONIC SCHIZOPHRENIA

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Autobiographic memory is important for the constitution of self identity and is generally differentiated into a semantic and a episodic domain which refer to life facts and vivid recall of personal episodes, respectively. In an ongoing study, we investigate autobiographical memory functioning in patients with chronic schizophrenia. Up to now, 33 nursing home residents with chronic schizophrenia (mean age: 47, SD: 9.9 years), 32 patienst with major depression (mean age: 55.0, SD: 0.9 years) and 71 otherwise healthy controls (mean age: 55.0, SD: 1.0 years) were included. Patients with schizophrenia were recruited among nursing home residents (duration of nursing home placement:10, SD:9 years), the comparison subjects were participants of the longitudinal study of aging (ILSE). Semantic and episodic memories from five lifetime periods were explored by using the Bielefeld Autobiographical Memory Inventory. Executive functioning and logical memory were assessed on the Trail Making Test and the Wechsler Memory Scale, respectively. Relative to both, healthy and depressive comparison subjects, patients with schizophrenia were significantly impaired in autobiographical memory, predominantly regarding episodic memory, relatively sparing semantic aspects. While the comparison subjects scored higher for the most recent lifetime period, this recency effect did not apply for the schizophrenic patients. Within the latter, these effects were not associated with psychopathological symptoms, duration of illness, immediate or delayed recall (Wechsler Memory Scale), nor executive functioning. Taken together, our findings demonstrate autobiographical memory deficits in patients with chronic schizophrenia. These deficits primarily involve episodic memories and may thus diminish quality of life and social functioning in chronic schizophrenia. Acknowledgement: The study was supported by the D.-Hopp-Foundation.

Table. Episodic memory performance in healthy subjects, patients with depression and patients with chronic schizophrenia within 5 lifetime periods: Results of an Analysis of Variance

Mean (Standard Deviation)	preschool period	elementary school period	secondary school period	young adulthood	last five years
Healthy Subjects	5.4 (4.4)	7.8 (4.3)	8.0 (4.2)	9.6 (3.0)	9.3 (3.5)
Depression	6.4 (4.3)	8.7 (3.5)	9.6 (2.3)	9.3 (3.1)	10.4 (1.6)
Schizophrenia	5.1 (4.7)	6.0 (4.7)	5.1 (4.8)	6.3 (4.6)	5.6 (5.1)

Main Effect "Diagnosis": $F = 14.19$ ($P < .01$) Main Effect "Lifetime Period": $F = 12.62$ ($P < .01$) Interaction "Diagnosis*Lifetime Period": $F = 2.24$ ($P < .05$)
ID: 551349

ADDITION OF COGNITIVE RETRAINING TO IMPROVE GLOBAL FUNCTIONING IN SCHIZOPHRENIA—A RANDOMIZED CONTROLLED STUDY

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Purpose: To examine the effectiveness of addition of cognitive retraining to psychoeducation and drug therapy (TAU) on neuropsychological functions, psychopathology and global functioning in first episode schizophrenia patients and the effectiveness of the intervention on psychological health, perception of level of family distress and attitude towards mental illness in caregivers of the schizophrenia patients. Method: 45 first episode schizophrenia patients and their caregivers were randomly allotted to experimental and control group. Patients were assessed on battery of neuropsychological tests, Positive Negative Syndrome Scale and WHO Disability Assessment Schedule. Caregivers of patients were assessed on General Health Questionnaire, Scale for Assessment of Family Distress and Orientation to Mental Illness. Patients and caregivers were assessed at baseline. Post assessment was after completion of 2-months from baseline assessment and follow-up assessment was after completion of 6 months from baseline assessment. The effectiveness of addition of cognitive retraining was examined using generalized linear mixed model ANCOVA and ANOVA. Results: TAU led to significant improvement in neuropsychological functioning, psychopathology and improvement in global functioning. Addition of cognitive retraining led to improvement in neuropsychological functions, a significant decrease in negative symptoms and a qualitative change in occupational functioning. In caregivers, psychoeducation led to significant improvement in psychological health, reduction in perception of family distress and decrease in unfavorable attitude towards mental illness. Conclusions: Addition of cognitive retraining along with psychoeducation and drug treatment led to improvement in cognitive domains of attention, executive functions, verbal learning and memory and visual memory as well as a significant decrease in negative symptoms in the initial phase of the illness. Effect sizes were large, although the sample size was small. Future studies with large sample size will prove the effectiveness of cognitive retraining further. Cognitive retraining should be part of total treatment package for schizophrenia.
ID: 551296

AN EXAMINATION OF VERBAL AND SPATIAL MEMORY ERRORS IN RELATION TO CLINICAL SYMPTOMS OF PATIENTS WITH RECENT-ONSET SCHIZOPHRENIA

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Deficits in serial recall in patients with schizophrenia (SZ) are considered as a key feature of the clinical manifestations of the disease. In order to further examine the role of memory deficits in SZ, the pattern of errors in verbal and spatial serial recall tasks committed by SZ patients was compared to that of healthy controls. The evaluation of the relationship between these memory errors and the clinical symptoms assessed with the PANSS and the SAPS was also computed. Twenty-seven outpatients with recent-onset SZ and 27 matched healthy controls had to remember sequences of items (digits or localizations) in a serial recall task. The results indicate that the number of omissions and transpositions can differentiate between patients suffering from SZ and healthy controls. The pattern of correlation for transpositions (positive association with general psychopathology and delusion subscales) was the same whether to-be-remembered information was verbal or spatial. Commission errors (intrusion, transposition) in verbal memory were associated with the negative subscale. The relationships between the observed memory errors for symptomatology are similar across the spatial and verbal domains. The failure to associate a to-be-remembered item and its temporal position (transposition) can be regarded as a form of confusion consistent with delusions observed in SZ (see also Woodward et al. 2006). The examination of error patterns, especially transposition errors, rather than the mere analysis of overall memory performance, should be considered for a better understanding of the disease and for a more targeted treatment.
ID: 551230

FACIAL EMOTION PERCEPTION IN SCHIZOPHRENIA: A META-ANALYTIC REVIEW

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Objective: Many studies have reported on facial emotion perception deficits in schizophrenia and clinical relevance. Potential factors that influence findings, ie, task design, demographic and clinical characteristics, and treatment status remain better understood. Methods: 86 studies reporting on schizophrenia patients and controls published between 1970–2007 were identified through a computerized search of public databases. A Quality of Reporting of Meta-analysis standard was followed, data were analyzed using Comprehensive Meta-Analysis version 2.0. Differences in perception scores between studies were standardized by calculating Cohen's d. Cochran Q-statistics assessed homogeneity of effect sizes. Results: 86 studies on emotion identification and differentiation employing photographic images were identified. Analysis revealed a large deficit in emotion perception ($N = 3822$, $d = -0.91, 95\%$ CI $= -0.97 < \delta < -0.84$), irrespective of task type, that was heterogeneous (QB $= 295.7$, $P < .001$). Effect sizes for schizophrenia ($N = 71$, $d = -0.98$) and the schizophrenia/schizoaffective diagnosis ($N = 15$, $d = -0.85$) were large and homogeneous. Greater age in patients ($N = 81$) (Z $= -5.25$, $P < .001$) and controls ($N = 84$) (Z $= -2.98$, $P < .01$) related to impairment. Percentage of male controls ($N = 80$) were negatively related to effect sizes (Z $= 3.53$, $P < .001$). Hospital status revealed heterogeneity (QB $= 19.65$, $P < .001$), inpatients were more impaired than outpatients (QB $= 16.01$,

$P < .001$) and mixed group (QB $= 10.57$, $P < .01$). Later age of onset ($N = 16$) related to greater impairment (Z $= -2.79$, $P < .01$). Studies that employed the Scheduled Assessment of Negative ($N = 20$, Z $= -4.13$, $P < .001$) and Positive Symptoms ($N = 18$ studies, Z $= -4.48$, $P < .001$) related higher symptoms to greater deficit. Medication studies were classified as medicated ($N = 57$), unmedicated ($N = 2$), mixed ($N = 20$) showing heterogeneity (QB $= 11.76$, $P < .01$). Unmedicated patients were most impaired, followed by medicated and mixed groups. Effect sizes were heterogeneous (QB $= 9.35$, $P < .01$) for first-generation ($N = 25$), second-generation ($N = 7$) and mixed groups ($N = 22$). FGA were more impaired than SGA (QB$_1 = 9.00$, $P < .01$) and mixed (QB$_1 = 4.12$, $P < .05$) groups. No effects were found for duration of illness, past number of hospitalizations, education and ethnicity. Conclusion: Emotion perception represents a robust impairment in schizophrenia moderated by certain clinical and demographic factors. Results may inform design of future studies that evaluate emotion perception in schizophrenia.
ID: 551166

THE PERCEPTION OF EMOTIONAL PROSODY AND AWARENESS OF ILLNESS IN SCHIZOPHRENIA

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Being able to understand not only what someone says, but also how it is said, is very important in social communication. People with schizophrenia have been found to be impaired in this ability, ie, they may have difficulties in understanding the emotional cues given in the intonation of spoken language. Problems in social functioning form one the most devastating symptoms in schizophrenia. Another problematic manifestation of schizophrenia is poor awareness on having psychotic symptoms (APA, 1987). We hypothesized that there would be a relationship between emotion processing and awareness of psychotic symptoms. An association between insight and facial emotion identification has been found (Goodman, 2005). The aim of the present study was to examine the relation between awareness of illness and the ability to perceive emotional prosody in schizophrenia patients. 32 patients (17 females, mean age 36 (SD 12.3)) with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder were included. Most of them were diagnosed with the paranoid subtype of schizophrenia. The Positive and Negative Syndrome Scale (PANSS; Kay, 1987) was administered and all patients completed an emotional prosody task, consisting of 24 sentences with neutral content spoken with an emotional intonation (anger, fear or neutral) by actors. This task was developed using stimuli derived from Vingerhoets (2003). Scores on PANSS item G12 (Lack of judgment and insight), and accuracy scores on the emotional prosody task were analyzed. A higher score on G12 was related to more errors in the detection of the emotional intonation from sentences over all emotions (Kruskal-Wallis $\chi^2 = 5.72$, $P < .05$). The detection of anger and fear was more impaired in patients who show reduced awareness of their symptoms as compared to patients who show good awareness of their illness. These differences did not reach significance (K-W $\chi^2 = 1.4$, $P = .2$ and K-W $\chi^2 = 2.8$, $P = .09$ respectively). Results from our study show that patients with poor symptoms awareness are less able to detect the emotion from intonations in speech. This finding is in line with the suggestion that there is an overlap in mechanisms related to emotion processing and to insight generation (Goodman, 2005).

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ID: 551124

HIPPOCAMPAL MEMORY FUNCTION OVER INITIAL TREATMENT PERIOD IN FIRST-EPISODE PSYCHOSIS: THE ROLE OF STRESS AND HPA AXIS FUNCTIONING

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Hippocampal dysfunction and structural abnormalities are commonly found in Schizophrenia. They are evident in the first episode of illness and have shown strong associations with functional outcome. However, the biological origins and stability of these deficits over the illness course remain unclear. One plausible hypothesis involves increased stress levels and dysfunction of the central cerebral region responsible for its regulation, the Hypothalamic-Pituitary-Adrenal (HPA) axis. Hippocampal function, particularly the ability to remember new associations, is highly sensitive to the neurotoxic effects of sustained increased cortisol levels. The aim of the current study was to test the stability of hippocampal function in drug-naïve first-episode psychosis (FEP) patients over the first three months of treatment, and test possible relationships with biological measures of stress and HPA dysfunction. The performance of FEP patients and normal controls (NC) were compared using a novel memory task that included standard list learning and paired associated learning (PAL). At baseline, FEP patients ($n = 26$) were significantly more impaired on a list learning task than NC ($n = 24$) ($P = .023$), as well as on a hippocampal PAL task ($P = .027$). Further, FEP patients showed greater impairment on paired associates considered to be more abstract, which have been postulated to require greater hippocampal involvement. 12 FEP patients repeated the assessment after 3 months of treatment with an alternate form of the task, and showed a significant improvement in list learning performance that was not seen in NC ($n = 18$) (time X group interaction $P = .019$). Conversely, FEP patients continued to be impaired on PAL ($P < .001$) and there was no effect of or interaction with time ($P = .447$). These findings suggest that hippocampal dysfunction is stable over the first 3 months of treatment in first episode psychosis. Future analysis to determine possible associations between these findings and biological measures of stress and HPA axis activity (post-dexamethasone cortisol levels and glucocorticoid receptor function) will be incorporated as a part of this presentation.
ID: 551121

NEUROCOGNITIVE DYSFUNCTION IN BIPOLAR AND SCHIZOPHRENIA SPECTRUM DISORDERS: THE ROLE OF HISTORY OF PSYCHOSIS

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Objectives: Neurocognitive dysfunction in bipolar disorder is less severe than in schizophrenia spectrum disorders. However, as lifetime history of psychosis has been related to neurocognitive deficits, we investigated whether bipolar disorder with a history of psychosis is neurocognitively closer to schizophrenia spectrum disorders than to bipolar disorder without a history of psychosis. Methods: From a large ongoing study on severe mental disorder (TOP), a sample of schizophrenia ($n = 102$), schizoaffective disorder ($n = 27$), bipolar disorder with history of psychosis ($n = 75$) and bipolar disorder without history of psychosis ($n = 61$) and healthy controls ($n = 280$) were included. Neurocognitive function was measured with an extensive neuropsychological test battery. Results: The three groups with a history of psychosis (schizophrenia, schizoaffective disorder and bipolar with a history of psychosis) did not differ from each other and performed poorer than the healthy controls across neurocognitive measures. The bipolar group without a history of psychosis was not reduced compared to healthy controls on any measures and performed better than the three groups with a history of psychosis on a number of neurocognitive measures. Conclusions: Our findings suggest that bipolar disorder with a history of psychosis is neurocognitively more similar to schizophrenia spectrum disorders than to bipolar disorder without a history of psychosis. This suggests that neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group belonging.
ID: 551096

NEUROCOGNITIVE FUNCTIONS AND SYMPTOMS IN SCHIZOPHRENIA: AN ANALYSIS OF FAMILIAL LIABILITY

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Associations between symptoms of psychosis and neurocognition seem most robust for the negative symptom cluster, although several studies have reported associations between specific neurocognitive deficits and positive symptoms. However, the aetiology of any association remains unclear. This study uses a genetically sensitive design to investigate whether any association between cognitive functioning and symptoms is due to a genetic aetiology. Subjects were recruited in the context of the GROUP study, site Maastricht. 235 patients with a DSM-IV diagnosis of non-affective psychosis, 118 of their siblings and 230 healthy controls completed a cognitive battery including measures of IQ (WAIS-III), verbal memory (WLT), sustained attention (CPT) and mentalising (Hinting task). Positive and negative symptoms were assessed with the Positive and Negative Syndrome Scale. Cross-trait cross-sib analyses were conducted between all possible patient-sibling pairs (120) to investigate associations between symptomatic expression of psychosis in patients and cognitive performance in siblings. Analyses revealed significant group differences on all cognitive measures (all $P < .01$). Patients performed worst, their siblings performed intermediate and controls performed best. In patients, cognitive deficits were strongly and significantly related with negative symptoms. Positive symptoms were significantly associated with lower IQ, but not with other cognitive test parameters. Within-trait cross-sib associations were significant for verbal memory ($\beta = 0.16$, $P = .01$), IQ ($\beta = 0.34$, $P = .00$), and sustained attention ($\beta = 0.23$, $P = .00$), but not for mentalising ($\beta = 0.07$, $P = .29$). Cross-trait cross-sib analyses showed a significant association between IQ in siblings and positive symptoms in patients, which remained equally large and significant after adjustment for the corresponding traits in the patient and sib ($\beta = -0.19$, $P = .05$). All other cross-trait cross-sib associations were small and non-significant. The findings indicate that in patients

cognitive deficits are primarily associated with negative symptoms. With the exception of the mentalising task, performance on cognitive tasks shows substantial familial clustering, indicative of genetic factors contributing to cognitive functioning. However, the lack of any familial covariation suggests that the overlap with negative symptoms is due to individual rather than shared factors.
ID: 551093

CORRECTING FOR THE PSYCHOMETRIC CONFOUND ON NEUROPSYCHOLOGICAL TASKS: BEYOND TRUE-SCORE VARIANCE

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The most prominent feature of behavioral experiments in schizophrenia patients is a pattern of impaired performance across a wide variety of tasks known as the generalized deficit. Tasks that measure this generalized deficit show larger or smaller effect sizes depending on those tasks' discriminating power, irrespective of the cognitive domains that they measure. This has come to be known as the psychometric confound. The current project tested several means of correcting for the psychometric confound that is caused by differential discriminating power using classical psychometric theory and a simulation study method. Method: Simulations mimicked task performance on free response and binary forced-choice tasks of different length (2–100 items), difficulty (1–99% correct), variability and internal consistency. The advantage of the simulation method was that the size of the generalized deficit and specific deficits could be assigned and varied in each case. We examined the extent to which various weightings of task characteristics accurately corrected for a generalized deficit and recovered specific deficits in a large group simulation ($n = 10\,000$ per group). Weightings were cross-validated in a second set of simulations ($n = 40$ per group). Results: True-score variance (the product of variance and reliability) was a poor proxy for discriminating power. Instead, there were independent effects on discriminating power from all the parameters that had been varied (length, difficulty, variance and reliability) as well as multiple interactions between these parameters. This multi-parameter approach was able to account for 97% of variance in discriminating power across tasks in the original samples and 79% of variance in discriminating power in the cross-validation sample for free-responses tasks. For forced-choice tasks, these psychometric parameters accounted for 84% of variance in task discriminating power in the original sample and 84% of variance in the cross-validation sample. Conclusion: The results suggest that the psychometric confound may be "corrected" post-hoc, based on the psychometric characteristics of a task within the context of classical psychometric theory, but not simply by using true-score variance. A spreadsheet that allows investigators to use these equations to correct for discriminating power is now available on the web.
ID: 551090

THE ROUGH RIDE OF EXPERIMENTAL PARADIGMS: FROM HYPOTHESIS TESTING IN UNDERGRADUATES TO CLINICAL APPLICATION

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Experimental psychology and cognitive neuroscience are dedicated to untangling the many mechanisms that underlie thought. There is a strong

appeal to applying the technologies developed for this purpose to address clinical questions. Direct transfers of tests developed to understand normative cognitive and brain functioning in undergraduates face the following limitations: such tasks are too long to be practical in clinical applications; they often suffer from ceiling effects; and, they do not allow for the interpretation of a deficit on the function of interest in patient groups. This talk will use a case study approach to describe the (many) failures and (a few) successes our laboratories have experienced when using basic cognitive tasks to address clinical questions. These scenarios include multiple, different versions of cognitive control and decision-making paradigms that have had to be scuttled in early phases because they were not sensitive to individual differences, did not measure the original construct in patient populations, or proved unworkable for other, unforeseen reasons. The talk will also describe on-going initiatives to prepare successful tasks for the higher standards required to measure change over time.
ID: 551077

ASSOCIATION BETWEEN WAIS-III PERFORMANCE AND SCHIZOTYPY IN HEALTHY VOLUNTEERS

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Evidence suggests that schizophrenia is associated with generalised deficits in intelligence measured using general scales such as the Wechsler Adult Intelligence Scales (WAIS-III) and that these deficits are associated specifically with negative and cognitive symptoms (Dickinson et al. 2004). It is not known whether this generalised profile extends to schizotypy. We therefore investigated a potential association between different dimensions of schizotypy corresponding to positive (Unusual Experiences) negative (Introvertive Anhedonia) or cognitive (Cognitive Disorganisation) symptoms in addition to total schizotypy scores and the full WAIS-III in healthy volunteers. 28 undergraduate/graduate students (19 F, 9 M, mean age 23.3 yrs) completed the short form O-LIFE (Oxford-Liverpool Inventory of Feelings and Experiences) schizotypy scale and the complete WAIS-III. Adopting the continuum model, bi-variate correlations were performed between the full scale score and three subscales (Unusual Experiences, Cognitive Disorganisation, Introverted Anhedonia) scores on the O-LIFE and the scaled subtest scores and four indices (Verbal Comprehension, Perceptual Organisation, Working Memory and Processing Speed) of the WAIS-III. There were no significant correlations between O-LIFE measures and overall intelligence, as measured by full Scale IQ (Total O-LIFE and IQ, $r = -.113$). A significant correlation was found between the Matrix Reasoning subtest and total O-LIFE score ($r = -.383\ P < .05$). Letter-Number Sequencing subtest was associated with Cognitive Disorganization ($r = -.387\ P < .05$), Impulsive Non-Conformity ($r = -.414\ P < .05$) and Total O-LIFE score ($r = -.441, P < .01$). The Working Memory Index showed a negative correlation with Cognitive Disorganisation ($r = -.438\ P < .05$). These results show that schizotypy is only weakly negatively associated with overall IQ in healthy volunteers. When subscales are examined schizotypy is negatively correlated with Matrix Reasoning and Letter-Number sequencing. When schizotypy subscales are examined, cognitive disorganisation is associated with reduced performance on both letter number sequencing and the Working memory Index subscales. This reduced performance is less generalised than that found in studies using the WAIS-III in patient studies. However, the letter-number sequencing and working memory association recapitulates findings of deficits in patients in abstract reasoning, attention and working memory.
ID: 551073

ACTION PLANNING IN ADOLESCENT ONSET PSYCHOSIS

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Cognitive deficits are core features on psychotic disorders. Executive function is one of the most affected cognitive domain on psychosis. An important aspect of executive functioning involves the ability to form and carry out complex plans, such us action planning. To date few studies have focused on planning performance in early onset psychosis. Objective: This study aimed to investigate action planning in 19 patient with adolescent onset psychosis compared to 20 healthy controls using an ecological planning subtask derived from the Behavioural Assessment of the Dysexecutive Syndrome (BADS) test battery, the "Zoo Map Test". Method: A total of 19 Patient (P) aged 18.11 ± 1.56, and 20 Healthy Controls (HC) aged 17.70 ± 2.27, completed the two versions of the "Zoo Map Test". In the first version consists of a "high demand" version of the subtask. The participants must plan in advance the order in which they will visit designated locations in a zoo. The second, is a "low demand" version, the participant is simply required to follow a concrete externally imposed strategy to reach the locations to visit. In this study, scoring was based on the: a) sequencing score, b) total number of errors, c) thinking times (time being taken to plan the action) and d) drawing time (time to execute this plan). Results: The adolescent psychotic group presented more drawing time in both version, high (P:148.53 ± 37.36 vs HC:119.60 ± 41.26; $U = 107.5$, $P < .005$) and low (P: 97.63 ± 32.04 vs HC: 64.95 ± 30.50; $U = 64.5$, $P < .005$) demand. Only in the low demand version, the patients presented more total number errors. (P:1.47 ± 1.61 vs HC:0.25 ± 0.44; $U = 90.0$, $P < .005$) Conclusions: These results suggest that adolescent psychotic group presents with more problems for executing complex plans, while planning was less affected. Execution was equally affected in both highly and low external imposed strategies.
ID: 551034

THE ORYGEN CLINICAL NEUROPSYCHOLOGY UNIT: IDENTIFYING AND MANAGING COGNITIVE DYSFUNCTION IN YOUTH EXPERIENCING EARLY PSYCHOSIS

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Objective: To describe the referral population and service characteristics of the first 200+ referrals to the ORYGEN Neuropsychology Unit (ONU), and the benefits of a neuropsychological approach to case formulation and treatment planning in at-risk and first-episode populations. Methods: We discuss key findings from a clinical audit conducted to 1) quantify service delivery key performance indicators and 2) further characterise the referrals from the Early Psychosis Prevention and Intervention Centre (EPPIC) and other clinics within ORYGEN Youth Health, to the ONU. Results: Of the referrals ($n = 216$, 65% male, mean age = 19 years) made to the ONU, ~70% were from EPPIC. The cognitive 'profiles' of cases from the early psychosis, ultra-high risk, and mood and anxiety clinics were indicative of significant impairments in multiple cognitive domains at, or prior to illness onset. The degree of impairment was similar between the broad clinic groups, although there were some differences in the pattern of impairment across the assessed domains. Comorbidity was very prevalent eg, ~44% had threshold or subthreshold personality disorder diagnoses and ~55% had problematic substance use. Around 60% of referrals had experienced trauma (either directly or observed). Neurodevelopmental 'insults' were also very common eg, ~70% had premorbid learning, intellectual or behavioural problems. Neuropsychological case formulation, however, revealed that rate-limiting factors for functional recovery (eg, social, vocational) were often not solely cognitive, but included dysfunctional schema/heuristics, substance misuse and reduced opportunity, amongst others. Conclusions: Cognitive impairment is common and at times severe, in at-risk and first-episode populations. Our data provides some support for 1) a paradigm shift away from crystallised DSM-type diagnostic labels and towards phenomenological and phenotypic characterisation, 2) the allocation of funds for the implementation of psychological interventions eg, cognitive therapies in these patient groups. Specialist neuropsychological consultation involves evaluating the specific characteristics that contribute an individuals' unique trajectory into mental illness, and providing a comprehensive formulation that outlines their potential capacity and current cognitive capabilities, with particular regard to what this means functionally in the context of history and current circumstances.
ID: 550933

IMPAIRED MOTOR CONTROL IN ADOLESCENTS AT HIGH RISK FOR SCHIZOPHRENIA

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We present evidence from the Harvard Adolescent High Risk Study designed to determine the association between motor control and lateralization performance and risk for schizophrenia. A frequent observation in high-risk studies has been that a significant number of individuals who are at risk for or who have developed schizophrenic disorder have experienced motor symptoms or impairment of motor control, especially fine motor coordination, prior to the onset of psychosis. Prior work has suggested that motor control, specifically coordination and precision of movement as measured with a line drawing task, is associated with an earlier age of diagnosis, and with higher scores on psychometrically estimated schizotypy in normal young adults. In contrast to many earlier studies, this investigation employed quantitative measures of motor behavior and a sample of younger high risk subjects. The study sample was composed of three groups, biological children and siblings of schizophrenia patient probands, biological children and siblings of affective psychosis patient probands and biological children and siblings of community control subject probands. All high risk and community control participants were between the ages of 13 and 25. Subjects were assessed psychiatrically and with an extensive battery of neuropsychological measures. We used the line drawing measure and standard assessments of handedness to estimate motor control and lateralization. We hypothesized that participants at risk for schizophrenia would exhibit deviant performance distinct from that of controls. The results of this investigation add plausibility to the notion that increased vulnerability to schizophrenia, reflected in a greater degree of motor abnormality, could be associated with earlier recognition and diagnosis of the manifest psychotic disorder. The refinement of a profile of measures to detect high levels of vulnerability to schizophrenia may have value in the development of preventive interventions that might delay and/or mitigate the disorder.
ID: 550887

COGNITIVE AND CLINICAL DYSFUNCTION IN CHINESE ADULT, NONPSYCHOTIC RELATIVES OF SCHIZOPHRENIA PATIENTS PREDICTS DEFICITS IN A WIDE RANGE OF NEUROPSYCHOLOGICAL, SOCIAL AND CLINICAL FUNCTIONS: FINDINGS FROM THE CHANGSHA STUDY

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Introduction: This study reports initial findings from a collaborative international study that seeks to identify vulnerability syndromes in relatives of schizophrenia patients, based on multidimensional measures of function. Methods: The Changsha study uses diagnostic (DIGS), neuropsychological, clinical and physical measures of function to assess adult (ages 18–59), non-psychotic, first-degree biological relatives of patients with schizophrenia. Phase I of the study involves the identification of: 1) neuropsychological deficits in declarative memory, sustained concentration and executive function; and/or 2) negative symptoms, in subjects assessed at the Mental Health Institute, Second Xiangya Hospital of Central South University, Changsha (Hunan, China). Additional measures of cognitive function are also administered, as are self-report measures of social function, and medical measures that emphasize cardiac, hepatic, lipid and glycemic control. Relatives are classified as affected ('schizotaxic') on the basis of diagnostic criteria in neuropsychological and negative symptom domains (ie, at least 1 standard deviation below expected mean values in selected cognitive measures, and/or at least 6 scores rated 3 or higher on the SANS), and are compared statistically with relatives who do not meet criteria, and with healthy control subjects ($n = 30$). Current analyses focus on data collected from the first 110 subjects to complete the protocol. Results: Based on diagnostic criteria described above, 45/110 relatives were classified as schizotaxic, and 65 were not. Age and education levels were used as covariates in analyses of cognitive, clinical and medical function (ANOVAs, with post-hoc comparisons). Among the major findings: 1) Non-schizotaxic relatives generally did not differ statistically from controls; 2) Schizotaxic relatives were impaired on a wide range of independent (ie, non-criterion related) cognitive, clinical and social measures compared to both other groups; and 3) Most physical measures, including glucose tolerance, did not differ between groups. Conclusions: Deficits in selected cognitive and clinical domains predict a wide range of additional independent cognitive and clinical deficits in a subset of non-psychotic, adult relatives of schizophrenia patients. These deficits are similar to those seen in schizophrenia, and may reflect identifiable areas of vulnerability that may eventually serve as useful treatment targets.
ID: 550860

USING A TWO-STEP CLUSTER ANALYSIS TO IDENTIFY NEUROPSYCHOLOGICAL SUBGROUPS IN SCHIZOPHRENIA

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One of the barriers to identifying the neurobiologic underpinnings of schizophrenia is the presence of substantial inter-person heterogeneity. Although clustering of neuropsychological data in people with schizophrenia has been done before, no one has looked at the pattern of performance rather than the magnitude effects of performance. In an effort to identify more homogenous neurocognitive subgroups, the present study involved application of a two step clustering procedure to neuropsychological data from 148 middle-aged and older (age > 40 years; mean [and SD] 52 [7] years) people with schizophrenia. Participants completed an expanded neuropsychological battery, as well as standard ratings of psychopathology (Positive and Negative Syndrome Scale; Hamilton Depression Rating Scale) as part of participation our Center research on mid-to-late life schizophrenia. The 23 individual cognitive test scores were factor analyzed to reduce the number of variables to 6 [verbal (Verb) and visual (Vis) abilities, working memory (WM), auditory and visual memory (Mem) speed/attention (SA) and executive functioning (EF). These 6 factor scores were then submitted to a two step clustering procedure: (1) Hierarchical cluster analysis (HCA) was conducted to determine the number of clusters, (2) K-Means analysis (KMA) utilized to define final cluster membership. The HCA indicated that a 5-cluster solution provided the best fit to the data. Membership of the clusters derived from KMA, was fairly evenly distributed (11%–27%), with the profiles demonstrating reasonable independence; these included: Cluster 1: Strength-Verb, Vis, PS, Weakness- Mem and EF; 2: Strength-PS, Weakness-EF; 3: Strength-PS, Weakness- Mem; 4: Strength-Verb, Weakness- EF and PS; 5: Strength-Vis Weakness- Mem and EF. There were no significant differences among the clusters in terms of age, other demographic characteristics, or severity of psychopathology. Replication of these findings is needed, but these findings suggest this method may be useful in identifying subgroups of schizophrenia patients with greater within-group homogeneity in the pattern of impairment. The relationship of such subgroupings to brain structure or function, course of illness, and independent functioning warrant further study.
ID: 550859

NEUROCOGNITIVE PREDICTORS OF CLINICAL AND FUNCTIONAL OUTCOME IN THE MEDIUM-TERM IN FIRST EPISODE PSYCHOSIS

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Objective: Verbal fluency at illness onset was the strongest neurocognitive predictor of global functioning at one-year in patients participating in the Northern Ireland First Episode Psychosis Study (Barrett et al. 2007). The following analyses aimed to replicate this finding using outcome data gathered at three years, and to examine predictors of employment status at this time point. Methods: Sixty-two patients (M/F = 59/23; age = 34 ± 10.4; 51.6% = SCZ) were included in the analyses. The following neurocognitive predictor variables were included in regression models: attention, working memory, verbal and visual memory, executive functioning, verbal fluency, language and callosal function. Age of onset, symptoms at onset and gender were subsequently assessed as possible additional predictor variables. Outcome was measured using the GAF, PANSS, BDI and employment status at three years. Results: Two factors accounted for 30% of the variance in GAF at three-year follow-up: verbal fluency ($\beta = 0.48$, $P < .001$) and baseline positive symptoms ($\beta = -0.32$, $P < .01$). Verbal fluency ($\beta = -0.31$, $P < .01$), attention ($\beta = -0.25$, $P < .05$) and baseline positive symptoms ($\beta = 0.4$, $P < .001$) accounted for 27% of the variance in negative symptoms at three-years. Attention ($\beta = -0.41$, $P < .001$), age of onset ($\beta = -0.25$, $P < .05$), positive symptoms ($\beta = .36$, $P < .01$) and depressive symptoms ($\beta = 0.29$, $P < .05$) at onset predicted depressive symptoms at three years (29% of variance). Verbal fluency also predicted employment status at three years

(Wald = 4.8, $P < .05$), but this was rendered non-significant once baseline employment status was included in the model. Conclusions: Reduced verbal fluency at illness onset is a strong predictor of global functioning and the severity of negative symptoms in both the short and medium-term. Attention is an additional neurocognitive domain that predicts negative and depressive symptoms at three-years in first episode psychosis patients.

Reference

1. Barrett SL, et al. Verbal Fluency is a Strong Predictor of Short-Term Outcome in First Episode Psychosis. Schizophrenia Bulletin. 2007; 33(2):582.

ID: 551925

THE COGNITIVE PROFILE OF THE 22Q11.2 DELETION: A UK SAMPLE

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Background: The 22q11.2 deletion is the most frequent microdeletion syndrome. Learning difficulties (LD) are frequently reported with marked variability both within cognitive domains and between subjects. Comorbid psychiatric disorder is common and by early adulthood up to 30% develop a schizophrenia-like psychosis (Murphy et al. 1999; Feinstein et al. 2002; Gothelf et al. 2004a; 2007b). A review of the literature presents the main findings and methodological limitations. Aim: The aim of the study is to explore the cognitive profile in children with the 22q11.2 deletion at Great Ormond Street Hospital in the UK. Method: Thirty one children with the 22q11.2 deletion were examined on standardized tests of intelligence, memory, literacy and numeracy. Results: The mean Full Scale IQ (FSIQ) was 65, in the Mild LD range. Verbal IQ was significantly higher than Performance IQ, with the discrepancy clinically significant in half the sample. Memory function was higher than FSIQ, with no significant differences between verbal and visual memory. Memory was significantly higher for simple than complex verbal information. Verbal rote learning was a strength. Basic reading was significantly higher than mathematics, especially in those with FSIQ below 70. All other results remained significant in children with an FSIQ above 70 and when controlling for age, gender and cardiac surgery. Conclusions: Children with the 22q11.2 deletion in this sample have LD with a specific but heterogeneous cognitive profile. Heterogeneity is contributed to by many factors including presence of schizophrenia, genotype, nature of microdeletion, developmental effects and cardiac defects. Implications for schizophrenia research are reviewed. This study replicates the findings of previous research, apart from the weakness of visual memory compared with verbal memory.

ID: 560094

NEUROTROPHIC FACTORS AND SCHIZOPHRENIA: RELATION TO COGNITION

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Gial cell line-derived neurotrophic factor (GDNF) and Brain derived neuritrophic factor (BDNF) may play an important role in various neurodevelopmental processes which are assumed to be abnormal in schizophrenia. The objective of this study was to determine the relationship between peripheral BDNF and GDNF serum and gene expression levels and cognition in schizophrenia. Thirty five patients diagnosed with schizophrenia according to DSM-IV (APA, 1994) and 17 healthy volunteers were included in the study. The patients were recruited from inpatient and outpatient departments of Psychiatry of Dokuz Eylül University Hospital. Patient and control groups were comparable for gender and years of education but not for age. Total RNA extracted from lymphocytes of individuals was amplified by RT-PCR. Quantitative real time PCR using SYBR Green I was used to quantify the expression of BDNF and GDNF genes. Relative expressions of BDNF and GDNF were normalized with beta-actin as housekeeping gene. The DeltaDeltaCt method was used for the analysis of relative expression. Serum BDNF and GDNF levels were measured by sandwich ELISA. Neuropsychological tests were administered to evaluate attention, executive functions, verbal and visual learning and memory, working memory, verbal fluency and motor function. The relationship between peripheral BDNF and GDNF serum and gene expression levels and measures of cognitive tests were examined with Pearson correlation test. Serum BDNF level was related to a measure of verbal learning and GDNF gene expressions levels were corelated to measures of verbal learning and memory, executive function and motor function in healthy subjects. Patient group revealed a neagtive correlation between Serum BDNF level and a measure of motor function ($r = -0.35$) and no other correlations were found between serum and gene expression levels of BDNF-GDNF and measures of neuropsychological tests in patiens with schizophrenia. There are few studies indicating a possible relation between BDNF and cognitive functions particularly learning-memory and executive functions in healthy subjects. The number of studies investigating the relationship between cognition and neutrophic factors in schizophrenia are a few and their results are conflicting. This study examined this relationship using a wide cognitive battery and did not find a significant relationship.

ID: 554815

VERBAL AND VISUAL THEORY OF MIND IN A SCHIZOPHRENIC AND BIPOLAR POPULATION

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Theory of mind (ToM) is described as the mental capacity to assign emotions, thoughts, or feelings to others. It has been hypothesized that this trait plays an integral role in social functioning and interpersonal relations. This study inquired into the existence of a deficit in ToM in schizophrenic (SZ) and bipolar populations (BPD), and whether this deficit is related to the level of social functioning, symptom severity, and/or intellect. The tests used included a verbal task, the Hinting Task, and a visual task, the Eyes Test, both originally established for autistic adult populations. This study aims to not only investigate group differences, but also to inquire into the possible strategic differences in ToM. SZ, BPD, and demographically matched healthy participants (CO) were given the Intelligence Quotient (IQ), Social Functioning Scale (SFS), the Hinting Task, the Eyes Test and a symptoms rating scale. In the Eyes Test, the participants completed a computer task in which they were asked to choose the appropriate emotion to describe the eyes presented from a list of four adjectives; all term definitions are provided. The Hinting Task is administered as an interview where ten scenes are described where one of the actors is hinting at an action. The subject is asked what the actor is hinting at based on the description. These scores were compared to a series of empathy, social functioning, and intelligence tests scores. SZ showed a deficit when compared to the CO, while BPD was not significantly different from either group. Eyes test scores over all groups were positively correlated with the Social Functioning Scale, as well as with IQ scores. The symptoms rating scale showed negative trend between positive symptoms and Eyes Test Score in SZ. Overall Hinting Task scores are not significantly correlated with the Eyes Test scores. Hinting Task is only positively correlated to the Verbal IQ and one subscale of SFS. There was a trend toward group differences in the Hinting Task, but BPD did not differ significantly from CO or SZ. This suggests that there is the possibility of a socially related deficit in ToM with

respect to SZ and also that the hinting task is not a very sensitive measure of ToM.
ID: 554745

PROCEDURAL LEARNING IN SCHIZOPHRENIA AND IN PATIENTS WITH AND WITHOUT TARDIVE DYSKINESIA

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This study re-examined the conflicting findings concerning whether procedural learning remains normal in schizophrenia, despite impairment in other areas of long-term memory. Forty-three patients with schizophrenia and 21 normal controls were administered motor, perceptual and cognitive procedural learning tasks: the pursuit rotor, mirror reading and probabilistic learning (weather prediction). All patients had a current WIAS III IQ of ≥ 80. Since procedural learning has been found to be impaired in basal ganglia disorders like Huntindon's disease and Parkinson's disease, the patients were also rated for presence of tardive dyskinesia. The schizophrenic patients showed comparable learning to the controls on the pursuit rotor and mirror reading. They showed impaired learning on the probabilistic learning task, but here the difference disappeared when subgroups matched for current IQ were examined. Patients with tardive dyskinesia showed a significantly lower level of performance on the pursuit rotor than those without. This study therefore finds that patients with schizophrenia show preserved learning on some, but not all procedural learning tasks. When procedural learning impairment is found, current IQ differences between patients and controls may be an important determining factor. Tardive dyskinesia is associated with impaired performance, but not learning on a motor skill task, the pursuit rotor. Acknowledgement: Supported by the Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM.
ID: 554451

NEUROCOGNITIVE CHANGES FOLLOWING ANTIDEPRESSANT OR ANTIPSYCHOTIC TREATMENT IN THE SCHIZOPHRENIA PRODROME

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Cognitive impairment is ubiquitous in schizophrenia. The severity of impairment after the onset of psychosis is such that small, yet statistically significant, improvements in cognition following treatment may not be clinically meaningful. Cognitive dysfunction is detectable in the prodromal phase of schizophrenia. Although the profile of impairments is similar to chronic schizophrenia, the attenuated magnitude in the prodrome offers promise for remediation. In a naturalistic treatment design, 49 individuals considered at clinical high risk for schizophrenia were treated with an antidepressant (AD; $n = 14$), second-generation antipsychotic (SGAP; $n = 14$), or no medication (Control; $n = 21$). All subjects were assessed pre-intervention and 12 weeks after initiating treatment with a symptom interview and cognitive tests measuring sustained attention, processing speed, working memory, verbal learning, verbal fluency, and executive functioning. Subjects did not differ at baseline on demographic or symptom variables. Repeated measures analysis of variance tests were conducted to examine changes over time by treatment group. Bivariate correlations were used to examine the relationships

among baseline symptoms and demographics with change in neurocognition. Chi-square analyses were conducted to examine the proportion of subjects who improved to a clinically significant degree (ie, z-score change of ≥ 0.5) by group. Significant visit by group interactions were found for verbal learning, working memory, and sustained attention. Pairwise comparisons revealed a significantly greater improvement for the AD group compared to the SGAP group on verbal learning, but a greater improvement for the SGAP group compared to the AD group on working memory. The control group of high risk patients showed significantly greater improvement on sustained attention than the SGAP group, which declined by a mean of nearly 0.5 SD. Clinically meaningful neurocognitive improvement was observed in a large minority of patients. For the entire sample, severity of disorganized symptoms at baseline was associated with change in processing speed, while severity of negative symptoms was associated with change in sustained attention. These data provide preliminary evidence for differential treatment effects on specific neurocognitive domains in the schizophrenia prodrome.
ID: 554362

CAN WE HARNESS COMPUTERIZED COGNITIVE BIAS MODIFICATION TO TREAT ANXIETY IN SCHIZOPHRENIA? A FIRST STEP HIGHLIGHTING THE ROLE OF MENTAL IMAGERY

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A new wave of computerised therapy is under development which, rather than simulating talking therapies, uses bias modification techniques to systematically target the core psychological process underlying anxiety. Such interventions are being aimed at anxiety disorders, but have not yet been adapted for co-morbid anxiety in psychosis. The cognitive bias modification (CBM) paradigm delivers repeated exposure to stimuli in order to train individuals to resolve ambiguous information in a positive, rather than anxiety provoking, manner. The current study is the first to report data from a modified form of CBM which targets co-morbid symptoms of anxiety within individuals diagnosed with schizophrenia. Our version of CBM involved exposure to one hundred vignettes presented over headphones. Participants were instructed to actively simulate the described scenarios via visual imagery. Twenty-one participants completed both a single session of CBM and a single control condition session in counter-balanced order. Within the whole sample, there was no significant improvement on interpretation bias of CBM or state anxiety, relative to the control condition. However, in line with previous research, those participants who engage in higher levels of visual imagery exhibited larger changes in interpretation bias. We discuss the implications and challenges for harnessing computerised CBM therapy developments for co-morbid anxiety in schizophrenia.
ID: 554349

PREFRONTAL COGNITIVE DYSFUNCTION IS ASSOCIATED WITH SMOKING CESSATION FAILURE WITH NICOTINE PATCH AND BUPROPION TREATMENT IN SMOKERS WITH SCHIZOPHRENIA

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Patients with schizophrenia have higher rates of smoking (58–88%) than in the general population (~22%), and endure frequent cessation failure. These patients also exhibit numerous neurocognitive deficits, some of which may be ameliorated by cigarette smoking. The neurocognitive benefits derived from nicotine may, in turn, contribute to elevated rates of smoking and smoking persistence in schizophrenia. The purpose of the present study is to examine the relationship between neurocognitive function and smoking cessation in schizophrenia. Treatment-seeking schizophrenic smokers ($N = 58$) participated in a 10-week placebo-controlled trial of sustained-release (SR) bupropion plus transdermal nicotine patch. Neuropsychological performance was evaluated in a subset of patients ($n = 30$), prior to pharmacological treatment, on a standardized battery including Wisconsin Card Sorting Test (WCST), Visuospatial Working Memory (VSWM) task, Continuous Performance Test (CPT), Iowa Gambling Test (IGT), California Verbal Learning Test (CVLT), Digit Span of the WAIS-III, and Trail Making Test (TMT) Parts A and B. Subjects were compared as a function of endpoint smoking status (Quit versus Not Quit, assessed by end of trial 7-day point prevalence abstinence, confirmed by CO level <10 ppm) on demographic traits, smoking, and clinical outcomes. While there were no significant baseline differences between quitters and non-quitters, non-quitters exhibited significantly greater deficits in performance on TMT-B ($P = .01$) and on Digit Span backwards ($P = .04$) compared to quitters. No associations were found between quit status and performance on other neuropsychological measures. Our findings extend results of previous studies (Dolan et al. 2004), which suggest deficits in working memory and executive function are associated with smoking cessation failure in schizophrenia. Specifically, cognitive deficits in frontal executive function and working memory associated with smoking cessation failure in this population. This suggests that targeting prefrontal deficits through pharmacological or behavioral interventions might improve smoking cessation treatment outcomes among individuals with schizophrenia. This is important for the development of tailored smoking cessation treatments in this population. This work was supported in part by NIDA grants RO1-DA-15757 and RO1-DA-13672 and KO2_DA-13672 (to TGP).
ID: 553571

AUTISM SPECTRUM DISORDER SYMPTOMS IN FIRST EPISODE AND ULTRA HIGH RISK PATIENTS

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Individuals with autism and schizophrenia spectrum disorders exhibit similar social, language, and sensory/motor behaviors. There have been no studies comparing specific differences in these domains in ultra high risk, first episode psychosis, and autism spectrum disorder patients. Four groups of 15 patients aged 12–18 diagnosed using gold standard measures as being ultra high risk (UHR), first episode (EPP), autism spectrum disorder (ASD) or typically developing (TYP) were ascertained from a clinically referred sample. Parents completed common autism research measures including the Social Communication Questionnaire, Social Responsiveness Scale, the Children's Communication Checklist-2, and Short Sensory Profile. Based on SCQ, 7 % of each UHR and EPP cohorts exhibited symptoms consistent with an ASD diagnosis. On the CCC-2, UHR and EPP exhibited deficits in the areas of articulation and phonology, coherence, nonverbal communication, increased scripted language, and language context violations. UHR resembled ASD in their tendency to talk repetitively about topics without regard for listener interest, while EPP resembled ASD in relational aspects of communication. On the SRS, EPP and UHR demonstrated impairments in reciprocal social behavior with similarities to ASD in reduced social motivation and increased autistic mannerisms. EPP exhibited unique resemblance to ASD in lack of social awareness and conversational skills. On measures of sensory issues, EPP and UHR differed from TYP in nearly all domains, yet shared many of the deficits exhibited by ASD: increased sensitivity to taste/smell, greater auditory filtering, and increased sensory seeking behaviors. Thus, preliminary findings suggest that ASD exhibit worse language, social, and sensory/motor symptoms than other groups. UHR and EPP show symptoms that are generally not different, however are of intermediate severity to TYP and ASD. Notable exceptions are that EPP, unlike UHR, show reduced quality of social awareness and communication of comparable severity to ASD; that UHR, unlike EPP, show inappropriate social initiations comparable to ASD; and that EPP and UHR are very similar to ASD with respect to some elements of sensory/motor atypicalities. This work has implications for understanding developmental precursors to psychosis, risk prediction, comparative neurobiology, and intervention.
ID: 551939

EFFECT OF ETHNICITY ON NEUROLOGIC PERFORMANCE AMONG FAMILY MEMBERS OF SCHIZOPHRENIC PATIENTS

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Neurologic exam abnormalities (NEA) are prevalent among patients with schizophrenia. Some studies of NEA find ethnic differences in performance, which may be relevant to understanding individual differences in NEA and for understanding inconsistencies among studies. Using a refined and distilled version of the Neurological Evaluation Scale (Buchanan and Heinrichs 1989), we found significant heritability estimates for certain individual NEA among extended multiply affected European-American (EA) families (Sanders et al. 2006). To evaluate the NEA in relation to ethnic factors, we compared individuals of African-American (AA) and EA ethnicity. EA samples formed part of a multi-generational, multiply affected family sample ascertained through schizophrenic probands (Sanders et al. 2006). We evaluated relatives who did not have schizophrenia or schizoaffective disorder, to avoid potentially confounding illness-related factors. Comparison of 108 AA and 212 EA relatives revealed significant differences with regard to the fist ring test (FR), audiovisual integration (AV), rapid alternating movements (RAM) and repetitive motor movements (RM), a global score comprised of FR, RAM and alternating fist-palm. Subsequent multivariate analyses suggested that ethnicity was a significant predictor in models including sex, age, ethnicity, psychiatric diagnosis, medical conditions and degree of relationship to proband ($P = .005$ or better, FR (right-errors), RAM (right-time), RAM (left-time). Separate analyses restricted to first degree relatives were significant with regard to RAM (right-time), RAM (left-time) and RM. The results were partly attributable to different speed-accuracy trade-offs: AA family members executed the tasks more quickly and less accurately than EA family members. If replicated and extended to probands and to the general population, these results would have implications for interpreting performance across ethnic groups.
ID: 551926

20. 20. Functional and Psychosocial Outcome

A RELIABLE RATING SCALE FOR WARD INTER-ACTION STYLE

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The purpose of the study was to create a simple, reliable ward atmosphere rating scale. The design of the study was the creation of a rating scale and then assessing inter-rater agreement. Based on the Staff-Resident Interaction Chronograph, a briefer rating scale for ward staff-patient interaction style was created. The new rating scale consistently has inter-rater reliabilities over 0.80 with ten minutes training time. Both staff and patients have been used as raters. Norms have been developed for formal groups, wards, and 1:1 interactions. This includes interactions per hour per staff member, interactions per hour per patient, and style of interaction (ratio of positive to negative to neutral). Judgments have suggested cutoffs for high, medium and low rates. By linking this with published data for the Staff-Resident Interaction Chronograph, there can be a very rough estimate of cut scores for the amount and style of interaction that relates to outcome, although this measure has not been tested for correlation with outcome. The tool has three columns and three rows. The three rows are "positive, neutral and negative" staff interactions, with the observer generating a hash mark (slash, "/") upon an occurrence of each staff interaction. The columns are for "definitions," "hash marks" and "write comments for further discussion." The "definitions" has multiple sub-sections within each main section, allowing further subtyping of ratings in the future. By recording the total observation time, average number of staff in the area during rating time, and average number of patients in the area during rating time, then rates per hour can be assessed. The rater observes an individual staff member, or an area such as a section of a day hall. The column "write comments for further discussion" is useful for generating group discussion on how to improve interaction. "I noticed you said … what about saying (different category)… instead?" Possible target rates include positives to neutral interactions at 2:1, no negative interactions, interaction rates at 15 per hour per patient, 100 per hour per staff, 250 per hour per ward. People at a variety of training levels (high school to doctoral, staff and patients) can reliably use the tool. The conclusion is that it is possible to create a simple reliable ward rating tool.
ID: 533934

INCREASING COHESION AND QUALITY OF LIFE AMONG RESIDENTS LIVING IN A BOARD AND CARE ENVIRONMENT

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Since the desinstitionalization of patients from psychiatric hospitals in the 1960s, most individuals with schizophrenia reside in community supported housing facilities. These community placements, however, are often ill-equipped to deal with residents' needs and have been described as "impoverished" (Hansson et al. 2002). Yet, research attempting to improve supported housing conditions for individuals with schizophrenia has been virtually nonexistent. The purpose of the present pilot investigation was to develop and implement a 9-month psychoeducational treatment program, based upon a family treatment model, aimed at improving the relationship among residents living in community housing facilities. Six residents living in a community board-and-care placement in San Diego participated in the study. Preliminary results indicate that residents who were highly negative in their attitudes toward the facility (as assessed by their level of expressed emotion) improved significantly in their perceptions of cohesion among residents ($t = 3.50$, $P < .05$) and improved marginally in their overall quality of life ($t = 2.43$, $P = .06$). These preliminary results suggest that psychoeducational interventions can be successfully implemented in a board-and-care facility and may lead to significant improvements in both perceptions of cohesion among residents and residents' quality of life.
ID: 550802

RELATIONSHIPS AMONG NEUROCOGNITION, THEORY OF MIND, SOCIAL COMPETENCE, AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

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Improving models of the relationships among variables that influence functioning will inform interventions targeting functional goals. This study examined how two constructs previously identified as important for functioning, neurocognition and social cognition, relate to functional capacity and functioning in a path analysis framework. 130 participants (M/F = 76/54; mean age = 46.4, SD = 11.0) with schizophrenia or schizoaffective disorder were evaluated. Neurocognition was indexed as a global composite of processing speed, working memory, verbal and visual learning and memory, and executive functioning. The Hinting Task was used to assess social cognition (Theory of Mind), the Maryland Assessment of Social Competence was used to assess functional capacity (performance-based social problem-solving roleplays), and a composite score for self-reported functioning was used from the Independent Living Skills Survey. The full model included neurocognition as a predictor of both social cognition and functional capacity; social cognition as a mediator between neurocognition and functional capacity; and functional capacity as a predictor of functioning. The model fit the data well ($\chi^2(df = 2) = 1.725$, $P = .422$; CFI = 1.0, RMSEA < .001), and accounted for 7.8% of the variance in functioning, 21.2% of the variance in functional capacity, and neurocognition accounted for 24.5% of the variance in social cognition. Social cognition served as a partial mediator between neurocognition and functional capacity. Examination of nested models (removing the direct effect of neurocognition on functional capacity, removing social cognition, or removing functioning) all resulted in poorer fit. In addition, adding the direct effect of neurocognition on functioning decreased model fit. These results support recent models of the relationships among these variables (eg, Green et al. 2000), and also suggest that theory of mind, in addition to social perception and emotion recognition, has a mediational role between neurocognition and functioning. Findings provide further evidence that neurocognition and social cognition are promising treatment targets for improving functioning in schizophrenia. However, it is clear that functional capacity demonstrates a strong relationship with predictor variables, and thus may be a vital measure to include in treatment studies targeting neurocognition and/or social cognition given that functioning is likely impacted by a myriad of other variables.
ID: 550777

DAILY LIFE CHANGES IN PSYCHOTIC SYMPTOM DIMENSIONS, APPRAISALS AND AFFECT DURING COGNITIVE BEHAVIOUR THERAPY

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Background: Experience Sampling Method (ESM) is a structured diary technique permitting 'on-line' measurement of daily psychotic experiences. It is ideally suited to detect the subtle changes in symptom dimensions and appraisals that are expected to occur with Cognitive Behaviour Therapy (CBT). Methods: This study assessed changes over time in appraisals of symptoms, characteristics of key symptoms, and affect. Twelve psychotic outpatients undergoing CBT participated, providing 1 273 datapoints in total. Individuals were signalled by a bleeping wrist watch to complete an ESM booklet at 10 random times of day for 6 consecutive days. They repeated this procedure at 5 time-points over a period of 15 months (baseline (at referral to the clinic); pre-therapy (after 6 months on the waiting list); mid-therapy (3 months into therapy); end of therapy (6 months post pre-therapy); follow-up (3 months after end of therapy)). Results: For hallucinations, significant changes compared to baseline were demonstrated from mid-therapy, and maintained at follow-up, in interference, controllability, beliefs about power of voices, insight, and 'decentring'("my problems are something to do with the way my mind works"). Intensity of voices was reduced at the end of therapy but was not maintained at follow-up, while voice-related distress did not reduce until follow-up. For delusions, significant changes were demonstrated from mid-therapy, and maintained at follow-up, in intensity, distress, interference, and preoccupation. Conviction was reduced at the end of therapy but was not maintained at follow-up, while insight did not increase until follow-up. Psychotic appraisals for both hallucinations and delusions reduced dramatically prior to, and during therapy, but these changes were not maintained. General negative affect, but not positive affect, was improved by therapy. Conclusions: This study demonstrates that ESM is a useful methodology to capture 'on-line' changes in psychotic phenomenology over the course of therapy. The pattern of results obtained in this small sample suggests that CBT has a significant impact on specific symptom dimensions and appraisals, while others such as delusional conviction and voice intensity are not affected.
ID: 550751

STRESS REACTIVITY, STRESS APPRAISAL AND COPING RESPONSES IN SCHIZOPHRENIA

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To date, research on the role of stress in schizophrenia has documented that individuals with schizophrenia experience more stress, although they do not necessarily report more stressful life events. Studies show that individuals with schizophrenia have an altered neuroendocrine stress response. There is also some evidence that individuals with schizophrenia are more likely to use ineffective coping strategies to alleviate stress. However, there has been no systematic investigation about how life events, appraisals of these events, perceived stress, HPA-axis stress response and coping strategies interact to increase the subjective experience of stress in individuals with schizophrenia. A better understanding of the mechanisms by which an event is experienced as a stressor in individuals with schizophrenia could further our understanding of the role of stress in triggering relapse of psychotic episodes. Results of this research may also provide a basis for the development of interventions targeted at stress management to prevent or delay stress-related relapse. Data will be presented on how individuals with schizophrenia differ from controls in their appraisal of and coping towards laboratory induced stress. We will also present similarities and differences in reported life stress (life events and daily hassles) as well as coping strategies and coping resources used to manage life stress.
ID: 550727

PERSPECTIVES ON THE ADHERENCE CHALLENGE: REPORT FROM AN NIMH-SPONSORED MEETING ON ADHERENCE METHODOLOGY

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The National Institute of Mental Health (NIMH) has a long history of supporting research on the problem of poor treatment adherence, the contributing factors to poor adherence, and interventions to improve adherence in those being treated for mental disorders, particularly schizophrenia. Although this support has produced a number of important findings and efficacious adherence enhancing interventions (AEIs), advances have been hindered by a number of methodological challenges, including poor translation of existing knowledge into clinical practice. In September 2007, NIMH convened a panel of treatment adherence researchers to discuss and articulate potential solutions for dealing with methodological adherence research challenges. The group discussed three primary methodological areas: participants, measures and interventions. When selecting patients for adherence-enhancing interventions (AEIs), a stepped-care approach was considered that draws from the universal, selective, and indicated prevention model and emphasizes the appropriate matching of interventions to the selected population. Suggestions were also made to reduce potential selection biases in patient recruitment and retention. The panel addressed the pros and cons of various methods that can be used to measure adherence, and concluded that it is appropriate to use multiple measures whenever possible. Finally, the panel identified a broad range of intervention approaches and conditions applicable to schizophrenia and other mental disorder treatments that are likely to be most effective at reducing barriers to adherence and reinforcing adherent behavior. Increased emphasis on patient-centered approaches and on ecological models that address not only the patient but also the broader environmental context of adherent behaviors were considered important directions for improving adherence to the treatment of schizophrenia and other mental disorders.
ID: 550724

FUNCTIONAL CAPACITY AND INTERVIEW-BASED MEASURES: RAND PANEL JUDGMENTS

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The ultimate goal of cognition enhancers for schizophrenia is to improve community functioning. However, changes in community functioning in schizophrenia may require long periods of time and depend on environmental factors such as the local economic situation that are beyond the scope of a clinical trial. Intermediate measures (ie, functional capacity or interview-based) are designed for use during the more limited time frames of clinical trials for cognitive enhancers. We convened a RAND panel to evaluate intermediate measures in order to select measures for a study of the relationship of intermediate measures to cognitive performance and functional outcome in the community. By review of the literature and contact with experts in the field, we identified nine performance-based measures and six interview-based measures of cognition. The

RAND panel included 11 members with expertise in cognition, clinical trials, community adaptation, neuroscience, biostatistics and other relevant disciplines. The panel met in February 2008 and their ratings form the basis of this presentation. Data for the performance-based measures were submitted to a formal RAND panel review involving advance ratings on specific criteria, in-person discussion and final rankings. The interview-based measures were not as well-suited for formal evaluation; the panelists reviewed measures in terms of criteria and provided consensus judgments. Based on the RAND panel ratings, five measures (three performance-based and two interview-based) were selected for inclusion in a reliability and validation study. They are: Independent Living Scales (ILS); Test of Adaptive Behavior in Schizophrenia (TABS); UCSD Performance-based Skills Assessment (UPSA) for performance-based; the Cognitive Assessment Interview (CAI) and the Clinical Global Impressions Scale for Cognition, for interview-based. These measures are all designed for administration in a clinical setting and have detailed training procedures available. They are all conceptually intermediate between laboratory measures of cognition and community functioning. The RAND panel process for decision making provided an effective method for reducing a number of potential candidate measures to a more limited number that can be subjected to rigorous evaluation.
ID: 550715

COMPARISON OF NEUROLOGICAL SOFT SIGNS BETWEEN UNTREATED AND ANTIPSYCHOTIC-TREATED SCHIZOPHRENIA PATIENTS

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The relationship between neurological soft signs (NSS) and antipsychotic in schizophrenia is sparsely studied. The purpose of this study was to compare the NSS in patients treated with antipsychotics and those who had remained untreated in a rural community of South India. The sample for the study comes from a project, in which community-living schizophrenia patients in Thirthahalli (an administrative block in South India with a population of 143 000) were identified and followed up. Of the initially identified 151 patients, 55 were not receiving any antipsychotics and 96 were receiving antipsychotics (85% were receiving atypical antipsychotics). A trained psychiatrist assessed their psychopathology using the Positive And Negative Syndrome Scale (PANSS; Kay et al. 1987). He also assessed the NSS using Neurological Evaluation Scale (NES; Buchanan and Heinrichs, 1989) in all the 96 patients on antipsychotics and 33 of the 55 patients not on antipsychotics (the rest 22 were too symptomatic to cooperate for a valid administration of NES). The table shows the comparison of the two groups. The treated group had significantly lesser scores (fewer soft signs) on two components of NES: complex motor sequencing and sensory integration signs. They also had lesser psychopathology scores. Pearson's correlation showed that the higher the NES component scores, the higher was the PANSS negative syndrome score in both groups. The association among higher NSS, greater psychopathology and untreated state could be a natural selection or a chance association, limiting interpretation on causality. Nearly all medicated patients received atypical antipsychotics. This leads to a speculation that NSS may be reversible if treated with these medications. This remains to be tested in a prospective design.

Table. Shows the difference between treated and untreated patients. Second and third columns represent mean (SD) except in case of sex

Variable	Treated patients ($n = 96$)	Untreated patients ($n = 33$)	t/χ^2	P
Age in years	41.6 (11.4)	40.2 (9.8)	0.62	0.52
Sex (Males:Females)	49:47	18:15	0.12	0.72
Duration of illness	11.4 (8.7)	9.7 (6.3)	1.01	0.31
Years of education	6.5 (4.8)	6.3 (4.4)	0.12	0.91
PANSS positive syndrome score	10.7 (5.8)	19.2 (8.8)	5.3	<0.01
PANSS negative syndrome score	17.6 (6.6)	27.1 (7.3)	6.94	<0.01
NES Motor coordination	2.01 (2.7)	2.51 (2.7)	0.91	0.36
NES complex motor sequencing	8.8 (3.9)	10.5 (2.8)	2.69	<0.01
NES sensory integration	5.4 (2.7)	7.0 (3.3)	2.65	<0.01
NES Primitive reflex	3.8 (2.5)	3.8 (2.9)	0.049	0.96

ID: 550579

EXAMINING THE RELATIONSHIP BETWEEN NEGATIVE SYMPTOMS AND SOCIAL SKILL IN SCHIZOPHRENIA: A PILOT STUDY OF THE NEW NIMH-MATRICS NEGATIVE SYMPTOM RATING SCALE

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An NIMH consensus development conference on negative symptoms (Kirkpatrick et al. 2006) recommended the development of a new negative symptom assessment instrument that addresses conceptual and psychometric limitations of existing instruments. The NIMH-MATRICS negative symptom workgroup has developed a new instrument, the Negative Symptom Rating Scale (NSRS), which represents a substantial step forward in the assessment of this critical symptom domain. As part of ongoing efforts to examine the reliability and validity of this new measure, the current study examined how the NSRS is related to social skill. Prior studies have shown that negative symptoms are associated with behavioral skills deficits in schizophrenia and we sought to replicate these findings with the NSRS. Further, we sought to examine which negative symptoms were most strongly associated with skills deficits and if these associations were independent of other psychotic or affective symptoms. Forty individuals diagnosed with schizophrenia or schizoaffective disorder will complete assessments of current symptoms, social functioning in the community, and social skill. Social skill will be assessed with a role-play-based social skills assessment, the Maryland Assessment of Social Competence (MASC). Other symptoms will be assessed with the BPRS and the Calgary Depression Scale. Functioning in the community will be measured with the Birchwood Social Functioning Scale. Results will provide additional information regarding the performance of the NSRS in schizophrenia and inform the further development of this instrument.
ID: 550519

FUNCTIONAL SIGNIFICANCE OF AFFECT RECOGNITION DEFICITS IN SCHIZOPHRENIA

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Affect recognition (AR) is a core component of social information processing, thus may be critical to understanding social behavior as well as functioning in broader aspects of daily living. Deficits in AR are well documented in schizophrenia (Sz), and have been associated with poorer independent functioning. However, studies also show variability in the degree of AR impairments, with some noting subgroups of patients with near-normal AR performance. Variability in the expression of AR deficits in Sz has previously been linked to differences in course, symptomatology, diagnostic subtype, and neurocognition. In the current study, we sought to evaluate the functional significance of AR deficits by comparing subgroups of Sz patients with normal-range AR performance to those with impaired AR performance on proxy and interviewer-rated measures of real-world functioning. Sz outpatients were classified as normal-range ($n = 17$) and impaired ($n = 31$) using logistic regression, in which BLERT scores were entered as a predictor of diagnosis against a normative sample of healthy control subjects ($n = 56$). The derived Sz subgroups were then compared on proxy (UCSD, UPSA, SSPA, MMAA) and interviewer-rated (QLS, ILSS) measures of functioning. Differences in demographics, symptom severity, and neurocognitive test performance were also evaluated. Because the normal-range AR subgroup scored significantly higher than the impaired subgroup on a number of cognitive variables, a neurocognitive composite score was computed for use as a covariate in primary analyses. Comparison on proxy measures indicated superior MMAA performance in the normal subgroup, but comparable UPSA and SSPA performance between groups. Covariate analyses indicated that the difference in MMAA was fully mediated by differences in neurocognitive ability. Group comparisons on interviewer-rated measures indicated significantly higher QLS in the normal-range AR subgroup, but comparable ILSS. Significant differences in QLS remained after entering the neurocognitive composite as a covariate. These results support three main conclusions. First, AR, like many other domains of psychopathology studied in Sz, is preserved in select subgroups. Second, there is a positive relationship between AR performance and functional outcome measures. Third, neurocognition appears to mediate the relationship between AR and proxy, but not interviewer-rated, measures of functioning.
ID: 550456

NEGATIVE SYMPTOMS AND MOTIVATIONAL DEFICITS AS PREDICTORS OF DISABILITY

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In schizophrenia, severity of cognitive impairments and performance on measures of functional capacity are clear predictors of real world disability. Various symptomatic factors serve to mediate the relationships between capacity and real world outcomes. Specifically, deficits in motivation and other negative symptoms may have greater impact on outcomes than ability variables alone. Two hundred and forty three older patients with schizophrenia were assessed with a neuropsychological (NP) battery, the Positive and Negative Syndrome scale (PANSS), rated by their case managers for real world social and community activities, and were assessed for social competence and functional abilities using the following scales: The Social Skills Performance Assessment (SSPA), Everyday Living Skills (UCSD) Performance-Based skills assessment (UPSA). Scores on the SSPA and PANSS negative subscale were accounted for variance in social outcomes (R-squared = .17), but NP impairments were not an independent predictor. When SSPA scores were forced in the equation first, PANSS negative symptoms still accounted for variance in real-world social outcomes; when the order of entry was reversed, the SSPA did not enter the equation. In contrast, community activities were well predicted by these variables: r-squared = .26. SSPA scores, UPSA scores, and NP impairments all entered the equation across combinations of entry order, but negative symptoms accounted for no variance unless they were entered into the equation first and then only accounted for 3% variance. Negative symptoms appear to have a substantial influence on social outcomes that exceeds that of social abilities. In contrast, community activities are not greatly influenced by the severity of negative symptoms. Efforts to treat real world disability will have to be aimed at the determinants of these outcomes; improving cognitive or social abilities may only influence real-world social outcomes if negative symptoms are reduced as well.
ID: 550417

A SYSTEMATIC REVIEW OF THE CORRELATIONS BETWEEN FUNCTIONAL CAPACITY, COGNITIVE IMPAIRMENT, AND FUNCTIONAL DISABILITY: IMPLICATIONS FOR TREATMENT STUDIES

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Background: Impairment on neuropsychological (NP) tests has been found to be correlated with the presence and severity of real-world functional disability in schizophrenia. A new feature of this research has been the development of performance-based measures of living skills, referred to as functional capacity (FC). As these measures seem to be more proximal to real-world disability, they may be more strongly correlated with real-world outcomes than NP impairments. Methods: For a different study, the existing English language literature was reviewed to identify all studies involving formal ratings of real-world disability in schizophrenia. We then selected the most widely used functional outcomes measures ($n = 11$) and all studies using these measures were examined to see if they also collected information on NP performance and FC. Results: We found a total of 25 studies using those 11 scales that collected NP performance, 9 studies that had measures of functional capacity, and 5 studies that had both. The averaged correlation between composite NP performance and real-world outcomes was $r = .41$, while the correlation between NP performance and FC was $r = .63$ and the FC to real world outcomes correlation averaged $r = .46$. In the studies where both NP and FC performance were examined, FC was in all cases more strongly correlated with real-world disability then was NP impairment and in some cases accounted for all of the variance in the correlation between NP impairment and real-world outcomes. Implications. Direct assessment of FC appears to give a stronger signal than NP performance for predicting real-world disability. Further, there is minimal evidence regarding associations between neuroscience measures and real-world outcomes. Later research will need to evaluate these relationships and determine if neuorscience measures add to the prediction of disabiity and improve treatment development efforts as a result.
ID: 550327

VALIDATING MEASURES OF REAL-WORLD OUTCOME: THE RESULTS OF THE VALERO EXPERT POLL AND RAND PANEL

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Background: Recent studies have shown that there is considerable discrepancy between self-reported real-world outcomes and several other aspects

of the functional outcomes construct, including informant reports, performance on neuropsychological tests, and measures of functional capacity. It is not clear whether these discrepancies originate from the psychometric instruments used to examine real-world outcomes or from the perspective of different informants. The VALERO (Validation of Everyday Real World Outcomes) was designed to directly compare different psychometric instruments across different informants. Methods: The first step of the study was an expert poll, where experts ($n = 75$) on real-world outcomes were asked to provide their opinions about the best measures for assessment of real-world outcomes. After these nominations were received, 11 outcome measures, examining social functioning, independent living, or combinations of these outcome domains, were identified as most highly regarded. All published data on these 11 scales was collected and provided to 9 members of a RAND panel. Panelists were asked to rate the scales on reliability, convergence with other elements of outcome, sensitivity to change, practicality, usefulness for multiple raters, independence from symptoms, and comprehensiveness. Results: Scales were selected on the basis of highest ratings for social, functional, and hybrid scales. The two highest rated hybrid scales were the Quality of Life Scale (QLS) and the Specific Levels of Functioning (SLOF); the two highest rated social functioning scales were the Social Behavior Schedule and the Social Functioning Scale; and the two highest rated functional scales were the Independent Living Skills Schedule (ILSS) and the Life Skills Profile (LSP). Two of these scales, the ILSS and SLOF are designed to used as questionnaire measures with no interview required. Implications. The results of this study reflect the current consensus of the field with regards to the assessment of real-world functional outcomes. All of these scales are being studied in terms of their convergence with other elements of outcome and suitability across multiple raters.
ID: 550320

PRELIMINARY VALIDATION OF THE ENGLISH VERSION OF THE SCHIZOPHRENIA QUALITY OF LIFE SCALE (S-QOL)

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Objectives: This study assesses the validity and responsiveness over changes of the English version of the S-QoL, first schizophrenia-specific health-related quality of life scale developed from patients' viewpoint on the need-based framework. Methods: The S-QoL, comprising 41 items exploring eight dimensions (Psychological Well-being, Self-esteem, Relations with Family, Relations with Friends, Resilience, Physical Well-being, Autonomy and Sentimental Life), was first developed and validated in French. After a standard backward-forward translation process, its English version was tested in a sample of patients with schizophrenia. Two assessments were performed: baseline and 12 weeks later. Psychometric properties (validity and sensitivity over changes) were evaluated using methods from Classical Test Theory, Rasch analyses and structural equation modelling. Results: A total of 128 patients filled-in the S-QoL. The factorial structure of the original version was globally retrieved. The questionnaire was well accepted (missing dimension rates lower than 3%). Cronbach's alphas were greater than 0.70 for 6 of the 8 dimensions. The S-QoL dimensions and total score were statistically correlated with depression assessed with the Calgary Depression Scale for Schizophrenia (CDSS), and severity of symptoms measured by the Positive and Negative Symptoms Scale (PANSS). Using

the sub-sample of patients rated "Very much Improved" or "Improved" on the Clinical Global Impression of Improvement (CGI-I) at Week 12, all the dimensions and the total score were statistically significantly improved. Five of the dimensions, as well as the total score, reached an effect size of at least 0.50 indicating an at least moderate change on health status. Conclusions: These results strengthen the usefulness of assessing the impact of schizophrenia on patients' everyday life with the S-QoL, specifically designed for assessing the health-related quality of life of patients with schizophrenia. Its sensitivity to changes in health state is of major interest for evaluative purposes.
ID: 550310

ALCOHOL AND ILLICIT DRUG USE AFTER ONE YEAR COMPARED WITH BASELINE IN NORWEGIAN FIRST-EPISODE PSYCHOSIS PATIENTS

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The study investigates stability of alcohol and illicit drug use over the first year after the first-episode of psychosis using Alcohol Use Disorders Identification Test (AUDIT) (1) and Drug Use Disorders Identification Test (DUDIT) (2), self-rating questionnaires that assess level, pattern, and behavioural consequences of substance use. Thirty-six women and 49 men with first-episode non-organic psychosis from the Thematic Organized Psychosis study (TOP) at University of Oslo, Norway who met DSM-IV criteria for schizophrenia spectrum disorder ($n = 45$), affective psychotic disorder ($n = 17$) or other psychotic disorder ($n = 23$) participated. AUDIT and DUDIT were administered at inclusion and at one year follow up. Maximum score of AUDIT and DUDIT is 40 and 44, respectively. AUDIT score of 6 for women and 8 for men are cut-off levels for hazardous or harmful use of alcohol. Cut-off scores for DUDIT are 6 for men and 2 for women (2). Level of functioning was assessed with Global Assessment of Functioning scale (GAF), split version. At baseline 33 (39%) patients had an AUDIT score above cut-off, whereas 32 (38%) scored above cut-off for DUDIT. There were no gender differences in proportion of patients above cut-off. Men scored higher than women by total DUDIT scores ($P = .008$), but not by total AUDIT scores. There was an increase in level of functioning over the year as measured by GAF-F (from 45.9 (SD 14.7) to 54.0 (SD 16.3), $P < .001$). At one year follow up, 22 (26%) patients scored above DUDIT cut-off, a significant reduction ($P = .002$) from baseline. When divided by gender, the reduction was significant only for men ($P = .005$). No significant change was seen for AUDIT scores at one year follow up. A reduction of hazardous or harmful use of illicit substances but not of alcohol was found over the first year after first-episode of psychosis. Levels of alcohol misuse among women were comparable to that of men. The results indicate that treatment strategies should increase focus on reducing alcohol misuse in this patient group.

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ID: 550295

INTENSIVE CASE MANAGEMENT OF CLIENTS AT HIGH RISK FOR SUICIDE: COMPARING OUTCOME TO TREATMENT AS USUAL IN A SPECIALISED EARLY PSYCHOSIS PREVENTION PROGRAM (EPPIC)

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Introduction: The first episode of psychosis is a critical period where early intervention can alter the trajectory of the young person's ongoing mental health and general functioning. The Intensive Case Management (ICM) team was developed as a sub-program of the Early Psychosis Prevention and Intervention Program (EPPIC- Melbourne Australia) in 2002 to provide assertive outreach to young people experiencing a first episode of psychosis who are at high risk due to level of risk to self/others, disengagement or suboptimal recovery. Method: Individual and general service key performance outcomes were assessed on 120 consecutive referrals within the first 5 years of operation relative to 50 EPPIC treatment-as-usual (TAU) clients matched for age, gender, year of entry, and diagnosis. Results: ICM clients had greater levels of anti-social personality disorder traits ($P < .01$), utilised significantly greater levels of illicit substances ($P < .03$), had no adverse events, had less days in crisis managed by a crisis assessment (CAT) team, and had reduced number of inpatients admissions ($P < .02$) and days in hospital ($P < .03$) relative to EPPIC TAU over 2 years. Conclusions: Our findings support a clinical rationale for incorporating an intensive case management team within an already unique service program targeted at the early detection and treatment of psychosis.
ID: 550240

ILLNESS PERCEPTIONS IN PATIENTS WITH A FIRST-EPISODE PSYCHOSIS AND THE ROLE OF CHILDHOOD TRAUMA

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Over the past two decades there has been increased interest and research into the potential causal role of childhood trauma (CT) in psychotic disorders. Since CT has been found to impact on cognitions and emotions, identifying the influence of CT on beliefs about current mental health concerns in first-episode psychosis (FEP) patients may hold important implications for formulation and treatment in this illness group. In this study forty-one ($n = 41$) FEP patients (25 males and 16 females, mean age 19.8 years) were recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC) at ORYGEN Youth Health and assessed on measures of psychopathology, retrospective accounts of CT, functioning, and current illness perceptions. Childhood sexual abuse (CSA), physical abuse (CPA) and emotional abuse (CEA) were reported by 31%, 41% and 63% of the patients, respectively. Histories of childhood physical neglect (CPN) and emotional neglect (CEN) were found in 63% and 36% of patients respectively. There were no significant differences in illness perception constructs between those patients that had experienced CSA or CPA and those that had not. FEP patients that had experienced CEA (M = 18.54, SD = 6.02) were more likely to perceive their illness as chronic ($t_{39} = 2.08$, $P < .05$) compared to those patients that had not experienced CEA (M=14.40, SD=6.39). Patients that had experienced CEA were also more likely to perceive their mental health problems as a consequence of difficulties in life ($t_{39} = 2.10$, $P < .05$), and have a less coherent understanding of their illness ($t_{39} = 2.31$, $P < .05$). Those patients that had experienced CPN also had a less coherent understanding of their illness compared to those that had not experienced CPN ($t_{39} = 2.05$, $P < .05$). Methodological issues in the measurement of CT across research studies remain, however, the high prevalence rates of CT in our group are comparable with previous research. Our findings suggest that CT has a clear role in modifying perceptions of subsequent illness, but that further exploration is required and an emphasis on CSA or CPA alone may not adequately address the complex issues related to CT in FEP. Further analysis is planned in order to determine if there are differences in levels of symptomatology or short-term functional outcome between those FEP patients that have experienced CT and those that have not.
ID: 550205

VALIDATING ASSESSMENTS OF REAL-WORLD OUTCOMES IN SCHIZOPHRENIA

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Among people with schizophrenia, impairment in everyday functioning skills (including social and occupational functioning, independent living, medication management, and basic self-care) is cognitively mediated. As new pharmacological and psychosocial treatments for cognitive impairment are tested, the need grows to demonstrate the real-world significance of neurocognitive gains by patients. The moderate correlations between neuropsychological measures and functional outcome measures vary depending on the kind of the functional outcome measures used (eg, self-report vs. informant report vs. performance-based), and it remains unclear which existing measures best characterize the real-world performance of patients. We have launched a series of three studies whose overall goal is to improve the assessment of real world functioning in schizophrenia. We will examine the convergence between a wide range of existing real-world rating scales and performance-based measures (including neuropsychological assessments and functional capacity assessments). In this report of the first study, we will include data from >100 geographically and ethnically diverse schizophrenia participants who have undergone assessment using six, RAND-panel nominated real-world functioning scales (both self-report and informant-report versions), neuropsychological assessment using the MATRICS Consensus Cognitive Battery, and the UCSD Performance-Based Skills Assessment. The RAND-nominated scales include the Independent Living Skills Survey, Life Skills Profile, Quality of Life Scale, Social Behavior Schedule, Social Functioning Scale, and Specific Level of Functioning Scale. We will present the correlations between these measures, including the convergence between self-reports and informant reports of functioning. Our goal is to identify (1) the best real-world functioning scale based on convergence with both other real-world outcome measures and with neuropsychological and functional capacity measures and (2) the best rater of functioning (eg, patient, relative, case manager, or medical prescriber). This work was supported by linked NIMH R01s, MH078737 (Patterson) and MH078775 (Harvey).
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THE SUBJECTIVE EXPERIENCE OF PEOPLE AT A HIGH RISK OF DEVELOPING PSYCHOSIS JOURNEYING INTO AND THROUGH AN EARLY DETECTION FOR PSYCHOSIS SERVICE

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The study aimed to explore how people who have been assessed as being at a high risk of developing psychosis entered into services and journeyed through them. We used a qualitative approach to study the subjective experience of the individual in keeping with the view that it is important to empower service users by allowing participants to give voice to their experiences. Individual semi-structured interviews were conducted with ten participants ranging in age from 16 to 30 years (mean age 21.8 years) recruited from an early detection of psychosis service in the United Kingdom. The interviews initially focused on the participants' perception of their experiences and their experience of professional involvement and were developed in line with theoretical sampling as a response to the themes that arose from the data. The data were analyzed using grounded theory. Three main themes were identified in the analysis: 1. Perception of needs which encompassed how the participants identified the need to access services and what they required from the service. This led to help seeking as their difficulties worsened, to an identification of what was required from the service and an acknowledgement of when these psychological needs were met. 2. Participants' subjective journey into and through the service which was recounted as at times progressive, regressive or static, and the identification of drawing upon personal resources when this journey became difficult. 3. Participants' orientation toward their personal future which was identified by all the participants but with a strong recognition that basic needs (such as housing) have to be met before psychological issues can be addressed. The study concluded that participants' journey into and through an early detection service is multi-faceted. The subjective accounts highlight a strong perception of needs and an acknowledgement of what is required from the service to meet these needs. There is also a recognition that the journey is arduous and at times it is necessary to rely on personal resources. Ultimately participants are orientated towards their future goals but identify a hierarchy that they must progress through before meeting their psychological needs. This research furthers our understanding of how people assessed as being at risk of developing psychosis make sense of their experiences whilst in an early detection service and what they perceive their needs to be during this time.
ID: 550091

IMPACT OF A SHORT-TERM SKILLS-BASED INTERVENTION PROGRAM ON LEVEL OF INSIGHT AND ENGAGEMENT IN FOLLOW-UP PSYCHIATRIC CARE

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The purpose of this NARSAD-funded study is to examine the impact of a psychosocial intervention program on insight into illness and the role of insight in adherence to rehabilitative efforts among individuals diagnosed with schizophrenia or schizoaffective disorder. Lack of insight is associated with treatment non-adherence, higher relapse rates and re-hospitalizations, and poorer social and occupational functioning. Psychosocial intervention programs show promising results in improving treatment adherence but research results are inconsistent in describing the role of insight in rehabilitation. Outpatients at the West Los Angeles VA Medical Center participate in the Community Re-Entry Program (CREP), aimed at increasing understanding and self-management of illness and improving participants' ability

to achieve successful community living. Insight into illness is assessed via two self-report questionnaires before and after participation in the psychosocial treatment program. Illness-management educational sessions include exposure to illness symptoms, warning signs of relapse, medication management, communicating with health-care professionals, and planning for psychiatric emergencies. Pre-and post tests designed for the CREP program are administered to assess retention of session content. After completion of the treatment program, study participants are monitored for six months and are compared to individuals receiving standard care. Preliminary results conducted with a limited data set yielded no support for the hypothesis that treatment group participants would report increased level of insight following completion of the intervention program ($N = 11$). The hypotheses that treatment group participants would report greater insight into illness ($N = 21$) and demonstrate greater involvement in rehabilitative efforts and lower relapse rates ($N = 9$) compared to participants receiving usual care were not supported. However, CREP test scores suggest that treatment group participants increased their knowledge of illness management, retained these skills after participation in the treatment program, and demonstrated greater self-management skills than individuals in the comparison condition. Lack of support for the hypotheses on the outcome variables may be associated with the small number of subjects to date and a floor effect due to low relapse rates among study participants during the observation period.
ID: 550065

METACOGNITION AS A PREDICTOR OF WORK FUNCTION OVER SIX MONTHS FOR PARTICIPANTS WITH SCHIZOPHRENIA

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Introduction: It has been widely suggested that impairments in the capacity for metacognition, or the ability to think about thinking, are a root cause of psychosocial dysfunction in schizophrenia. To date, however, most of the literature supporting this has come from cross sectional studies which report significant correlations between assessments of metacognition and function. Thus it is unclear whether metacognitive capacity is prospectively linked with behavior in real life settings. To explore this possibility we sought to determine whether metacognition assessed as baseline predicted work performance in a vocational rehabilitation program over the following six months. Methods: Participants were 56 adults with schizophrenia in a post acute phase of illness enrolled in a 6 month study of the effects of cognitive therapy on work outcome, all of whom worked for at least 66% of the weeks they were assigned work. Metacognitive capacity was assessed using an abbreviated form of the Metacognition Assessment Scale (MAS) using personal narratives elicited with the Indiana Psychiatric Illness Interview. Participants were then assigned to a work placement and work performance was assessed biweekly using the Work Behavior Inventory (WBI) by raters blind to MAS ratings. Results: Participants were divided into three groups on the basis of their score at baseline on MAS subscale Awareness of One's Own Mind: Poor self-awareness ($n = 21$) Limited self-awareness ($n = 23$) and In tact self-awareness ($n = 13$). A repeated measures ANOVA was then conducted comparing work performance across 13 rating points (biweekly for 26 weeks). This analysis revealed significant effect for time ($f_{2,12} = 3.77$ $P < .001$) with all groups showing better work performance over time and a significant group effect ($f_{2,53} = 6.86$ $P < .001$) with participants rated as having in tact self-awareness having better ratings of work performance than the groups with poor or limited self-awareness beginning in the fifth week of work. A significant interaction was also noted ($f_{2,12} = 1.57$; $P < .001$) with the group showing limited self-awareness making an initial gain in work performance which they could not sustain. When analyses were repeated covarying for executive function using the

Wisconsin Card Sorting Test, the main group effect was found to persist. Discussion: Results suggest the deficits in awareness of one's own thoughts may be a barrier to effective vocational function over time in schizophrenia. ID: 549846

EFFECTS OF COGNITIVE BEHAVIORAL THERAPY ON WORK QUALITY AND QUANTITY FOR ADULTS WITH SCHIZOPHRENIA

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The Indianapolis Vocational Intervention Program (IVIP) is a manualized program of cognitive-behavioral group and individual interventions which was designed to help persons with schizophrenia to persist and perform better at job placements. To date, two studies have supported its feasibility and revealed high levels of participant satisfaction. However, the effects of IVIP on work quality and quantity have yet to be tested in a randomized controlled trial. In this study, 100 participants with schizophrenia or schizoaffective disorder were offered a six month job placement and randomized to receive IVIP ($n = 50$) or support services ($n = 50$) matched for treatment intensity. Assessments revealed groups were equivalent at baseline in terms of symptom severity and readiness for rehabilitation. Once participants were working number of hours worked was recorded weekly and job performance was assessed biweekly using the Work Behavior Inventory (WBI) with raters blind to condition. To examine whether IVIP led to greater levels of work quantity T-tests were performed which revealed that participants in the IVIP group worked significantly more hours and weeks than participants in the support condition. To determine whether IVIP led to greater work quality, repeated measures ANOVA were conducted comparing biweekly ratings of work performance using the WBI for 56 participants who worked for at least two-thirds of the intervention. This analysis revealed that participants in the IVIP group had generally better work performance than those in the support condition. Results suggest that receiving a cognitive-behavioral interventions concurrent with work placement services may improve rehabilitation outcomes in people with schizophrenia.
ID: 549684

EFFECTS OF THE DURATION OF UNTREATED PSYCHOSIS ON TREATMENT OUTCOME IN CHRONICALLY INSTITUTIONALIZED PATIENTS WITH SCHIZOPHRENIA

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Objective: Duration of untreated psychosis (DUP) is widely cited as a factor in predicting treatment response in schizophrenia. Studies have found that longer DUP is associated with more severe negative symptoms and cognitive deficits, and less improvement in positive symptoms during the first 6 months of treatment. Most studies have concentrated on relatively short DUP and short-term social or vocational outcomes, and they have been confounded by clinical and socioeconomic factors that interfered with the onset of the treatment. Our previous study of 101 autopsy subjects with schizophrenia, chronically hospitalized in psychiatric institutions in New York State, found that the introduction of antipsychotic medications in these institutions in 1954 did not reduce the number of positive symptoms over the years. This failure may have been related to prolonged duration of illness before antipsychotic treatment. By studying the extensive records of subjects who were admitted to the state hospitals prior to the widespread introduction of chlorpromazine in 1954, we have obtained a sample in which DUP was determined only by the date of onset of psychosis and institutional initiation of neuroleptic treatment. Method: We have evaluated positive, negative and cognitive symptoms in 95 schizophrenia subjects: 44 with long DUP, admitted between 1941 and 1943, and 51 with short DUP, admitted between 1951 and 1953. Diagnoses were determined and positive and negative symptoms catalogued with the modified Diagnostic Evaluation After Death. Cognitive function was evaluated with the Scales of Cognitive Impairment Rated From Institutional Records. Results: Many of the short DUP patients experienced a gradual improvement in overall functioning. Seventy-one percent were discharged, after a mean duration of treatment of 14 years, to outpatient facilities or to their own custody with a year of follow-up by a state social worker. According to the registry, they were not readmitted to the state system. In contrast, 77% of the long DUP patients never achieved a state of relative independence longer than 6 months and remained hospitalized ($P < .00001$). Discharges of patients with long DUP were mostly to nursing homes after a mean treatment duration of 19 years. Conclusions: Earlier treatment with phenothiazines was associated with better long-term outcome and a very gradual improvement in symptoms. Acknowledgements: NARSAD Wodecroft Award, MH60877, Lieber Ctr. for Schizophrenia Res.
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MEASURING FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA: RESULTS OF AN EXPERT SURVEY AND RAND PANEL

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Recent research on functional outcomes in schizophrenia has highlighted problems with many of the existing measures. Researchers often use different outcome measures which evaluate different types of outcomes (social vs. living skills). Further, there is a often a substantial discrepancy between the level of functioning reported by a patient when compared to an informant. It has not been determined whether the discrepancies in ratings originate from inadequate measures, is the result of differing opinions of the patient and caregivers, or a combination of these problems. In Fall 2007, 49 experts in the field of schizophrenia and severe mental illness were asked to nominate what they felt were the best scales measuring real world outcomes in schizophrenia. Fifty-nine measures were nominated. The investigators examined the results of the poll and selected 11 scales that a) were the most highly nominated, b) had the most published validity data, and c) best represented the domains of interest. Information regarding the reliability, usefulness, sensitivity to treatment, practicality, and convergence with measures of symptomatology and cognition for the 11 scales was provided to the 9 experts who served as RAND Panelists. Of the 11 measures selected, panelists were asked to rate each measure in each area on a 5-point Likert scale. Ratings that were discrepant (determined by a SD > 2) were discussed by the panelists until each panelist could agree on a score ±1. The two scales that scored the highest in each of the three domains (Hybrid, Social Functioning, and Everyday Living Skills) were selected for use in Study 1 of the Validation of Everyday Functioning in Schizophrenia (VALERO) study. The scales selected were: Quality of Life Scale (QLS), Specific Levels of Functioning scale(SLOF); Social

Behavior Schedule, Social Functioning Scale, Independent Living Skills Schedule (ILSS) and the Life Skills Profile (LSP). The results of the first phase of the VALERO initiative show that although there are significant discrepancies in scales used for the assessment of functional outcome, a convergence in opinions is possible. All scales nominated are currently being evaluated for their usefulness and applicability in measuring functional outcomes as reported by the patient and informant, as well as performance based measures of cognition and social and everyday living skills. NIMH Grant MH 78775.
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OPERATIONALIZING COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA: MATRICS CONSENSUS COGNITIVE BATTERY AND ALTERNATIVES

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The NIMH-funded academic-FDA-industry partnership known as MATRICS delineated seven cognitive domains to assess cognitive impairment associated with schizophrenia (CIAS) and created a consensus test battery (MCCB), which represents one operationalization of the concept of CIAS. Fully computerized batteries now commercially available offer alternative ways to operationalize CIAS. Whether these alternatives assess the same constructs as MCCB remains to be fully explored. As part of a noninterventional, cross-sectional study all subjects were tested on the MCCB ($N = 202$) while half were randomized to do one of two fully computerized tests, CNS Vital Signs ($N = 103$) or Cogstate ($N = 99$). Subjects were stable, outpatient schizophrenia patients aged 18–65 years under treatment with FDA-approved antipsychotics. Clinical (PANSS, CGI) and functioning (UPSA-2, SCoRS) measures were administered. Two global clinician-rated functioning items were also included.The correlational structure of the computerized batteries and MCCB were examined using linear regression and factor analytic methods. The influence of symptom measures on functional endpoints was explored. Correlations between composites for the two fully computerized batteries and the MCCB were fairly high ($r = .75$); at the domain level they were in the moderate range (.30–.50). Fit for a one-factor model was good for MCCB, marginal for CNS Vital Signs, and poor for Cogstate. Across all three, the domains of working memory and attention domains were among the highest loadings. The comparability of these different operationalizations of CIAS is analyzed in terms of domain structure and associations with the clinical severity and functioning measures. Source of Funding: Pfizer, Inc.
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ECOLOGICAL VALIDITY OF COGNITION AND FUNCTIONING IN SCHIZOPHRENIA: A RELIABLE METHOD TO ASSESS NATURALISTIC BEHAVIORS IN EVERYDAY CONTEXTS

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Objective: Evaluating the ecological validity of the constructs of cognition and functioning has emerged as an important area in schizophrenia research. Two types of ecological validity, verisimilitude and veridicality, are relevant. Our focus is on veridicality, which concerns whether cognitive or functional measures are empirically related to what individuals do when they are directly observed in their daily lives in naturalistic community settings. The purpose of this study was to develop a reliable and valid method to rate daily cognitive and functional tasks as they occur in the course of daily life. Method: Ten subjects with SCID-diagnosed schizophrenia were videotaped in situ during their usual daily activities over two weeks, yielding approximately 160 hours of video data. Subjects were selected whose composite score on the MATRICS Consensus Cognitive Battery fell in the top ($n = 5$) or bottom ($n = 5$) third from the mean. A consensus-based strategy was used to demarcate cognitive and functional behaviors as they occurred in everyday settings. Three raters blind to subjects' MATRICS scores rated cognitive and functional behaviors for complexity, accuracy, independence, and novelty. A coding strategy was also used to quantify subjects' level and range of activity over a unit of time. The coding scheme was elaborated and refined until adequate inter-rater reliability was reached. The coding scheme is currently undergoing further validation in an additional sample of 10 subjects. Results: Everyday behaviors performed by subjects varied substantially, although all subjects performed a core set of cognitive and functional tasks that were thoroughly captured on video- and audiotape. We reached adequate levels of inter-rater reliability for these daily cognitive and functional tasks. Reliability was reached on scores of independence, accuracy, complexity (but not novelty), as well as on the level and range of activity. Preliminary evidence on the validity of the ratings will also be presented. Conclusions: This pilot study of 10 subjects with schizophrenia yielded a reliable strategy for rating everyday cognitive and functional behaviors in naturalistic, community settings. The method signifies a substantial advance, since it will now be used to assess the veridicality (ecological validity) of neurocognitive and functional instruments. In addition, the method can be used to clarify moderators and mediators of everyday disability in schizophrenia.
ID: 549572

MEDIATORS AND MODERATORS BETWEEN NEUROCOGNITION AND FUNCTIONAL STATUS IN SCHIZOPHRENIA

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Neurocognitive deficits in schizophrenia have been reliably demonstrated across studies and consistently reported to affect patients' functional status. However, despite the important link between neurocognition and adaptive functioning, the nature of this relationship is complex and multidimensional. In an effort to better understand this relationship, the present study utilized the structural equation modeling (SEM) approach to examine potential mediators and moderators hypothesized to influence the connection between neurocognition and functional outcome. An important advantage of this approach is that it can be used to simultaneously examine the relationships among measured variables and their respective latent constructs, as well as the direct and indirect interconnections among these constructs. Using data from 180 schizophrenia outpatients, we have tested several models, examining the direct and indirect relative contributions of visual information processing, social cognition, anhedonia, and premorbid functioning to functional status in schizophrenia. First, we have replicated, in a substantially larger sample, our recently reported findings that a direct

and significant association between visual information processing and functional status was fully mediated by a measure of social perception. Second, we have found that an inclusion of a measure of anhedonia significantly improved model fit. This measure explained a significant amount of variance in functional outcome, especially in the social component of the construct of functional status. Third, we have found that adding a measure of patients' premorbid functioning has also significantly improved model fit. Interestingly, premorbid functioning did not directly affect functional status, but rather accounted for unique variance in visual processes and social perception. These findings thus offer a more comprehensive insight into the complex nature of the various processes that are influencing adaptive functioning in schizophrenia.

ID: 549480

THE EPIDEMIOLOGY OF SUICIDE ATTEMPTS AMONG PERSONS WITH A PSYCHOTIC DISORDER IN THE GENERAL POPULATION

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Objective: We investigated the epidemiology of suicide attempts in a general population -based sample of middle-aged people with a psychotic disorder (Perälä et al. 2007). Method: The study was based on a nationally representative survey of 8028 persons aged 30 years or over from Finland. Psychotic disorders were diagnosed according to DSM-IV-TR criteria using the SCID-I interview and/or case note data. Lifetime severity of symptoms and course and outcome of the disorder were assessed using the Major Symptoms of Schizophrenia Scale and the GAF and SOFAS scales. Based on information from the interview and case notes, we assessed lifetime history of suicide attempts. We examined the prevalence of suicide attempt in different psychotic disorders and clinical differences in persons with psychotic disorder with vs. without a history of suicide attempts. Results: Of persons with a lifetime history of any psychotic disorder, 30.7% had a history of at least one suicide attempt. The lifetime prevalences of suicide attempts in the largest diagnostic groups were as follows: schizophrenia: 33.3%; schizoaffective disorder: 37.5%; delusional disorder: 0%; major depressive disorder: 41.4%; bipolar I disorder 30.5%; and substance-induced psychotic disorder: 46.3%. The difference in prevalence between persons with delusional disorder vs. other psychotic disorders was statistically significant ($P = .0059$). Persons with psychotic disorder with a lifetime history of suicide attempt had more severe depressive symptoms ($P < .0001$) and symptoms of avolition ($P = .043$), but did not differ from those without suicide attempts in any other symptom measures. The groups did not differ in overall course and outcome, but the lifetime duration of hospitalizations was longer in persons with a history of suicide attempts. Conclusions: Suicide attempts are common in all psychotic disorders except for delusional disorder. Suicide attempts are associated with depressive and negative symptoms but not with positive or disorganized symptoms. History of suicide attempts is associated with longer hospitalizations but not with outcome.

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ID: 549411

THE MULTIDIMENSIONAL SCALE OF INDEPENDENT FUNCTIONING (MSIF): ASSESSING THE DISCRIMINATION BETWEEN SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS

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The Multidimensional Scale of Independent Functioning (MSIF; Jaeger, et al., 2003) is a measure of real-life performance among patients with schizophrenia. It was designed to improve on the shortcomings of existing scales, such as the Social Adjustment Scale II (SAS II; Schooler et al. 1979), by including multiple dimensions and a global indicator of functional outcome, and relying on both self-report and informant information. Moreover, by including separate measures of key domains sensitive to the schizophrenia illness, it allowed for the detection of meaningful changes in functional status. One shortcoming, however, is that the authors' validation study included only patients with schizophrenia, and so it remains unclear if non-psychiatric adults will perform in the desired range and whether the measure discriminates meaningfully between patient and healthy participants. Accordingly, this study had several aims; 1) assess the functional status profile of healthy adult participants, 2) assess the discriminability of the MSIF between psychiatric and healthy adult populations, 3) assess the stability of the MSIF. Demographic, clinical, and MSIF data were obtained from 156 patients with schizophrenia or schizoaffective disorder, and 128 were retained for follow-up assessment approximately 10-months later. Demographic and MSIF data were obtained for 74 healthy adult participants. On the global indicator of functional independence, healthy adult participants scored in the normal range (M = 1.78, SD =1.18), whereas the schizophrenia patients scored in the moderately-to-significantly disabled range (Baseline: M = 4.42, SD = 1.09; Follow-up: M = 4.37, SD = 1.03). Independent samples t-tests revealed significant differences between the two groups on all domains of the MSIF, with effect sizes (Cohen's d) ranging from 0.21–2.58. Paired-samples t-tests revealed no differences between the two assessment points. The MSIF demonstrates exceptional discriminative validity; healthy adults score in the highly independent range, whereas schizophrenia patients score in the impaired, dependent range. Moreover, the effect size differences are extremely large relative to those typically seen in this field. Researchers should strongly consider including the MSIF in future research studies aimed at evaluating the functional status of patients with schizophrenia.

ID: 549263

SUBJECTIVE QUALITY OF LIFE OF NIGERIAN PATIENTS WITH SCHIZOPHRENIA

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Objectives: to examine the perceptions of patients with schizophrenia on their overall QOL and determine the clinical and socio-demographic correlates of the patients' ratings on the indices of subjective quality of life. Methods: A total of 99 adult patients (males = 58, females = 41) with schizophrenia completed questionnaires detailing their sociodemographic profiles and living conditions. Clinical (illness-related and medication-related) details were obtained by means of rating scales and assessment of their case files. They also completed the World Health Organisation Quality of Life Scale—Brief version (WHOQOL-BREF) as a subjective assessment of their quality of life. Results: Patients had problems relating to physical health, relationships, work, leisure and finance. Despite these problems,

their level of satisfaction with items of subjective QOL was generally high, with the highest satisfaction with self (82.8%) and overall QOL (78.8%).The highest levels of dissatisfaction were with availability of money for everyday needs (76.8%) and sex life (71.7%). There was low to moderate correlation between the patients' reported living situations and their satisfaction with their life Poor overall subjective quality of life was significantly determined by when last worked (OR 4.6, 95% CI 1.9–21.7), poor perceived family support (OR 6.4, 95% CI 2.0–19.9), multiple relapses or exacerbations of symptoms (OR 6.5, 95% CI 1.2–51.6) and negative attitude towards antipsychotic medication (OR 3.1, 95% CI 1.3–11.5). Conclusion: This study have showed that despite their deplorable living situations, Nigerian patients with schizophrenia still have a high level of satisfaction with their quality of life. Also the subjective QOL was adversely affected by both sociodemographic and clinical variables. Functioning in social roles and access to resources and opportunities are the prerequisite for the possibility that such well-being and happiness can also be present in the future. In order to help these patients an appropriate balance between lowering of their expectations and increasing their achievements should be sought. Programmes to improve the QOL of Nigerian patients with schizophrenia should specifically focus attention on providing opportunities for equal employment, investment in drugs with less side effects and increasing the level of social support from the family and friends.
ID: 549168

PREDICTORS AND CONSEQUENCES SUBSTANCE USE IN PATIENTS WITH SCHIZOPHRENIA: A DAILY LIFE STUDY USING ECOLOGICAL MOMENTARY ASSESSMENT

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Background: Investigations of both clinical and community samples have repeatedly demonstrated high comorbidity between schizophrenia and substance use disorders, but the mechanisms underlying these association remain widely debated. Recent advances in computerized ambulatory monitoring techniques provide the opportunity to assess the temporal dynamics of these variables in a manner which is inaccessible to standard research protocols. Method: 130 adults with schizophrenia participated in an investigation of daily life experiences and behaviors using Personal Digital Assistants (PDAs). The PDAs were programmed to administer electronic interviews four times per day for a one-week period, and to collect information concerning the experience of psychotic symptoms, substance use, and mood states. Results: The sample completed an average of 72% of all programmed assessments, resulting in 2460 observations collected across daily life contexts. Multilevel modeling of time-lagged data demonstrated that psychotic symptoms predicted decreases later alcohol use ($P < .000$) and cannabis use ($P < .000$), while cannabis use itself predicted the onset of new psychotic symptoms ($P = .014$). Happy moods were also associated with increases, and sad moods with decreases, in the use of both substances over subsequent hours. Only anxious moods were associated with increases in later alcohol use ($P < .000$), but with similar decreases in later cannabis use ($P < .000$). Mood states were generally not predicted by earlier substance use, despite some increase in sad mood following cannabis use ($P = .037$). Conclusion: With the exception of the well-established association of anxious moods and alcohol use, no evidence was found for self-medication in this sample. Rather, substance use decreased when psychotic symptoms or negative affect was experienced, indicating that the management of alcohol or cannabis use in this population should emphasize alternative theories when developing intervention or prevention strategies.
ID: 549004

THE RELATIONSHIPS AMONG CHANGE IN NEUROCOGNITION, INTRINSIC MOTIVATION, AND FUNCTIONAL OUTCOME DURING COMMUNITY-BASED PSYCHOSOCIAL REHABILITATION

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This study included 130 individuals diagnosed with schizophrenia who were recruited upon admission to community-based psychosocial rehabilitation and followed prospectively for 12 months. Measures of neurocognition were taken at baseline and 12 months. Measures of intrinsic motivation, functioning (social, work, independent living) and symptoms were taken at baseline, 6, and 12 months. Latent growth modeling was used with constructs representing baseline neurocognition (NC), intrinsic motivation and functional outcome, as well as constructs reflecting change in NC, change in motivation, and change in functional outcome over time. Two models were estimated (see Table). There was significant change in NC, motivation, and functional outcome over time. Both latent models fit the data extremely well while controlling for symptoms. There were notable findings across both models. First, in both models motivation at baseline was strongly associated with functioning at baseline. Second, change in motivation was strongly related to change in functional outcome. Third, in model 1 baseline NC was strongly related to both baseline motivation and psychosocial functioning, and to change in psychosocial functioning; however, baseline NC was not related to change in motivation. In model 2, the findings were very similar. Change in NC was strongly related to both baseline motivation and to the rate of change in psychosocial functioning; however, NC change was not related to change in motivation. These findings suggest that functioning and motivation are strongly associated both cross-sectionally and dynamically over time. They also suggest that while functioning and motivation are very closely linked, change in functioning is driven by change in NC, while change in motivation is related to more non-cognitive contextual factors such as behavior change. This reflects a theoretical perspective which suggests that intrinsic motivation is related to an interplay between cognition, behavior and environmental context (Deci and Ryan 2002). These results also suggest that interventions designed to facilitate rehabilitative or NC change should distinctly target cognitive and motivational factors. Interventions designed to enhance intrinsic motivation should consider contextual factors that facilitate functional change. The findings also improve our theoretical understanding of the dynamic relationships among NC, motivation and functional outcome in schizophrenia.
ID: 548971

PREDICTORS OF CHANGE IN LIFE SKILLS IN SCHIZOPHRENIA AFTER COGNITIVE REMEDIATION

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Few studies have investigated predictors of response to cognitive remediation interventions in patients with schizophrenia. Predictor studies to date have selected treatment outcome measures that were either part of the remediation intervention itself or closely linked to the intervention with no studies investigating factors that predict generalization to measures of everyday life-skills as an index of treatment-related improvement. In the current study we investigated the relationship between four

measures of neurocognitive function, crystallized verbal ability, auditory sustained attention and working memory, verbal learning and memory, and problem-solving, two measures of symptoms, total positive and negative symptoms, and the process variable of treatment intensity to change on a performance-based measure of everyday life-skills after a year of computer-assisted cognitive remediation. Thirty-eight patients with schizophrenia or schizoaffective disorder were studied. Results of a linear regression model revealed that auditory attention and working memory predicted a significant amount of the variance in change in performance-based measures of everyday life skills after cognitive remediation, even when variance for all other neurocognitive variables in the model was accounted for. Stepwise regression revealed that auditory attention and working memory predicted change in everyday life-skills across the trial even when baseline life-skill scores, symptoms and treatment intensity variables were controlled. These findings emphasize the importance of sustained auditory attention and working memory for benefiting from extended cognitive remediation and suggest the addition of supplementary training in elementary attention and working memory skills prior to remediation in those patients unlikely to show benefit.
ID: 548920

THE THREE-YEAR COURSE OF FUNCTIONAL STATUS AND COGNITION IN OLDER PATIENTS WITH SCHIZOPHRENIA

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Background: Cognitive and functional disability is present over the lifespan in schizophrenia, starting at the time of the first psychotic episode. There has been some suggestion of functional decline in very poor outcome older patients with schizophrenia while, better outcome patients did not show this decline. Earlier longitudinal studies have focused on younger patients suggesting there may be age-associated risks of cognitive decline. Therefore, the current study is a longitudinal follow-up (36 months) with patients varying in their history of long term institutional stays. Method: Subjects were older, ambulatory schizophrenia patients with a history of current active illness ($n = 98$, mean age, 60.1 yrs). All were receiving atypical antipsychotic treatment. The length of the longest consecutive hospital stay ranged from 1 to 330 months (mean = 25.7 months). Patients were divided into two groups for the purposes of these analyses: 55 Longer Stay (LS) patients, 43 Shorter Stay (SS) patients, with a 3-month stay as the dividing line. Subjects were cognitively assessed with a comprehensive neuropsychological (NP) battery. Functional disability was assessed using the UCSD Performance-based Skills Assessment (UPSA). Correlations with longest stay were also calculated for changes in cognition and functional (everyday living) status. Results: Patients with longer hospitalizations were more impaired on all cognitive measures, and had more social and functional disabilities (all P's < .05; all effect sizes (d) > 0.5). There were no differences found in age, age at first admission, education, or total number of admissions. In the NP measures, there was a significant difference between performance after time between LS and SS patients, with SS patients showing practice effects and LS patients appearing to worsen, $P < .05$. On the UPSA, again SS patients showed a practice effect and LS patients appeared to worsen ($P < .05$). There was a significant correlation between UPSA changes and NP changes, ($r = .53$, $P < .001$), with longer stays correlating with more decline. Discussion: Patients with longer continuous hospitalizations showed evidence of cognitive and functional changes over 3 years. Patients who never had a long stay actually improved their performance. While the worsening seen is only moderate in nature, it is consistent with the results of previous studies examining institutionalized patients. NIMH Grant #MH 63116.
ID: 548860

DOES MEDICATION EFFICACY PREDICT ADHERENCE IN FIRST EPISODE PSYCHOSIS? A LONGITUDINAL PROSPECTIVE STUDY

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Adherence to medication helps achieve and maintain remission in psychotic illnesses, but efforts to understand and maximize adherence have had limited success. Cost-benefit models of decision-making suggest that clinical efficacy should be an important determinant of medication taking, but the relationship between changing clinical status and adherence has rarely been examined. This study investigated the link between efficacy and adherence by monitoring clinical status and adherence behaviour in 77 first episode psychosis patients. Our design employed four time points: clinical evaluations at months 1 and 6 (including BPRS, SAPS, SANS, GAF, Calgary Depression and Hamilton Anxiety Scales) and adherence assessments at months 3 and 9. This design allowed us to observe the impact of changing symptoms on subsequent changes in behaviour. Subjects in our study sample had been treated for an average of 8.1 months (SD 6.8) and displayed a range of patterns of adherence and clinical evolution. Examining the entire sample ($n = 77$), we found no direct correlation between change in adherence behaviour and change in any clinical index. Demographic factors (age, gender, diagnosis, DUP) also failed to predict adherence in the complete sample. However, analysis of two important subgroups revealed links between clinical condition and adherence. First, subjects with the poorest adherence (adherence in the lowest quartile at both time points or dropping significantly; $n = 24$) showed an inverse correlation between change in BPRS and medication-taking: subjects with greater clinical improvement showed larger reductions in adherence (R = −0.467; $P < .05$). These subjects differed demographically from the full study population only in age, being slightly younger (22.7 vs. 24.9 years, $P < .02$). A second, smaller subgroup comprised those subjects who maintained very high levels of adherence despite achieving less clinical improvement than the group mean ($n = 6$). We found that all subjects in this subgroup had experienced more dramatic clinical improvement before the initiation of our study, demonstrating that maintenance of high adherence without substantial reduction in psychopathology is extremely rare. Despite this suggestion that medication efficacy is required to maintain very high levels of adherence, our overall conclusion is that patients have a variety of behavioural responses—both positive and negative—to the clinical improvement brought by medications.
ID: 548740

CLINICAL AND COGNITIVE CHARACTERISTICS OF HIGHLY FAVORABLE AND UNFAVORABLE FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA

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Cognitive performance rather than symptom severity is regarded as the primary predictor of functional outcome in schizophrenia. However, contradictory evidence exists and many studies fail to sample from the extremes of outcome measures. This study tested whether the differential importance assigned to symptoms and cognitive impairment is supportable in schizophrenia patients with high and low levels of community independence. Schizophrenia patients with highly unfavourable ($n = 24$) and highly favourable ($n = 28$) functional outcomes as defined by community support

requirements were drawn from a pool of patients ($n = 156$) attending a range of rehabilitation and community treatment programs. Standard cognitive and symptom measures were analyzed with independent groups comparisons and logistic regression methods. Positive, negative and general symptom measures as well as cognitive tasks generated statistically significant group differences and large effect sizes. Symptom severity and cognitive data separately predicted community independence at greater than 80% accuracy, with cognition adding new validity over and above the contribution of symptoms. However, the conditional validity of symptoms was not significant. Proportions of patients receiving second generation antipsychotic medications were statistically similar in the 2 outcome groups, but rates of anti-Parkinsonian medication were 4 times higher in the unfavorable outcome group. Results suggest researchers may have underestimated the role of psychopathology as a determinant of functional status in schizophrenia. Psychotic and non-psychotic symptom severity should be considered along with cognitive performance as key features and potential mediators of functional outcome in the illness.

ID: 548678

FUNCTIONAL CAPACITY ASSESSMENTS FOR SCHIZOPHRENIA CLINICAL TRIALS

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This presentation will describe the longitudinal stability and validity of two widely used functional capacity instruments, the UCSD Performance-based Skills Assessment (UPSA) and the Schizophrenia Cognition Rating Scale (SCoRS), and a real-world measure of functioning, the Independent Living Skills Inventory (ILSI). In one study, 60 patients with schizophrenia were assessed at baseline and 23 assessed after 3 months of care at a rehabilitation unit at John Umstead Hospital and Duke University. At baseline, the UPSA was significantly correlated with cognitive performance as assessed by the Brief Assessment of Cognition in Schizophrenia (BACS) composite scores ($r = .65$, $df = 55$, $P < .001$), and real-world functional outcome as assessed by the ILSI ($r = .40$, $df = 56$, $P < .01$). SCoRS global scores were also correlated with BACS composite scores ($r = .54$, $df = 55$, $P < .001$) and ILSI total scores ($r = .48$, $df = 56$, $P < .001$). Longitudinal data analyses suggested that the UPSA had excellent stability (ICC = 0.81) and no practice effect ($d = -0.06$) over 3 months. The SCoRS rater mean item scores had better stability (ICC = 0.77) than the SCoRS rater global scores (ICC = 0.56), and the practice effect for both was small ($d = .08$ and $d = .25$). In the second study, patients were assessed with the SCoRS and the tests from the MATRICS battery before and after treatment with lurasidone or ziprasidone. The cognitive measures showed minimal effects, yet the SCoRS ratings demonstrated significant improvements in patients treated with lurasidone. These data suggest that interview-based and performance-based assessments both demonstrate construct validity. Interview-based assessments are prone to instability over time, even when informants are included as sources of information, yet may be sensitive to treatment effects. Performance-based functional assessments are more stable over time and have the advantage that they do not require informant involvement. We will also discuss in this session a virtual-reality measure of functional capacity that could be used as a co-primary measure in clinical trials of cognitive enhancement in schizophrenia. This Virtual Reality Functional Capacity Assessment Tool (VRFCAT) uses a realistic environment simulating daily activities. Outcome measures are based on error rates and times to completion

for each of the assessment activities. Pilot data on the reliability and feasibility of this measure in schizophrenia patients will be presented.

ID: 548362

COMPARISON OF CORRELATIONS BETWEEN FUNCTIONAL CAPACITY, CASE-MANAGER RATINGS, AND REAL-WORLD OUTCOMES IN PEOPLE WITH SCHIZOPHRENIA IN THE U.S. AND SWEDEN

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Functional disability is a central feature of schizophrenia and has been reported to occur across different countries and systems of care. Recent advances in the assessment of functional disability have separated the measurement of functional capacity (ability to perform everyday functioning skills) from that of real-world functional outcomes. In this study, samples of schizophrenia patients living in generally rural areas in Sweden ($n = 146$) and in urban areas in New York ($n = 197$) performed the brief version of the UCSD Performance-based Skills Assessment (UPSA-B) and were rated by their case managers with the Specific Levels of Functioning (SLOF). Information from archival records and case managers was used to determine the occurrence of different real-world outcomes, including living independently, employment status, and having ever experienced a stable romantic relationship. Correlations between these measures were then analyzed for each sample. Performance on the UPSA-B was essentially identical in the two samples (mean raw score in New York, 13.8; Sweden, 13.3). Scores on the case manager ratings of real-world work performance were also strikingly similar for both work (New York: 24; Sweden: 22) and everyday activities (New York: 34; Sweden: 33). Further, the correlation between UPSA-B scores and ratings of everyday activities were quite similar (New York: $r = .43$; Sweden: $r = .36$), as were the correlations between work outcomes and UPSA-B scores (New York: $r = .30$; Sweden: $r = .33$). The proportion of cases who had never been married or had never had a close relationship was 66% in New York and 61% in Sweden. In notable contrast, 76% of the Swedish patients and 25% of the New York patients were living independently. Scores on performance-based measures of functional capacity related to everyday living skills were very similar across samples of people with schizophrenia living in very different environments. These results are consistent with previous studies showing that measures of cognition in people with schizophrenia are also quite similar across different countries. While measures of functional ability and case manager estimates of patients' real-world outcomes were very similar in level of impairment and correlational structure, real-world residential outcomes were very different. These data suggest that cultural and social support systems can lead to very divergent outcomes in individuals who have evidence of the same levels of ability and potential.

ID: 546640

THE CANADIAN OBJECTIVE ASSESSMENT OF LIFE SKILLS (COALS): A NEW MEASURE OF FUNCTIONAL COMPETENCE IN SCHIZOPHRENIA

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The purpose of this study is to develop a new instrument for the assessment of functional competence and life skills in people with schizophrenia. There is little consensus on the best way to measure functional status, and there are concerns about the accuracy, reliability and suitability of instruments currently in use. The Canadian Objective Assessment of Life Skills (COALS) was undertaken to address limitations of existing measures while building in features of our own analysis of functional competence. The following methods were used to generate test items, content and structure for the measure: 1) focus groups and feedback sessions with clinicians and peer support workers at clinical settings, 2) review and content analysis of existing instruments including the University of California Performance Skills Assessment (UPSA), the Test of Adaptive Behaviour in Schizophrenia, the Test of Grocery Shopping Skills and the Medication Management Ability Assessment and 3) patient feedback and clinical observations during administration of 153 UPSA protocols. We hypothesize two key components in relation to successful independent living: (a) procedural knowledge routines (PKR), or "knowing how" to carry out an adaptive action or activity, and (b) executive operations (EXO), which reflect "knowing what to do and when to do it". PKR are highly specific to particular tasks and situations and require direction, cues, prompts and focused probes for assessment. In contrast, EXO involve primarily self-cued and self-initiated behaviours and these are more readily elicited by novel or ambiguous and therefore less constrained situations. These two components are evaluated in 5 domains relevant to independent functioning in the community: Health and Hygiene, Time Management, Trip Planning, Crisis Management and Domestic Activities. The COALS incorporates the advantages of objective, performance based evaluation criteria, along with the insights of cognitive science. Work is in progress to evaluate the value of this instrument in measuring treatment and program effectiveness as well as individual patient needs, vulnerabilities and skill profiles. This research is supported by the Ontario Mental Health Foundation.

Reference

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ID: 540707

ANXIETY AND VULNERABILITY TO PSYCHOTIC EXACERBATIONS IN RESPONSE TO LIFE STRESSORS

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Life events and social environment stressors have been associated with a higher risk of relapse in schizophrenia patients. Some patients may be especially vulnerable to psychotic symptom exacerbations in response to life stressors. The present longitudinal study assessed recent life events of outpatients with schizophrenia or schizoaffective disorder, and the level of criticalness of each patient's "most influential other" person toward the patient. It tested three main hypotheses: (1) Patients with life stressors in the form of either high-critical "most influential others" or recent stressful life events would show increases in psychotic symptoms at the nine-month follow-up session, compared with patients who did not experience either of these stressors; (2) compared with patients low in anxiety, patients high in anxiety at the baseline assessment would show increases in psychotic symptoms at follow-up; and (3) patients with high levels of anxiety at baseline who experienced either of the stressors would show the greatest exacerbation of psychotic symptoms at follow-up. All of these hypotheses were supported. The results indicate that (a) most patients showed some improvement over time, (b) the occurrence of life stressors predicted relative increases in severity of psychosis, and (c) level of anxiety at baseline predicted level of vulnerability of psychotic symptoms to stressors.

ID: 539009

CHARACTERIZING INSIGHT IN EARLY PSYCHOSIS: A PILOT STUDY

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It is well known that impaired insight is common among patients with chronic psychosis, but only in recent years have investigators begun to examine insight in young people with early psychosis. The objective of this study was to examine the clinical and cognitive correlates of insight in young people with recent-onset psychosis and how these differ from findings in chronic phases of the illness. Insight, clinical symptoms, cognitive performance, and social functioning were assessed in a preliminary sample of 14 young adults (mean age of 22.2, SD = 4.4) with recent-onset schizophrenia or schizoaffective disorder (first psychotic episode within the prior 3 years). A reference sample of 69 clinically stable outpatients with chronic schizophrenia or schizoaffective disorder was also assessed (mean age of 43.1, SD = 9.8). There were no differences on clinician ratings of insight between the recent-onset and chronically ill patients, with mean ratings of mildly impaired insight in both groups. In the recent-onset sample, poor insight was associated with lower scores on tests of working memory ($P = .03$) and attention ($P = .04$) and with lower Full Scale IQ ($P = .04$). There were no associations between insight and cognitive measures in chronically ill patients. Poor insight in recent-onset patients was associated with greater negative symptomatology ($P = .01$), but not with overall social functioning or depression. In contrast, poor insight was associated with depression ($P = .003$) and poor social functioning ($P < .001$) in chronically ill patients. The preliminary results from this cross-sectional study suggest a complex relationship between insight, negative symptoms, cognitive problems, and depression that may change over the course of a psychotic illness. Future research requires a prospective longitudinal design.

ID: 550834

RELIABILITY AND VALIDITY OF A BEHAVIORAL MEASURE OF SOCIAL COGNITION IN AN INTER-PERSONAL SETTING

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Social functioning impairments are a hallmark of schizophrenia. It is believed that studies of social cognition (ie, the application of cognitive skills to social situations) will lead to better understanding of these impairments. However, current laboratory measures neglect to include a fundamental element of the interpersonal context: perspective-taking within an interactive social setting. The Interpersonal Block Assembly Task (IBAT) is a novel laboratory assessment of social cognition that addresses this deficit in established measures. Using verbal communication, the participant must explain to a researcher how to orient blocks in order to successfully

construct a design. This study aims to establish reliability of the IBAT and demonstrate its validity as a measure of social cognition. Also of interest is whether performance on the IBAT is associated with diagnostic group (ie, schizophrenia versus healthy individuals). A battery of established measures of social cognition (eg, Theory of Mind (ToM)) and the IBAT were administered to all participants. The IBAT showed excellent internal consistency with a Cronbach alpha coefficient of .96. Intraclass correlation coefficients (ICC) were calculated and demonstrated good inter-rater reliability (ICC = .84). The IBAT demonstrated construct validity through an association with other established measures of social cognition. Performance on the IBAT was found to be positively correlated with first order ToM ($r = .21$, $P < .05$) and second order ToM ($r = .47$, $P < .001$). Convergent validity was tested by examining the association between the IBAT and measures of social functioning and psychiatric diagnosis. IBAT performance was found to be correlated with educational achievement ($r = .28$, $P < .01$), occupational achievement ($r = .41$, $P < .001$), and financial difficulty ($r = -.33$, $P < .05$). Diagnosis of schizophrenia was associated with poor performance on the IBAT ($r = -0.29$, $P < .01$). Non-social cognitive measures were administered to determine discriminant validity; the detectability parameter of the Continuous Performance Test was not correlated with the IBAT ($r = .04$, $P = .68$). These findings support the IBAT as a novel, reliable, and valid measure of expressive social cognition that improves upon the limitations of existing measures. Findings indicate that the IBAT is a useful tool to distinguish social cognitive abilities between people with schizophrenia and healthy individuals.
ID: 551909

IS A DEFICIT OF MENTALIZATION A MISSING LINK BETWEEN ALEXITHYMIA AND SCHIZOPHRENIA?

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Difficulties of emotion regulation are known to be very common and socially incapacitating among people suffering from schizophrenia (SZ) and schizophrenia spectrum psychotic disorders (SZSPD). Alexithymia, which refers to a deficit of the mentalization of emotions that leads to an important difficulty to identify and express one's feelings, has been found in about 30% of SZ and SZSPD patients. Despite this high prevalence, very few studies have explored the characteristics of alexithymia in people with SZ, and most of them that did have provided inconsistent results, particularly on its relationships with the negative and positive symptoms. The current study aimed at examining the relationships between alexithymia and other concepts associated to mentalization, such as social cognition and insight, among 30 patients suffering from SZ or SZSPD and 30 healthy controls. The relationships between alexithymia and the symptoms of SZ, as well as the social functioning, have also been explored. Preliminary results showed a weak negative association between alexithymia and the performance on social cognition tasks, especially among patients with SZ and SZSPD. Alexithymia was independent from insight, social functioning, and psychotic symptoms. Significant moderate positive correlations were found between alexithymia and symptoms associated to general psychopathology among patient with SZ and SZSPD. The preliminary results showed that the ability to mentalize emotions may be required to understand accurately the social interactions and contexts of day to day life. Alexithymia appeared to be independent from psychotic symptoms while it was associated with depression and anxiety, the latter association being in line with what is generally found among other Axis I disorders. The findings support the construct validity of alexithymia among people suffering from SZ and SZSPD and encourage further exploration of its characteristics among this population.
ID: 551906

IMPACT OF SCHIZOPHRENIA CANDIDATE GENES ON SCHIZOTYPY AND COGNITIVE ENDOPHENOTYPES AT THE POPULATION LEVEL

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Background: Aspects of cognitive function and schizotypy have been proposed as potential endophenotypes for schizophrenia. It is unknown whether the expression of these endophenotypes at the population level is modulated by the genetic variability of candidate susceptibility genes for schizophrenia. Methods: We examined the potential impact of 23 a priori selected single nucleotide polymorphisms (SNPs) within the DTNBP1, NRG1, DAOA/G32, DAAO, COMT and RGS4 genes, on cognition and self-rated schizotypy, in a representative population of 2243 young male military conscripts. Single SNP and haplotype associations were evaluated. Results: a) The DTNBP1 SNPs rs2619522 and rs760761 exhibited several single marker associations, the minor alleles being associated with lower attention capacity but also a decrease in positive and paranoid schizotypy scores. The DTNBP1 haplotype load had borderline associations with non-verbal IQ, paranoid schizotypy, and sustained attention. b) For individual NRG1 polymorphisms, isolated but weak signals of association were noted with sustained attention and working memory but not schizotypy. The risk allele of functional SNP8NRG243177 was associated with reduced spatial working memory capacity. However, individual NRG1 risk alleles and haplotypes were associated with stress induced hostility and psychotic symptoms at military induction, indicating a potential susceptibility role of NRG1 under a gene X environment (stress) interaction model. c) An isolated effect of DAAO, RGS4 and COMT variability was noted on negative schizotypy but not cognition. No convincing association of DAOA/G32 variability was detected. Conclusions: Several candidate susceptibility genes for psychosis might exert specific modulating effects on subclinical psychosis and cognitive ability at the population level.
ID: 551901

THE DEVELOPMENT OF THE MENTAL-STATE REASONING TRAINING (MSR) PROGRAM

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Social cognition, the cognitive operation that underlies social interactions and the understanding of the intention of others, is profoundly impaired in schizophrenia. Thus, improving social disability in schizophrenia is now a high priority in schizophrenia research. This study describes a group-based program designed to improve general understanding of other people's thoughts and feelings (mental state reasoning training; MSR). This is a manual-based program developed around videos, computer games, and group games and is delivered in ten sessions over five weeks, twice-weekly. The MSR program is based on errorless learning techniques and uses probes to target mental-state reasoning aspects of program activities. Our aim is to examine whether the MSR program produces improvements in social cognitive abilities and social functioning in individuals with schizophrenia. Participants undergo baseline testing to assess their social cognitive abilities (emotion recognition, 'Theory of Mind', and attributional style) before entering into the five week training program. Participants are then retested following completion of the program to assess potential improvements in social cognitive abilities. To assess the impact of training on real-world social functioning, participants complete the

Empathy Quotient at baseline and immediate post-training to examine whether they self-report any subjective changes in their abilities to relate with other people. Clinicians with the best knowledge of participants also complete the Role Functioning Scale at baseline and then again one month after training to assess objective changes in social functioning. Initial pilot testing has involved nine individuals with schizophrenia or schizoaffective disorder. Qualitatively the pilot participants have shown an increased use of social cognitive language when describing their own and others' social experiences. Further empirical findings will be reported. In conclusion, although the research is in the early stages, the MSR program shows good potential for use in clinical practice. The program is designed to be implemented by any clinical staff (it does not require clinical psychologists or neuropsychologists) and it provides an enjoyable and non-threatening environment for participants.
ID: 551880

SOCIAL AND ROLE FUNCTIONING: CRITICAL OUTCOME DOMAINS INDEPENDENT OF PSYCHOSIS

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Profound deficits in social and role functioning characterize schizophrenia and result in the severe disability associated with the illness. Nevertheless, prevention research in schizophrenia traditionally has not as yet focused on the underlying biology and characteristics of impaired functioning and few studies have been concerned with interventions developed specifically to improve functional outcome. In this report, we analyze pooled data contributed by the 8 sites included in the North American Prodromal Longitudinal Study (NAPLS) consortium. All subjects included met NAPLS attenuated positive symptom criteria (APS) and had one or more clinical follow-ups over a two-year period ($n = 291$). The sample was further divided into a nested case-control design (total $n = 100$). Cases are subjects converting to psychosis over follow-up; controls are matched for APS symptoms at baseline, age, gender, site and length of follow-up. There were a total of 50 case-control pairs. Of these, 26 pairs had short term follow-up (6 months); 24 longer term follow-up (up to two years). For both short and long outcome groups, social functioning was found to be significantly impaired from the outset in converters relative to clinically stable matched controls and to be stable over time (p ranges from .01 to <.0001). No impact on functioning resulted from baseline depression, emergence of psychosis, or treatment with either anti-depressants or anti-psychotics. Role functioning followed a very similar course, with the exception that some improvement was shown in the short-term ($P = .006$ for non-converters). Subjects converting to psychosis were also significantly impaired in role (school for adolescents) at baseline and throughout follow-up relative to matched CHR controls ($P = .0004$). Level of role functioning remained stable throughout follow-up and was not impacted by depression, emergence of psychosis or medication. The current NAPLS findings are supportive of the hypothesis that the two critical functional domains—role and social—are long standing traits associated with a vulnerability to schizophrenia and resistant to conventional treatment. Of particular interest,

the finding that entrenched functional level does not further worsen with the emergence of positive symptoms supports the notion that these are independent domains, most likely related to different etiologies and developmental pathways and possibly associated with different parts of the brain.
ID: 551864

CORRELATES OF THERAPEUTIC ALLIANCE ACROSS SIX MONTHS OF THERAPY IN SCHIZOPHRENIA

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While therapeutic alliance in schizophrenia has been linked with treatment adherence and outcome, less in known about its clinical correlates. This study explores neurocognition as a possible predictor of therapeutic alliance in schizophrenia. Participants were 84 persons with diagnoses of schizophrenia spectrum disorder who participated in a 26-week study of the effects of cognitive behavior therapy on work outcome. Three measures of neurocognition were administered at baseline: Hopkins Verbal Learning Test (HVLT:verbal memory), Continuous Performance Test-II (CPT-II:vigilance) and Wisconsin Card Sorting Test(WCST: executive function). The Marlowe Crowne Social Desirability Scale (MCSD)was also administered to detect any bias effects of culturally approved responding. Participants were randomized to either a CBT intervention designed to enhance work function or a supportive therapy control condition, both of which involved attending weekly individual and group therapy sessions. All participants were paid for up to 20 hours per week of concurrent work activity. Participants completed the Working Alliance Inventory, Short Form, Client version (WAI-S-C) following one randomly selected individual therapy session every 4 weeks of the study. Baseline assessments were correlated with all seven time points of the WAI-S-C therapeutic alliance ratings. Pearson Product Moment correlations revealed that there was no significant relationship between therapeutic alliance and the total score on the MCSD. Therapeutic alliance ratings were significantly correlated with CPT-II t-scores measuring omission errors (month 3; $r = -284$, $P = .05$) and a pattern of erratic responding (months 2,3,5, and 7: $r = -.403$, $P = .05$; $r = -.351$, $P = .01$; $r = -.336$, $P = .05$; $r = -.361$, $P = .05$, respectively). The WAI-S-C scores were also significantly correlated with the WCST t-score for non-perseverative errors in month 1 ($r = -.270$, $P = .05$). There were no significant correlations between WAI-S-C scores and HVLT t-scores for immediate and delayed recall. Findings suggest that impairments in aspects of vigilance and abstract thinking may be related to difficulties forming and maintaining the therapeutic alliance during individual therapy as judged by persons who have schizophrenia. Further study is needed to understand how these factors and others not measured or reported here might combine to predict the strength of therapeutic alliance perceived by persons who have schizophrenia over the course of therapy.
ID: 551857

THE IMPACT OF CANNABIS USE ON ILLNESS COURSE IN FIRST EPISODE PSYCHOSIS

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The prevalence of comorbid cannabis use in patients presenting with a first psychotic illness is high. Studies in people with established schizophrenia

have implicated cannabis in a worse illness course in terms of relapse and hospitalisation. However, longitudinal studies of first episode patients who report substance use at time of first presentation to services indicate the majority give up illicit substances over time. In a cohort of 109 patients experiencing their first psychotic episode, we sought to compare outcome at two years in those reporting different patterns of cannabis use over the first year of treatment. Self-report data on cannabis use in the three months prior to first presentation and the use of cannabis in the three months prior to time of one year follow-up revealed that 65% of the sample were non-users throughout, 21% gave up cannabis use and 11% persisted with cannabis use. A further 3% of the sample had commenced use at time of follow-up and were excluded from further analysis. When comparing the three groups, there was a significant difference in terms of total number of days in hospital, and trend-level differences in whether or not they were re-admitted to hospital and the number of the readmissions during these two years. These results reflected longer and more frequent hospitalisations in the persistent cannabis users than the non-users and those that discontinued use. When just the persistent cannabis users were compared with those that gave up, the difference in all these measures became highly significant. The results suggest that, in patients with comorbid cannabis use at the time of a first psychotic episode, discontinuing use has a substantial benefit in terms of hospitalisation.
ID: 551851

PARANOIA STRIKES DEEP: A CONTINUUM OF SUSPICIOUSNESS AND ITS RELATION TO SOCIAL ANXIETY AND SCHIZOTYPY

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Paranoia is a key component of schizotypy and schizophrenia. Paranoia has been alternatively described as part of the positive schizotypy/schizophrenia dimension, given that paranoia is characterized by unusual ideas, and as a separate dimension of schizotypy/schizophrenia. However, some studies have found that paranoia is also related to negative schizotypy/schizophrenia, although it appears that this relation may be due to social aversiveness resulting from paranoia, not from core ideational components of paranoid thought. Furthermore, social anxiety commonly co-occurs with paranoia and positive schizotypy. Paranoia and social anxiety share many features, including self-consciousness and social fear and discomfort. Disentangling the overlap and boundaries of positive and negative schizotypy, paranoia, and social anxiety should enhance our understanding of the etiology and development of schizophrenia and spectrum disorders. The present study examined: 1) whether paranoia is best conceptualized as part of positive schizotypy or as separate dimension, 2) the relation of paranoia with negative schizotypy, 3) the relation of social anxiety with these dimensions of schizotypy, and 4) the expression of these constructs in daily life using experience sampling methodology (ESM). Confirmatory factor analyses tested a series of competing models. The best fit was found for a four-factor model with positive and negative schizotypy, paranoia, and social anxiety. As hypothesized, the paranoia factor was most strongly associated with positive schizotypy. Although some measures of paranoia correlated with negative schizotypy, measures of core features of paranoid ideation were minimally associated with negative schizotypy. Social anxiety comprised a separate factor outside of schizotypy, but was strongly associated with positive schizotypy and paranoia. ESM findings indicated that paranoia and social anxiety are differentially experienced in daily life. The results are consistent with a multidimensional model of schizotypy/schizophrenia and support the idea that paranoia and social anxiety are differentially experienced within schizotypy. Identification of the multidimensional structure of schizophrenia (including paranoia) across a broad continuum of clinical and subclinical manifestations should en-

hance our understanding of relevant etiological factors and lead to better targets for prophylactic interventions used to prevent the development of clinical disorders.
ID: 551847

AGE OF SIGN LANGUAGE ACQUISITION, LINGUISTIC ABILITY, AND COGNITION AMONG DEAF PEOPLE WITH SCHIZOPHRENIA

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We have an extensive understanding of the cognitive and social cognitive deficits associated with schizophrenia among hearing people. Similarly, a large knowledge base exists regarding these domains among nonclinical deaf samples. Well-established associations found across literatures were recently manifest in a sample of deaf and hearing people with schizophrenia (PWS). Cognition significantly predicted outcome (Horton and Silverstein, 2007) and, SC mediated the relationship for both groups (Horton and Silverstein, 2007, in press). Between-group differences fell along lines of the communication medium upon which each group relied. For deaf subjects, visuospatial memory (VSM) was the strongest predictor of outcome and, was most consistently mediated by SC; among hearing subjects, verbal memory served these same roles. The current study tests relationships between deafness-related variables, and, the predictors and mediators in the cognition-outcome relationship. Diverse study participants were recruited from a community-based psychosocial rehabilitation agency. A quasi-experimental design was employed. Sixty-five subjects with a SCID-based diagnosis of schizophrenia (34 deaf, 31 hearing) were evaluated on linguistic ability, visuospatial memory (VSM), SC, and functional outcome. SC was operationalized by measures of Theory of Mind (ToM) and facial affect processing (FAP). Controlling for illness severity, early SLA significantly predicted superior linguistic ability among deaf subjects; and, fluent signers displayed an increased ability to infer another person's intentions. Although strong signing skills predicted higher levels of functional outcome, the relationship only approached significance when illness severity was controlled. Deaf and hearing subjects unexpectedly displayed similar levels of performance on measures of nonlinguistic cognitive processing and FAP. Like nonclinical samples of deaf people, age of SLA and linguistic ability are important factors in the lives of deaf PWS. Additionally, a complex relationship exists between linguistic ability and ToM. Schizophrenia researchers studying hearing people, and psychologists studying nonclinical deaf people share common interests that can contribute to expanding our understanding of deaf PWS. Attending to the linguistic and nonlinguistic characteristics of tasks may clarify whether pathways to impairment are similar across groups.
ID: 551808

SUICIDAL BEHAVIOR IN CHILDREN AND ADOLESCENTS WITH FIRST EPISODE PSYCHOSIS

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Patients diagnosed with schizophrenia have a 10 to 20 years reduction in life expectancy compared to the general population. A large proportion of these premature deaths are accounted for by suicide. Patients in the earlier phase of the disease (adolescents) have the highest risk for suicide. For schizophrenic patients, the strongest predictor of suicide risk is a previous suicide attempt, increasing the risk by 40 times. Adolescents with psychotic symptoms and a past history of suicide attempts have higher risk of committing suicide in the next 5 years than an adolescent with no history of psychosis. Schizophrenia and first-episode psychosis increase risk for depression, self-harm and suicide. Most available reports focus on adult

patients with schizophrenia and/or first episode psychosis. Our hypothesis was that first episode psychosis, is associated with an increased risk for depression and suicidal behavior. We studied patients admitted to a pediatric inpatient psychiatric unit between 2003–2006. Patients ($n = 102$) were diagnosed with new-onset psychosis using DSM-IV TR criteria for Psychosis NOS, schizophreniform disorder or schizoaffective disorder. A control group of ($n = 102$) patients with other psychiatric diagnosis admitted to the same unit, and match by age, gender and ethnicity was selected. Study participants were administered the BPRS-C to assess severity of psychiatric symptoms. The suicidality subscale was analyzed separately. Thirty two percent of the patients had attempted suicide compared to 28% in the control group, 104 total suicide attempts in the group of psychotic patients and 51 total suicide attempts in the group of controls. Individuals with depression were found to be 2.8 times more likely to attempt suicide than those without in the patient group. Our results are double of those identified in adult studies. Depression was the second most frequent co morbidity in this patients ($n = 36$), and ADHD the first ($n = 49$).Duration of untreated psychosis has been and independant indicator of self harm. Our sample demonstrated an interesting pattern with patients with the highest suicidality scores having had 7 months or more of untreated psychosis. It is imperative to address depressive symptoms in children and adolescents with first episode psychosis or schizophrenia to prevent potential suicidal behavior. There should be a low threshold for hospitalization of adolescents with psychosis. The quality of initial treatment is critical.
ID: 551756

COMPARISON OF ACADEMIC AND CONSUMER DEFINITIONS OF RECOVERY IN SCHIZOPHRENIA: THE POSSIBILITY OF RECOVERY WITHOUT REMISSION

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Academic consensus criteria for remission from schizophrenia emphasize only remission from positive symptoms, whereas academic definitions operationalize recovery as requiring both symptom remission and adequate psychosocial functioning. In contrast, consumer models focus on recovery as a process and identify people as "in recovery," regardless of whether symptoms are fully controlled. The current study compares academic and consumer definitions of recovery and explores the possibility of functional recovery without achieving symptom remission. The study included 141 participants with schizophrenia or schizoaffective disorder (M/F = 92/49, x age = 56, SD = 8.2 years) who were assessed annually over a period of three years. Assessments included social functioning (Social Functioning Scale-SFS), symptoms (Positive and Negative Syndrome Scale- PANSS), and independent living (Independent Living Skills Survey-ILSS). Approximately one in five people with schizophrenia were found to be in recovery, according to a consumer definition that included only functional achievement, as defined by Harrow and Jobe (2007; The Journal of Nervous and Mental Disease; the following criteria met over two consecutive assessments [ILSS Appearance items 7, 8 about clothing, Personal Hygiene items 7, 8, 11 about skin, hair and nail cleanliness] AND [any 4 Leisure Activity Items 1–11 OR ILSS Employed], AND SFS Social Engagement and Interpersonal Communication ≥ 1) compared to one in ten who meet academic definitions of recovery (same functioning criteria + PANSS ≤ 3 on items P1, G9, P3, P2, G5, N1, N4, N6 over two consecutive assessment points). One third to half of all participants met consensus criteria for symptom remission at any given assessment point (PANSS criteria only). The findings showed that functional recovery, from the perspective of consumers, can be achieved despite the persistence of positive symptoms. This study is an important preliminary step toward a clinically relevant definition of re-

covery that may be useful for measuring outcomes and change in real world environments relevant to consumer goals.
ID: 551754

DEFEATIST PERFORMANCE ATTITUDES AND DIMINISHED MOTIVATION IN SCHIZOPHRENIA

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This study examined whether defeatist performance attitudes (eg, failure expectancy) are associated with low performance effort and negative symptoms in schizophrenia. Defeatist performance attitudes may be associated with diminished motivation to apply effort to cognitive and social functioning tasks, especially more difficult tasks. Performance attitudes were assessed in participants with schizophrenia or schizoaffective disorder ($n = 93$) and healthy controls ($n = 53$) using the Defeatist Performance Attitude Scale. To index the amount of effort applied to a task with varying difficulty, pupil dilation responses were recorded as an index of cognitive effort during a digit span recall task with low, moderate and high difficulty conditions (3, 6, and 9 digit spans). People with schizophrenia showed significantly more defeatist attitudes relative to controls, and defeatist attitudes were significantly correlated with poor performance in people with schizophrenia in the high difficulty condition. People with schizophrenia were divided into mild, moderate and severe defeatist attitude subgroups (tertile split). The subgroup with severe defeatist attitudes showed a decrease in effort (reduction in pupil dilation) when task difficulty increased from low to moderate load, whereas the mild and moderate subgroups and healthy controls increased their effort from low to moderate loads. When challenged by an increase in cognitive task difficulty, therefore, defeatist performance beliefs in people with schizophrenia were associated with poor effort and poor performance. Furthermore, the subgroup with severe defeatist attitudes showed significantly more severe negative symptoms on the Diminished Motivation factor (but not other factors) of the Scale for Assessment of Negative Symptoms. Defeatist performance attitudes, therefore, may be an important treatment target for psychosocial interventions, like cognitive behavioral therapy, which can be used to modify defeatist beliefs associated with diminished motivation to perform difficult social and daily functioning tasks.
ID: 551703

THE PREDICTIVE VALUE OF FIRST-RANK SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA VERSUS BIPOLAR MANIA WITH PSYCHOSIS

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Objective: This study prospectively examined the degree to which Schneiderian First-Rank Symptoms (FRS) predict later psychopathological symptoms, functional outcome, and periods of recovery over a 20-year period in patients with schizophrenia versus bipolar mania with psychosis. Method: The Chicago Followup Study prospectively examined 59 subjects with a diagnosis of schizophrenia and 27 subjects with bipolar disorder at index hospitalization and followed prospectively with 6 subsequent assessments over the next 20 years. The study was designed to evaluate multiple factors at each time point that provided data on premorbid adjustment,

phenomenology, severity of illness, course of illness, prognosis, outcome, and treatment. Results: FRS are not exclusive to schizophrenia; however they are less frequent in bipolar patients. Schizophrenia patients who have FRS at the 2-year follow-up are more likely to exhibit future episodes of psychosis over the next 20 years ($P \leq .05$). Overall, the reoccurrence of FRS at follow-up assessments was more likely in schizophrenia patients when compared to patients with bipolar disorder ($P \leq .05$). The data on 6 follow-ups over 20 years showed that patients with schizophrenia were less likely to experience periods of recovery when compared to patients with bipolar disorder ($P \leq .05$). As expected, when we looked at "voices commenting" and "voices commanding," which are considered two of the more serious symptoms in DSM IV diagnosis of schizophrenia, we found that a higher percentage of patients with schizophrenia presented with these types of FRS ($P \leq .05$). Additionally, schizophrenia patient who presented with FRS at 2-year follow-up were more likely to have future periods of psychosis and FRS than schizophrenia patients without FRS at the 2-year follow-up ($P \leq .05$). Conclusions: FRS are no longer considered pathognomonic for schizophrenia. Although Schneider's classic work remains a useful heuristic tool, FRS should not be used exclusively as criteria for diagnosis of schizophrenia. FRS at 2-yr follow-up are predictive of a more severe course of illness, regardless of diagnosis. Current data suggest that outcome may be predicted by specific patterns of symptoms over time as well as diagnosis.
ID: 551701

ENVIRONMENTAL SUPPORTS AND TECHNICAL ADVANCES IMPROVE ADHERENCE TO MEDICATION IN SCHIZOPHRENIA

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Cognitive Adaptation Training (CAT) is a psychosocial treatment that uses environmental supports such as signs, checklists, alarms and the organization of belongings to bypass cognitive deficits and to cue and sequence adaptive behaviors in the home. CAT has been found to improve multiple domains of outcome for individuals with schizophrenia. From CAT, our group has developed a number of interventions to primarily target medication adherence in schizophrenia. In an ongoing study, 69 outpatients with schizophrenia (SCID-DSMIV) were randomly assigned for 9 months to one of three treatment groups; 1) Pharm-CAT–CAT focused only on medication and appointment adherence 2) MM- A treatment using the Med-eMonitor™; and electronic device with the ability to store up to five different medications, cue the taking of medication, warn patients when they are taking the wrong medication or taking it at the wrong time, record side effect complaints, and through modem hookup promptly alert treatment staff to failures to take medication as prescribed. Early identification of adherence problems with the monitor was followed with rapid telephone intervention to overcome barriers to adherence or 3) treatment as usual (TAU). Data for these participants are available for the first 3 months of treatment. Medication adherence was assessed during a one month baseline period and then monthly using in-home pill counts. Symptoms and functional outcomes were assessed at baseline and at 3 month intervals. Analysis of covariance for mixed models for pill count adherence indicated a non-significant trend for treatment group effects. Participants in treatments utilizing environmental supports had better adherence to prescribed medication ($P < .07$). Although treatment groups had lower levels of positive symptoms than TAU, these differences were not significant after 3 months of treatment. These preliminary findings add further evidence to reinforce the notion that environmental supports targeting medication adherence may improve this behavior.
ID: 551683

THE RELATION OF CORTISOL SECRETION WITH SOCIAL AND ROLE FUNCTIONING DEFICITS IN CHR YOUTH

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The goal of this study was to test the hypothesis that cortisol elevations are linked with role functioning impairment in youth at-risk for psychosis. Functional impairments in social and occupational domains are among the most debilitating aspects of psychotic disorders. Retrospective and prospective research indicates that these impairments are present before the onset of clinical symptoms, however biological and psychosocial determinants of the deficits are unknown. The present longitudinal study examines the relation of cortisol secretion with social and role functioning deficits in adolescents (mean age 14.75 at baseline) who are deemed at clinical high risk (CHR) for psychosis based on the presence of schizotypal syndrome and/or prodromal symptoms. Multiple measures of salivary cortisol were obtained at three times; at baseline, interim follow-up, and 1-year follow-up. Area under the curve (AUC) was computed based on these measures. Role functioning and symptoms were rated using the Structured Interview for Prodromal symptoms (SIPS) at baseline and 1-year later. There was a positive relationship between cortisol AUC and ratings of role function deficits at both baseline and one-year follow-up. This relation was not accounted for by reports of stressful life events. These findings suggest that elevated HPA activity is associated with impaired role functioning in CHR youth. This relation is assumed to reflect bidirectional influences that include the stress-inducing effects of impaired role function, as well as the contribution of stress sensitivity to impaired functioning.
ID: 551682

EARLY LIFE EXPERIENCES PREDICT SELF-ESTEEM IN FIRST-EPISODE PSYCHOSIS

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Low self-esteem seems to be related to the etiology, understanding and treatment of a wide range of psychiatric conditions, including psychotic disorders. Vracotas et al. found that distress experienced by individuals with first-episode psychosis (FEP) was associated with level of self-esteem, depression, and anxiety, but not positive or negative symptoms. Self-esteem has repeatedly been implicated in the formation and maintenance of delusions and hallucinations. Moreover, self-esteem seems to predict clinical outcome in FEP. Little is known about what factors influence the level of self-esteem in psychosis. It has been well established that the quality of received parenting has direct and lifelong effects on psychological well-being. Thus, early life experiences such as parental care and attachment could contribute to the development of self-esteem. Our aim was to investigate the influence of early life experiences and parenting variables on the level of self-esteem in a FEP sample. Methods: The study included a sample of 45 individuals with FEP (non-affective and affective) receiving treatment at the Prevention and Early Intervention Program for Psychoses in Montreal, Canada. The Parental Bonding Instrument (PBI; subscales for Care and Overprotection) and the Measure of Parental Style (MOPS; subscales for Indifference, Abuse, and Overcontrol) were used as indicators of early life experiences and parenting. Patients completed the PBI and MOPS retrospectively, separately for their mother and father. The Self-Esteem Rating Scale was administered during the first six months of treatment.

Pearson's bivariate correlations were derived between self-esteem scores, PBI and MOPS measures. Results: In relation to mothers, self-esteem was positively correlated with PBI Care ($r = .316$, $P < .05$), and negatively correlated with the PBI Overprotection ($r = -.510$, $P < .001$), MOPS Overcontrol ($r = -.323$, $P < .05$) and MOPS Abuse ($r = -.345$, $P < .05$) subscales. There was no association between self-esteem and any father rated subscales. Conclusions: Better self-esteem is associated with higher levels of mother care and lower levels of overprotection, overcontrol and abuse. Interestingly, none of the father-related parenting variables predicted self-esteem. Given the relationship between self-esteem, early childhood and parenting, efforts should be made to assess patients' early life experiences and its effects on self-esteem and to provide specialized interventions that address these issues.

ID: 551633

EXAMINING THE IMPACT OF A WELLNESS-BASED GROUP INTERVENTION FOR RECENT-ONSET SCHIZOPHRENIA PATIENTS: PRELIMINARY RESULTS FROM AN ONGOING TRIAL

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Despite substantial progress in the treatment of schizophrenia, medical morbidity remains the domain least improved by recent treatment advances.[1] We can no longer think of wellness programs as adjunctive psychosocial treatments that are beneficial, but not essential, to recovery. This poster explains the development, implementation, and preliminary evaluation of a 50-session health behavior training program that is part of the Developmental Processes in Schizophrenic Disorders Project (PI: Keith Nuechterlein, Ph.D., ClinicalTrials.gov Identifier: NCT00333177), conducted at the UCLA Aftercare Research Program. We designed this wellness program specifically for recent-onset schizophrenia patients, a group that has received little, if any, attention in the health behavior change literature. Patients learn skills in (1) relaxation training, including progressive muscle relaxation and diaphragmatic breathing techniques; (2) basic nutrition and healthy eating habits; and (3) light exercise. For six months, patients attend three hours of the wellness group per week while receiving other outpatient case management and psychiatric care. To understand factors that contribute to and maintain behavior change in this population, outcome measures were chosen to assess both subjective health attitudes (ie, quality of life, perceived stress) and objective global health indicators (ie, physical fitness, metabolic blood tests). Although current analyses are limited due to a small sample size ($n = 13$), paired sample t-tests indicate statistically significant pre-post increases in overall life satisfaction ($t = -3.24$, $df = 12$, $P = .007$) and satisfaction with health ($t = -2.76$, $df = 12$, $P = .017$) as well as a significant decrease in perceived stress ($t = 2.36$, $df = 12$, $P = .036$) after six months of wellness group training. Changes in objective health measures are not statistically significant after six months, but patients are beginning to show improved physical fitness along with directional tendencies toward decreased LDL and total cholesterol. Encouraged by these preliminary findings, we plan to evaluate outcome measures with a larger sample to determine whether patients sustain changes when treatment exposure is reduced to 1.5 hours per week for an additional six months.

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ID: 551610

HEALTH SERVICES OUTCOMES IN VETERANS WITH SCHIZOPHRENIA AND TRAUMATIC BRAIN INJURY

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Of the 1.4 million traumatic brain injuries (TBI) that occur yearly, nearly 100 000 patients have severe, long-term sequelae and still more suffer from milder, though debilitating, symptoms. TBI is strikingly important among veterans, as nearly 25% of soldiers returning from Iraq and Afghanistan report injuries to the face, head, or neck. TBI is associated symptoms such as headache, irritability, disinhibition, visual changes, poor concentration, and apathy and, in more severe cases, severe cognitive deficits, sensory loss, seizures, and paralysis. TBI is associated with increased rates of many psychiatric illnesses including PTSD, substance use disorders, schizophrenia, bipolar disorder, and Alzheimer disease. However, there is a paucity of research regarding the excess disability imposed by TBI on chronic mental illness. We sought to address this deficit by examining the excess disability created by TBI in the face of schizophrenia. Our study extracted data from the Veterans Affairs (VA) Sierra-Pacific aggregate database for fiscal years 2003 to 2007 for patients with TBI, schizophrenia, and TBI+schizophrenia. Outcome measures included the number of medical and psychiatric hospitalizations and length of hospitalization. The predictors of health service utilization included pharmacological interventions, medical comorbidities, psychiatric comorbidities, substance abuse/dependence, marital status, homelessness, and income. Results are discussed in the context of health service and treatment implications for patients with TBI and schizophrenia. Our results are relevant to psychosocial interventions that can benefit patients with TBI and schizophrenia and provide insight into current psychopharmacological interventions.

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COGNITIVE REMEDIATION IN SCHIZOPHRENIA: ARE WE PROCEEDING CAUTIOUSLY?

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The recognition of the prominent role that cognitive impairment plays in the functional disability associated with schizophrenia has led to substantial pharmacological and psychosocial intervention development efforts. Cognitive remediation is one such intervention with a growing research base of randomized controlled trials (RCT). Recent meta-analyses of cognitive remediation indicate a 'medium' effect size for cognitive and functional improvement and have been generating considerable enthusiasm and some

calls for dissemination efforts. Yet these meta-analyses have given limited attention to the substantial methodological issues that may bias this body of research. Such concerns include, for example, very small samples, "treatment as usual" control groups, odd or limited outcome measures, unblinded assessments, and limited a priori data analytic strategies. As a result of these concerns, we are in the process of investigating the methodological quality of the evidence for cognitive remediation in schizophrenia by conducting several moderator analyses, using previously published meta-analytic findings supplemented with more recently published studies. Our primary analysis addresses the relationship of methodological rigor to treatment effect size using the Clinical Trials Assessment Measure (CTAM), developed by Tarrier and Wykes (2004). Through pilot work with a sample of published studies ($n = 9$) we have established reliable CTAM ratings (mean CTAM score = 55; s.d. = 13.73; range 32–74). Pilot analyses revealed a negative correlation between cognitive treatment effect size and CTAM scores ($r = -.54$), raising the concern that this inverse relationship between effect size and methodological rigor will hold for the broader literature. In continuing work, we will rate all studies and include analyses of treatment effects for both cognitive and functional outcome measures. Additional moderator analyses will evaluate the impact of related key study design issues such as type of comparison condition (eg, treatment as usual vs. active comparator) and sample criteria (eg, inpatient vs. community) on treatment effect sizes. We will also present an evaluation of whether a publication bias exists in the cognitive remediation literature, and analyses investigating historical trends in treatment effects and methodological quality. These preliminary findings suggest that a more cautious evaluation of the evidence for cognitive remediation may be warranted. ID: 551578

A PRELIMINARY INVESTIGATION INTO THE ROLE OF FAMILY ENVIRONMENT, PERSONALITY, AND POSITIVE SCHIZOTYPY IN PREDICTING SUBSTANCE USE DISORDERS IN SOCIAL ANHEDONICS AND CONTROLS

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Schizophrenia is characterized by high rates of comorbid substance use disorders (Blanchard et al. 2001). Unfortunately, the factors that give rise to high substance use in schizophrenia are as yet unknown. It may be productive to examine how schizophrenia-spectrum characteristics are associated with substance use in populations that are not yet ill. The current study examined how social anhedonia (a putative indicator of risk for schizophrenia spectrum disorders) is associated with substance use. We also examined the role of individual differences in family environment and personality traits. This study utilized participants in the Maryland Longitudinal Study of Schizotypy, an ongoing study that screened 2,434 18-year-olds in the community. Two groups were selected based on initial self-report scores: individuals high in social anhedonia ($N = 86$) and a healthy control group with low schizotypy scores ($N = 89$). Participants completed structured diagnostic interviews at a baseline assessment and again at a 3-year follow-up. Substance use disorders were measured dichotomously (0 = absent, 1 = threshold). Social anhedonics had significantly less education, less family cohesion, higher negative affect, and PerAb scores than controls. In social anhedonics, at baseline, family cohesion and perceptual aberration were significantly associated with having a substance use disorder (P's < .05). Only perceptual aberration was significantly correlated with SUDs at follow-up in this group. Negative affect, disinhibition, and magical ideation were not significantly associated with SUDs in this group both at baseline and follow-up. In the control group, disinhibition was associated with SUDs at baseline and follow-up (P's < .05). There were no other significant associations in the control group at baseline or follow-up. These findings

suggest that family environment a may play a role in the development of substance use disorders in social anhedonics. Implications of other findings in this study are discussed. ID: 551518

DISORGANIZED SYMPTOMS AND NEUROCOGNITIVE DEFICITS, PREDICT IMPAIRED SOCIAL FUNCTIONING IN INDIVIDUALS AT RISK FOR PSYCHOSIS

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Individuals identified as putatively prodromal or "at clinical high risk (CHR)" for schizophrenia, based on the Structured Interview for Prodromal Syndromes, have significant neurocognitive and functional deficits at initial evaluation which may be potential indicators of increased vulnerability for psychosis. We have previously reported that CHR subjects show neurocognitive (Eastvold et al. 2007) and social functioning (Ballon et al. 2007) deficits at baseline assessment. Here, we present prospective longitudinal data and assess whether baseline clinical, neurocognitive and social functioning variables can predict social functioning at 1-year follow up. Twenty-two CHR subjects were assessed at 1-year follow-up using the Social Adjustment Scale. Despite improvement in attenuated positive symptoms and some neurocognitive domains, CHR subjects continued to have impairment in social functioning regardless of whether they converted to psychosis. To explore predictors of the observed functional disability in at risk subjects, multiple regression analyses were performed using baseline social functioning, clinical and neurocognitive variables as predictors to determine which baseline variables were associated with poor functional outcome. Bizarre and disorganized behavior, along with impaired executive functioning accounted for a significant amount of the variance in overall social functioning at follow-up. Work role impairment was accounted for by deficits in processing speed, whereas social role deficits were related to high disorganized symptoms. The association of baseline neurocognitive deficits and disorganized symptoms with impaired functional outcome suggests important treatment targets that may alter the course of illness. Psychosocial treatment efforts that focus on social interaction and cognitive remediation might improve functional outcome in these help seeking individuals. Further research, using larger samples and longer follow-up, such as the North American Prodromal Longitudinal Studies (NAPLS) consortium, will help to elucidate the development of functional deficits and their relationship to presenting clinical symptoms and neurocognitive functioning. ID: 551480

FUNCTIONAL IMPAIRMENT: THE HALLMARK OF RISK FOR PSYCHOSIS

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Poor social functioning is a hallmark of schizophrenia. Retrospective studies have long suggested that social deficits appear before the psychotic symptoms. By examining functional outcome in individuals who appear

to be at clinical high risk (CHR) ie, putatively prodromal for psychosis we can now examine this prospectively. We first present evidence that in a large sample (*n* = 86) from the PREDICT (Prodromal Research for Early Detection in a Collaborative Team) study, CHR individuals do not differ significantly in social and role functioning from a sample of individuals who are presenting with a first episode of psychosis nor from a sample of individuals who have a more chronic course of illness. All three patient groups are significantly impaired compared to a young healthy control group. These results are supported by evidence of similar functional impairments in the 371 CHR subjects of the large North American Prodromal Longitudinal Study (NAPLS) consortium. Furthermore, in the NAPLS data set using cluster analyses, we identified in the CHR group four patterns of social functioning from early childhood until the onset of the attenuated psychotic symptoms. These patterns of stable-good, stable-moderate, deteriorating and poor-deteriorating are identical to patterns of premorbid functioning observed in individuals who have a chronic course of schizophrenia. We explore this further in a third study, ADAPT (Access, Detection and Psychological Treatments) and demonstrate that in this clinical high risk group, these young people in addition to functional impairments, exhibit levels of social defeat and poor self schema. What is of concern is that these data demonstrate that these clinical high risk individuals do not differ in their functioning from those with a diagnosed psychotic illness yet less than one-third are likely to go onto to develop full blown psychosis. The conclusion from these data is that social impairment is not only a hallmark of schizophrenia but also of a period of risk. It is from such data in this CHR period that we will attempt to identify potential targets of intervention. ID: 551461

DIFFERENTIAL IMPACT OF NEUROCOGNITION ON THE PREDICTION OF SOCIAL AND ROLE FUNCTIONAL OUTCOME IN THE SCHIZOPHRENIA PRODROME

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The Recognition and Prevention Program is a longitudinal study of adolescents (12–22) considered prodromal for schizophrenia based on attenuated positive symptoms assessed using the Scale of Prodromal Symptoms (SOPS). In addition to focusing on psychotic outcomes, we prospectively study cognition, social and school functioning, both as part of the vulnerability for schizophrenia and as independent outcomes. This study focuses on prediction of functional outcome using baseline neurocognitive and clinical variables. Of 102 subjects (mean age = 16.02) with baseline data, 71 had follow up data at about 2 years. Subjects were evaluated at baseline with extensive cognitive and clinical batteries. Cognitive scores were calculated consistent with the MATRICS battery. Clinical measures include positive, negative, and disorganized symptoms, as well as anxiety and depression. Functioning was assessed longitudinally with the Global Functioning: Social and Role scales. Pearson's correlations were used to screen for predictors and multiple regression was used to identify the strongest predictors of functioning. Social functioning is correlated significantly with processing speed (r = .31, P = .009), and negative symptoms (trend level: r = −.22, P = .08). Role functioning is significantly correlated with verbal memory (r = .43, P < .005), executive function (r = .25, P = .04) and working memory (r = .34, P = .004) and processing speed (trend level: r = .23, P = .06), but not with clinical features. The relative contribution of cognitive and clinical domains to functional outcomes was assessed using stepwise multiple regression with cognitive variables entered first and symptoms entered second. Controlling for intercorrelations among measures, processing speed predicts social functioning (Adj R^2 = .08, $F_{\Delta(1,64)}$ = 6.99, P = .01; β =

.50, t = 2.64. P = .01) and verbal memory predicts role functioning (Adj R^2 = .17, $F_{\Delta(1,64)}$ = 14.15, P < .0005; β = .69, t = 3.76. P < .0005). Consistent with findings in schizophrenia patients, cognitive and functional deficits are prominent features of the prodromal phase. Plausible relationships between cognition and social and role functioning were found: good social functioning requires rapid processing of a wide array of inputs (ie, speed of processing), and academic role functioning requires following instructions and remembering verbal information (ie, verbal learning and memory). Clinical features did not play a significant role in prediction of functional outcome. ID: 551444

DIFFERENCES BETWEEN EARLY RESPONDERS AND EARLY NON-RESPONDERS TO ATYPICAL ANTIPSYCHOTICS ON FUNCTIONAL OUTCOMES IN THE TREATMENT OF SCHIZOPHRENIA

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Objectives: In this study, we extend the findings from a prospective clinical trial assessing the effects of early response to an atypical antipsychotic across multiple functional outcome measures. Methods: This was a randomized, double-blind, flexible-dose, 12-week study that enrolled chronically-ill patients (*n* = 630) diagnosed with schizophrenia or schizoaffective disorder who were experiencing an acute symptom exacerbation. Patients were initially assigned to risperidone drug therapy (2–6 mg/day), and their response status at 2 weeks determined. Early responders continued with risperidone therapy, whereas early non-responders were randomized (1:1) in a double-blind manner to either continue on risperidone or switch another atypical antipsychotic for 10 additional weeks of therapy. Subsequent improvement in functioning was measured by the Schizophrenia Objective Functioning Instrument (SOFI), Quality of Life Scale (QLS), and Subjective Wellbeing under Neuroleptics (SWN) scale. Results: Early response to risperidone was observed in 27.6% of patients. Compared to early non-responders, early responders to risperidone showed significantly more improvement from baseline to endpoint on the SOFI total score and 4 subdomains (P < .001), the QLS total score and 4 subdomains (P < .01), and the SWN total score and 5 subdomains (P < .05). Most of these differences in functioning were already evident and significantly different between the early response and early non-response groups by 2 weeks of treatment. Conclusion: Patients who show an early response to antipsychotic treatment as measured by improvement in psychiatric symptom severity show early and consistent improvement across multiple domains of functioning, a finding that was concordant between both physician- and patient-rated quality of life scales. ID: 551425

EXPOSURE TO "THE TROUBLES" IN NORTHERN IRELAND INFLUENCES CLINICAL PRESENTATION FOLLOWING A FIRST EPISODE OF PSYCHOSIS

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The effects of violence on the mental health of patients with psychosis has been under researched (1) but there has been a recent important study in the literature, this study examined eighty-two participants who had a diagnosis of schizophrenia and a history of exposure to "The Troubles". This study found that these patients had significantly higher levels of symptoms compared to those patients with no such exposure. The purpose of this study is to examine the impact exposure to the troubles made to symptomology following a first episode of psychosis. The Global Assessment of Functioning scales (GAF), the Positive and Negative Syndrome Scale (PANSS), and the "Troubles" survey was administered to 175 patients recruited to the Northern Ireland (NI) First Episode Psychosis Study, at one year. The exposure to the Troubles was based on the responses to two survey questions one asking about the impact "…on your area"; the second about the impact "… on you or your family's life". Four ordered response categories ranging from "not very much at all" to "a lot" were possible. Mean age of onset was 30.8yrs ± 10.7; m/f = 115/60.Median DUP was 6 months (IQR = 1–12). Diagnosis breakdown was non-affective psychosis 66% as apposed to affective psychosis 34% of population sample. While exposure to the troubles was similar across the sexes and across diagnoses, some effects of the "Troubles" in the patient's area were observed in 67.4% following their first episode of psychoses. 32.6% related that the "The Troubles" had "a lot" of impact on their area. 63.4% of patients related that the "The Troubles" had some impact on their lives 63.4% responded that they had experienced "a lot" of impact on their lives or on the lives of their families. Relationships were observed between the effects on area and the GAF total score (Rho = .186, $P < .005$) and between patients who were in remission. (Rho = .205, $P < .005$. No significant relationship was observed between the effect of the "Troubles" and the PANSS Scale. While it appears that the population of NI in general has shown resilience to the effects of "The Troubles", those suffering from first episode psychoses who have been directly effected show increased rates of psychological morbidity and a poorer outcome.

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ID: 551419

EVALUATION OF COGNITIVE FUNCTION IN PATIENTS SWITCHED FROM RISPERIDONE TO ARIPIPRAZOLE USING DIFFERENT TITRATION STRATEGIES: AN OPEN-LABEL STUDY

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Analyses of secondary endpoints related to cognitive function were performed on data from a 12 week, open-label study of 400 patients with schizophrenia with efficacy and/or safety issues with risperidone who were switched to aripiprazole (1). Patients were randomized to either a titrated (5 mg/day to 15 mg/day by Week 4) or fixed dose (initiated at 15 mg/day) aripiprazole

switching strategy. Changes in cognitive function were summarized at Weeks 4 and 12 (LOCF) using the Grupo Español para la Optimización y Tratamiento de la Esquizofrenia (GEOPTE) scale for social cognition and the PANSS Cognition subscale. The GEOPTE scale (2) is a 15 item scale that measures both the patient and caregivers' subjective perception of the patients' deficits. A negative change score signifies improvement. The scales' mean changes were summarized using descriptive statistics with 95% confidence intervals. GEOPTE summary scores and PANSS Cognition subscale scores were decreased at Weeks 4 and 12 (LOCF) for both switching strategies. Aripiprazole was well tolerated with the most common adverse event reported being insomnia (8.5%, $n = 34/399$). Non-optimally treated schizophrenia patients switched from risperidone to aripiprazole showed reductions in the GEOPTE Patient and Caregiver summary scores, as well as the PANSS Cognition subscale. Additional research is warranted to evaluate the potential impact of ariprprazole on cognition.

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Table.

		Titrated dosing—mean change, (95% CI)	Fixed dosing—mean change, (95% CI)
GEOPTE patient summary	Baseline (BL)	37.39, $n = 194$	37.97, $n = 191$
	Week 4 [Change from (BL)]	−3.2, (−4.67, −1.73), $n = 192$	−2.56 (−3.84, −1.29), $n = 188$
	Week 12 (LOCF) [Change from (BL)]	−5.27, (−6.80, −3.73), $n = 194$	−6.12 (−7.84, −4.40), $n = 191$
GEOPTE caregiver summary	Baseline (BL)	40.98, $n = 102$	44.31, $n = 100$
	Week 4 [Change from (BL)]	−4.17, (−6.45, −1.90), $n = 98$	−7.19, (−9.38, −4.99), $n = 95$
	Week 12 (LOCF) [Change from (BL)]	−5.43, (−7.82, −3.04), $n = 102$	−9.92 (−12.79, −7.05), $n = 100$
PANSS Cognition subscale	Week 4 [Change from (BL)]	18.27, $n = 198$	18.79, $n = 195$
	Week 4 [Change from (BL)]	−2.19, (−2.69, −1.70), $n = 198$	−2.72 (−3.39, −2.05), $n = 194$
	Week 12 (LOCF) [Change from (BL)]	−3.36, (−3.99, −2.73), $n = 198$	−3.97 (−4.85, −3.09), $n = 195$

ID: 551392

ASSESSMENT OF VOCATIONAL CAPACITY IN SCHIZOPHRENIA

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COMPASS (Computerized Assessment), a standardized vocational assessment, is a battery of computerized and hands-on tests designed to measure ability in specific work domains. This assessment was administered in a treatment study examining the effectiveness of supported employment. We expected COMPASS scores to be correlated with baseline neuropsychological performance, functional capacity, and previous work history. Eighty-nine unemployed outpatients with schizophrenia or schizoaffective disorder, ranging in age from 22 to 60, all stating a goal of work, were enrolled in the study. Baseline assessments included the COMPASS (reasoning development, mathematical development,

language development, general learning ability, verbal aptitude, numerical aptitude, spatial aptitude, form perception, clerical perception, motor coordination, finger dexterity, manual dexterity, eye hand foot coordination, and color discrimination); neuropsychological tests (attention, processing speed, working memory, learning, memory, and executive functioning); measures of psychiatric symptom severity (positive, negative, and depressive symptoms); measures of quality of life (physical and mental); and an assessment of everyday functioning capacity. Past work variables included recency of last work and percentage of adult lifetime employed. The COMPASS total score was examined as a putative measure of the participant's current vocational capacity. Higher COMPASS scores were correlated with better performance in every neuropsychological domain (r = .48 to .74, P's < .001), with the exception of memory (P = .21). Higher COMPASS scores were also correlated with greater everyday functioning capacity (r = .49, P = .001). Higher COMPASS scores were correlated with younger age, shorter illness duration, higher levels of education, and ethnic non-minority status (r = −.29, −.27, .51, and −.37, respectively, P's $\leq$ .02). Lower levels of negative symptoms and greater physical quality of life were also associated with higher COMPASS scores (r = −.32 and .42, respectively, $P \leq$ .006). Neither recency of last work nor percentage of adult lifetime employed was correlated with COMPASS performance ($P \geq$ .30). The expected relationships between the COMPASS total score and neuropsychological and everyday functioning emerged, but COMPASS performance was not associated with recent or lifetime work history and may not predict return to work in work rehabilitation participants.
ID: 551359

COMPARISON OF OLANZAPINE AND RISPERI-DONE TREATMENT FOR FIRST EPISODE SCHIZO-PHRENIA: THREE YEAR FUNCTIONAL OUTCOMES

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Background: We examined the independent functioning outcomes of first episode subjects over the first three years of treatment with olanzapine or risperidone. Method: 112 subjects aged 16 to 40 years old with a first episode of schizophrenia, schizophreniform or schizoaffective disorder were randomly assigned to treatment with olanzapine (2.5 to 20 mg daily) or risperidone (1 to 6 mg daily) and followed for a total of 3 years. Independent functioning was assessed with the Multidimensional Scale of Independent Functioning (MSIF). Domains assessed were work, education, combined work and education role, residential and a global assessment of disability. Ratings for each domain varied from 1 (normal functioning) to 7 (total disability). Results: Based upon a RMANCOVA model, overall functioning improved over time in all areas. For work and education, ratings improved approximately half a rating point for each year in study. Functioning did not differ between medication conditions in any area. The least square mean estimates for functioning with each medication were between 4 (mod-

erately disabled) and 6 (markedly disabled) for all areas. Women compared with men had better work, residential and global functioning. Older compared with younger subjects also had better work, residential and global functioning. Marijuana use before study entry was associated with poorer educational functioning. Subjects at the suburban study site compared with subjects at the inner city site had better educational, combined work and educational and global functioning. We also examined the time until subjects achieved a rating of no or very mild disability. A substantial majority of subjects were able to achieve this on the combined work and education role. In a multivariate Cox regression model, subjects taking risperidone compared with those taking olanzapine were approximately half as likely to achieve good work functioning. Women compared with men were approximately twice as likely to have good work performance and approximately eight times as likely to have little or no disability related to residential functioning. Discussion: Our subjects on average had substantial disabilities during the first 3 years of treatment but improved to a clinically meaningful degree over time. Olanzapine and risperidone treatment did not differ on overall effect on disability but olanzapine was associated with more likelihood of achieving little or no work disability.
ID: 551301

RECOVERY FROM SCHIZOPHRENIA: DOES RESILIENCE MATTER? TEN AND 20-YEAR FOLLOW-UPS OF FORMER PATIENTS WITH SCHIZOPHRENIA

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The main purpose of this study is to follow up a group of 27 persons with a former diagnosis of schizophrenia 20 years after first assessment in order to examine how many are still recovered and to evaluate the impact of resilience on clinical outcome. A retrospective study of ten persons who had fully recovered from schizophrenia was carried out in Norway in the mid-80s. An expansion of this study, with methodological improvements, was designed in 1989/1990. During a 4-year period 20 people were recruited through several mental hospitals in Norway; 17 fulfilled the inclusion criteria. A semi-structured interview is designed for the 20-year follow up study based on previous research on course and prognosis of schizophrenia. In addition to the interview, the Global Assessment of Functioning Scale (GAF) is used to examine each subject's present overall psychosocial functioning. To assess remission, the criteria for remission in schizophrenia by Andreasen and collaborators (2005) will be used as well the operational criteria for full recovery developed by Liberman et al. (2002). The Connor-Davidson Resilience Scale (CD-RISC) (2003) is chosen to assess resilience. The scale comprises of 25 items, each rated on a 5-point scale, with higher scores reflecting greater resilience. The inclusion of subjects is still going on. Data-analysis is under preparation, but preliminary results (n = 7, mean age 50.6 years) show a significant correlation between resilience and present GAF score and how the subjects rate their subjective well-being. There is also a significant difference between fully recovered subjects and those with remission concerning resilience score. These results indicate that a majority of the subjects have maintained their recovery and that subjects who are still fully recovered are more resilient. Further analyses with the whole sample is needed to see if these tendencies are confirmed.

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ID: 551299

TALKING ABOUT SCHIZOPHRENIA—PSYCHOEDUCATION IN THE CONSUMER'S PERSPECTIVE

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Psychoeducation is very challenging in schizophrenia due to its psychopathological complexity, heterogeneous clinical presentations and outcomes. Psychiatrists' descriptions of symptoms and jargons are not well understood by patients and families. There is a need of consumer friendly materials using more appropriate language to the lay public. Objective: To develop a psychoeducational material from patient's and parent's point of view using illustrative cartoons. Methods: A schizophrenic patient, a family member and an occupational therapist trained in the WHO anti-stigma program (Open the Doors), together with a psychiatrist and a cartoonist where involved in the development of the psychoeducational material. Instead of communicating psychiatric knowledge to consumers, the aim of the material was to bring different perspectives together showing using three characters to express the complexity of schizophrenia with a realistic hope. Results: The content was divided in 6 booklets. The 1st—"How does it occur" focused on the prodrome symptoms and the first psychotic episode; the 2nd, "The construction of a diagnose" focused on the issues related to the diagnostic criterias; 3rd, "The relevance of treatment" focused on the treatment challenges; 4th, "Stigma—how people perceive it" focused in perception of stigma in real life; 5th, "Family environment" focusing on the families perspectives, 6th, "Recover and new perspectives" showing the different aspects of recover and the new scientific advances. Each booklet had 30 000 copies which that were distributed in most mental health centers all over Brazil by Astra-Zeneca's representatives every two-months. Discussion: The booklet was extremely well accepted by patients and families with several reprint requests. Psychiatrists also evaluated very positively the material, some clinicians use the material in their regular appointments. A website was recently developed (http://proesq.institucional.ws/psicoeducacao) and is widely accessed by patients and families.
ID: 551265

CLINICAL RECOVERY IN FIRST EPISODE PSYCHOSIS

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Introduction: Generally agreed outcome criteria in psychosis are required to evaluate the effectiveness of new treatment strategies and surmount therapeutic pessimism. The aim of this study is to explore recovery and its relation to symptomatic and functional remission in first episode patients and to find predictors of recovery. Method: In a sample of first episode patients (N = 125) symptomatic and functional remission during the last nine months of a two years follow-up period were examined, as well as recovery and its predictors. Recovery was clinically defined by the two dimensions of symptomatic and functional remission. Results: Half the patients (52.0 %) showed symptomatic remission, a quarter (26.4 %) showed functional remission, while one fifth (19.2 %) met both criteria-sets and were considered recovered. Functionally remitted patients recovered in 72.7% (OR = 2.7), symptomatically remitted patients in 36.9% (OR = .6). Recovery was sig-

nificantly associated with short duration of untreated psychosis (OR = .531, df = 1, P = .008). No recovery occurred in patients with long duration of untreated psychosis (> 6 months). Another significant predictor of recovery was better baseline functioning (OR = .858, df = 1, P = .021). Conclusion: Functional remission is more selectively associated with recovery than symptomatic remission. Treatment delay reduces chance of recovery. Baseline functioning levels also significantly predict recovery. Our results clearly show that social functioning is an important parameter in schizophrenia outcome research, both as a predictor of future course characteristics, and as a more selective index of recovery than symptom remission.
ID: 551249

SYMPTOM REMISSION AND MODIFIED RECOVERY IN THE EARLY COURSE OF SCHIZOPHRENIA

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Recent studies suggest that, decades after initial onset of schizophrenia, a substantial number of patients can achieve full recovery, eg, sustained improvement in both symptoms and social/work functioning. Patients in the early course of schizophrenia can also achieve recovery, although reports indicate that the overall rate of early recovery is low (13.7%; Robinson et al. 2004). Patients in the early course of schizophrenia (N = 73), who were being treated at UCLA with a first generation antipsychotic medication and psychosocial interventions, were assessed at 3-month intervals during their first post-hospitalization year. Positive and negative symptom remission required subclinical ratings on all relevant BPRS items (Nuechterlein et al. 2006). Modified functional recovery criteria required adequate social and work functioning. Both had to be met for three months duration. At 12 months, 51% of the subjects achieved both positive and negative symptom remission and 19% had adequate social and work functioning. Only 14 % of subjects showed both symptom remission and functional recovery at 12 months. Level of insight predicted recovery, but age at onset, patient education, parental education, prodromal course of illness, premorbid prodromal social and work functioning did not. Patients with good insight or no insight were more likely to recover than patients with partial insight. Although some schizophrenia patients can achieve both symptomatic and functional recovery in the early course of illness, the overall rate during the first post-hospitalization year might be relatively low. Some traditional predictors of poor outcome, eg, low levels of education, were not related to this combination of symptom and functional recovery. The evidence that partial, but not good or poor insight is related to recovery is consistent with a previously found relationship between insight and neurocognitive functioning.
ID: 551197

CBT FOR SCHIZOPHRENIA: MOLDING TECHNIQUES FROM THE UK TO FIT SYSTEMS IN THE USA CBT FOR SCHIZOPHRENIA: MOLDING TECHNIQUES FROM THE UK TO FIT SYSTEMS IN THE US

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The challenges and rewards of adapting and implementing techniques of CBT for schizophrenia developed in the UK to "real world" clinical settings

in the USA will be outlined in this presentation. The programs to be discussed are based upon the results of clinical trials and programs first practiced in the UK and utilize features (normalizing, reality testing, developing alternative explanations for delusions, etc.) taught and supervised by experts from the UK. They have developed within the very different and less uniform medical system in the USA. Various ways of disseminating both the specific "hands on" techniques and the paradigm shift required for conceptualizing "psychotherapy for schizophrenia" to clinicians in the USA will be discussed. Two clinical trials which grow from and build upon the UK programs will be presented. One, from Drs. Yulia Landa and. Paul Chadwich presents a Group Cognitive Behavioral Therapy intervention for paranoid delusions and cognitive biases compared to Treatment as Usual (TAU). Twenty four patients with Schizophrenia or Schizoaffective Disorder were randomly assigned to CBT or control, with one group and one individual session weekly. At week 8 the initial assessment showed significant changes in the CBT condition, but not in the TAU condition (reduction in delusions, suspiciousness and poor rapport from the PANNS, reduction in delusional conviction and amount of distress from PSYRATS and increase in ability to dismiss a paranoid thought and decrease in worry from the CDRS). A second pilot trial from Drs. Peter Weiden, Douglas Turkington, Nina Schooler and. Page Burkholder looked at implementing CBT for schizophrenia in a large public psychiatric clinic in the "inner city" and at medication adherence as an outcome measure for CBT (given the crucial role adherence to treatment and medication plays in better clinical outcomes, including the CATIE trial). 16 outpatients with schizophrenia or schizoaffective disorder were randomized to TAU or CBT-Adherence Intervention. While the small sample size and low completion rates (only 4 of 9 CBT patients attended all 12 sessions) the CBT-AI appeared to increase subsequent medication adherence rates.
ID: 551174

OASIS: FIRST 3 YEARS EXPERIENCE CARING FOR THOSE AT RISK, AND THOSE IN THE EARLY YEARS OF PSYCHOTIC ILLNESS IN CHAPEL HILL, NORTH CAROLINA

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There remains hope that appropriate early intervention in the first years of psychotic illness can reduce chronicity of symptoms and improve functioning. In the United States the challenge is to provide these services within a fee for service system in which this population is particularly at risk for inadequate mental health insurance. Here we describe the first 3 years experience of OASIS, a community-based specialty clinic providing comprehensive services to teens and young adults (ages 16 to 35) with new onset psychosis, and those at high risk for developing psychosis. Services include psychiatric evaluation and management, individual, group, family and multifamily therapies, as well as keyworker services. Since opening June 2005, OASIS has admitted 209 clients. Twenty-six (12.4%)were identified as 'at high risk' for developing psychosis. Clients have a mean age of 22.66 years (SD 4.49), are predominantly male (71%), Caucasian (67.4 %), and single (93% never married). 25 % were in school (or recently on medical leave from school) at time of entry into our program, and 67.9 % were unemployed. At entry into our program, the mean GAF score was 50.82 (SD 11.43) demonstrating the severe symptoms and functional impairment of our clients. 58% of our clients have private insurance, 22% have Medicaid, and 20% are uninsured. OASIS was founded with the support of two grants, KB Reynolds and Duke Endowment. Data collection at six month intervals shows improvement from baseline in GAF, symptom response and functional outcome. Our data highlight the importance of comprehensive treatment of those at risk for psychosis and those in the early years of illness, where

symptoms adversely affect school, transition to work, and social relationships. Service provision for this population requires coordination of limited resources.
ID: 551146

SELF-ESTEEM AND PSYCHOTIC SYMPTOMS: A QUESTIONNAIRE STUDY IN THE GENERAL POPULATION

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A component of self-esteem, negative beliefs about the self, may be associated with psychotic symptoms in clinical and non-clinical populations (Barrowclough et al. 2003; Gracie et al. 2007). This study re-examines whether positive and negative beliefs are associated with paranoia, positive symptoms, negative symptoms and depression. It also investigates the relationship that self-esteem has with perceived stress, stressful life-events and schizotypy. 268 healthy volunteers completed several questionnaires online. These included: the Green et al. Paranoid Thought Scale, designed to be less confounded by depression than more commonly used measures of paranoia; an adapted version of the Holmes-Rahe Life Events Scale; and the Brief Core Schema Scale. Participants will be contacted to complete follow-up questionnaires in October, 2008. Preliminary multiple regression analyses show that negative, but not positive beliefs about the self, are associated with paranoia ($P < .001$), positive symptoms ($P < .001$) negative symptoms ($P < .001$), depression ($P < .001$) and total symptom scores ($P < .001$) at baseline. The number of life events deemed by the participant to be 'very stressful' was associated with negative beliefs, whereas life events appraised as even 'moderately stressful' were associated with the formation of psychotic symptoms. Initial consideration of the data confirms that negative beliefs about the self are strongly associated with the positive, but also the negative symptoms of psychosis. Future analysis will control for depression and examine a model of stress, self-esteem and symptom severity using structural equation modelling. Data from the follow-up assessments will also be analysed. Negative beliefs about the self may act as a vulnerability factor for psychosis, and further research is needed to assess its suitability as a target for intervention in clinical and at risk groups.
ID: 551036

CIBERSAM: THE SPANISH NETWORK ON MENTAL HEALTH

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The Center for Biomedical Research in Mental Health (CIBERSAM) is composed of 25 research groups in the field of psychiatry and neuroscience (www.cibersam.es). The groups, comprising more than 500 researchers, are located in public and private hospitals, universities, and research institutions. This virtual center, funded by the Spanish government, has a main objective of seeking increased efficiency by coordinating basic and clinical research groups and achieving effective and productive management of assigned resources. A number of multicenter trials, including clinical trials assessing the efficacy of antidepressants for the treatment of negative symptoms ($n = 250$ patients), gene x environmental interaction studies in patients and families ($n = 1000$ patients) , longitudinal studies of first-episode childhood-onset schizophrenia assessing progressive changes and oxidative stress markers, the search for new therapeutic targets, and post-mortem studies, are being conducted, focusing on schizophrenia and related psychoses. We will present the highlights of those studies

and will testify on behalf of the benefits of such a structure that includes both clinical and basic research facilities, working to foster innovation and the transfer of results to society, the scientific community, and the enterprise sector.
ID: 551012

EARLY DETECTION OF FIRST PSYCHOSIS: TIPS SAMPLE FIVE YEAR OUTCOMES

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Reducing the duration of untreated psychosis (DUP) through early detection is associated with better PANSS negative (PNeg), depressive (PDep), and cognitive (PCog) outcomes at baseline, 1 and 2 year follow-up in the TIPS first episode psychosis sample. Here we report differences in early detected (ED) versus non-early detected (NoED) samples at 5 years. A total of 281 patients with first psychosis (DSM-IV) were recruited to baseline over 4 years. The two samples entered equivalent treatment programs for the first 2 years. At 5 year follow-up 193 (69%) of the baseline sample participated (74% and 64% of ED and NoED samples, respectively). The PNeg score at 2 years was: ED = 15.7, NoED = 18.7, $P = .013$ and at 5 years was ED = 15.8, NoED = 17.0, $P = $ ns. Drop outs between 2 and 5 years in the NoED group had significantly higher 2 years PNeg than ED drop-outs (ED = 14.9, NoED = 21.0, $P = .008$). The PDep score at 2 years was ED = 8.2, NoED = 9.9, $P = .001$ and at 5 years was ED = 8.1, NoED = 9.0, $P = $ ns. Again PDep scores at 2 years were higher in NoED dropouts (ED = 7.7, NoED = 10.1, $P = .015$). The PCog score at 2 years was ED = 4.3, NoED = 5.6, $P = .0001$ and at 5 years remained significant (ED = 4.2, NoED = 5.4, $P = .0001$) with no difference in the PCog scores among dropouts between 2 and 5 years. Treatment utilization was not different across the two groups for the first 2 years as per the standard protocol. After 2 years treatment was optional. ED/NoED medication utilization was equivalent at years 3, 4, and 5, but the rate of individual treatment contacts ("talking therapies") was significantly lower ($P < .01$) in the ED group at years 3, 4, and 5 compared to the NoED group. Overall, ED/NoED baseline differences in negative, cognitive, and depressive components appear to persist to 5 years. Apparent attenuation of differences is likely to be secondary to higher drop out rates of sicker NoED patients between 2 and 5 years. By years 3, 4, and 5 more ED patients have less structured treatment contacts but continue pharmacotherapy suggesting greater treatment selectivity by the ED group.
ID: 550970

THE EFFECT OF NEUROCOGNITIVE CHANGE ON HETEROGENEOUS TREATMENT RESPONSE SUBGROUPS OF FUNCTIONAL CHANGE IN COMMUNITY-BASED PSYCHOSOCIAL REHABILITATION FOR SCHIZOPHRENIA

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The present study aimed to test two hypotheses. The first hypothesis proposed that there would be heterogeneous subgroups of functional change in community-based psychosocial rehabilitation. The second hypothesis was that subgroups in neurocognitive change would predict the subgroups of individual trajectories of functional change The notion of heterogeneity in treatment responsiveness has been repeatedly addressed in literature but the heterogeneity in the impact of community-based psychosocial rehabilitation across individuals is not well documented. Method: Data were gathered on 130 individuals diagnosed with schizophrenia recruited upon admission to community-based psychosocial rehabilitation who were followed over a 12 month period. Psychosocial functioning data were gathered at baseline, 6 and 12 months. Tests of neurocognition and social cognition were administered at baseline and 12 months by testers blind to the psychosocial data. Data were analyzed using latent growth mixture models. Results: Growth mixture modeling showed that there was two latent classes in functional change that discriminate those individuals who showed a strong relationship between treatment intensity and functional change during rehabilitation (treatment responders) and those who did not show a significant relationship between service intensity and functional change during rehabilitation (treatment non-responders). The subgroup of neurocognitive change significantly predicted the treatment response subgroups, indicating that individuals with neurocognitive enhancement were five times more likely to belong to the treatment responders than the trajectory class of the treatment non-responders (OR = 4.978; 95 % CI = 1.666–14.877). Additional analyses showed that individuals at baseline who were younger (OR = .919), had more social contacts (OR = 1.566), had better neurocognition (OR = 1.194) and who had less symptomatology (OR = .937) were more likely to be in the treatment responder class in which functional improvement was significantly predicted by treatment intensity. Implication: These findings suggest a neuro-psycho-social model for understanding responsiveness to intensive psychosocial rehabilitation in the community. This is a multi-factorial model which spans phenomenological levels, and suggests that comprehensive and interdisciplinary theoretical approaches are needed to understand complex issues like treatment responsiveness in schizophrenia.
ID: 550950

NEGATIVE SOCIAL INTERACTION APPRAISALS, MOOD AND SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Research on the complex interplay between factors that might contribute to poor social functioning in schizophrenia has been hampered by limitations of traditional measures, most notably the ecological validity of retrospective self-report and interview measures. Computerized Experience Sampling Methods (ESMc) permit the real-time assessment of relationships between daily life experiences, thoughts, feelings and behaviors. ESMc was used to assess number of daily social interactions, appraisals of these interactions (eg, "I succeeded/failed;" "I was liked/rejected"), and mood in outpatients ($n = 111$) with schizophrenia. Participants completed electronic questionnaires on a personal digital assistant (PDA) four times per day for one week. In time-lagged HLM analyses, more negative interaction appraisals at any point in a day were associated with less positive mood, which in turn, was a strong predictor of fewer social interactions over subsequent hours. Social isolation, therefore, was linked to defeatist beliefs about social interactions that were associated with reduced positive mood. Greater positive mood may have been more reinforcing of prior social interactions or less likely to activate negative defeatist beliefs that would interfere with later interactions. The findings may suggest a useful treatment target for psychosocial interventions, like cognitive behavioral

therapy, which can be used to challenge defeatist beliefs and improve mood and, therefore, might improve social functioning in schizophrenia.
ID: 550944

ASSESSING THE ABILITY TO TAKE MEDICATION

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The Test of Adaptive Behavior in Schizophrenia– Medication subtest (TABS-MED) assesses a person's ability to follow medication instructions, to identify problems such as running out of medication, and to get appropriate medication refills. The TABS is designed to assess capacities including initiation, planning, problem identification, sequencing, and problem-solving that are necessary to complete a range of instrumental skills. The TABS-MED assesses these capacities as they relate to the ability to take medication as prescribed. As part of an NIMH trial examining the efficacy of different psychosocial treatments to improve adherence, we examined the reliability and validity of the TABS Medication Subtest in a sample of 69 individuals with schizophrenia (DSM-IV-R). At baseline, the TABS-MED, the Medication Management Ability Assessment (MMAA)–a performance-based test of medication taking ability from the UCSD Performance-Based Skills Assessment, and a comprehensive neuropsychological test battery were administered. Subjects were followed for one month to examine adherence to medication using randomly scheduled, unannounced in home pill counts. Results indicated that the TABS and MMAA were significantly but not strongly correlated ($r = .30$; $P < .01$). Only the TABS was significantly correlated with a summary cognitive function score ($r = .34 < .003$) and measures of prospective memory (.46; $P < .0001$), working memory (.44; $P < .0001$), secondary verbal memory ($r = .38$; $P < .002$) processing speed ($r = .25$; $P < .04$), sustained attention ($r = .32$; $P < .01$) and card sorting ($r = .40$ $P < .0002$). Neither the TABS nor MMAA was significantly correlated with fluency measures. Only the TABS was significantly correlated with pill count adherence ($r = .31$; $P < .03$). The relatively weak correlation of the TABS with pill count adherence underscores the notion that adherence is multi-determined and ability is only one contributor to taking medication as prescribed. The TABS-MED may be a useful performance-based assessment for examining the capacity for adherence in studies where direct assessment of adherence behavior is not possible.
ID: 550922

ANTIPSYCHOTIC DRUGS AND QUALITY OF LIFE IN SCHIZOPHRENIA: A META-ANALYSIS

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Background: Improved quality of life and psychosocial functioning have been recognized as desirable goals of effective antipsychotic drug therapy; and second generation antipsychotic drugs held the promise of fulfilling this need. We sought to review all studies that formally evaluated the impact of antipsychotic drugs on quality of life of people treated for schizophrenia. Methods: Clinical trials and other evaluation studies on the effectiveness of antipsychotic drugs in schizophrenia published between 1953 and July 2008 were identified; and studies that included quality of life or functional outcome measures were specifically examined to assess the impact of antipsychotic drug therapy on these domains. 67 studies that met the study criteria were critically reviewed, ascertaining the process and outcome of quality of life evaluations. Results: There is a dearth of data on quality of life evaluation in clinical trials, considering the vast number of published studies on the efficacy of antipsychotic drugs. Design issues such as lack of an explicit evaluation strategy, use of disparate quality of life measures and relatively short duration of trials significantly limit the validity and generalizability of results. Studies suggested, however, that antipsychotic drug therapy (compared to no treatment) improved quality of life; and second generation antipsychotic drugs fared better in improving functional outcomes. Conclusions: Measuring quality of life, let alone improving it, remains a challenge in schizophrenia research and antipsychotic drug evaluation. The review highlights the need to broaden the scope of evaluation batteries in clinical trials and develop standard guidelines, and stresses the inclusion of patient reported outcomes.
ID: 550875

IMPAIRED OLFACTORY IDENTIFICATION ABILITY IS ASSOCIATED WITH POORER FUNCTIONAL OUTCOME IN PATIENTS WITH FIRST EPISODE PSYCHOSIS

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Background: Olfactory deficits are found in a significant proportion of patients with psychotic disorders, however, the full prognostic significance of these findings has yet to be determined. Our group has previously reported that patients with olfactory deficits ('microsmic') are less likely to remit on negative and cognitive symptoms of the PANSS in follow-up (Good et al. 2006, AJP 163(5): 932–933). In the current study, we identified first episode psychosis patients who were microsmic at first presentation and compared them to first episode psychosis patients who had normal olfaction ('normosmic'), on functional outcome using the SOFAS and Levels of Functioning Scale (LOFS) after at least 2 years of treatment in the Nova Scotia Early Psychosis Program (NSEPP). Premorbid functioning, measured with the Premorbid Adjustment Scale (PAS), was compared between groups. Method: Seventy six (76) first episode psychosis patients (52M; 24F) were assessed with the University of Pennsylvania Smell Identification Test (UPSIT) as soon as it was clinically feasible at baseline. UPSIT scores served to classify patients into subgroups. The PAS was completed by an informed relative (usually the mother) at baseline. The patients' psychiatrists completed the SOFAS and the LOFS at standardized time points post-baseline assessment Results: 40% of the sample was identified as microsmic. LOFS scores were significantly lower in the microsmic group than the normosmic group ($F_{9,40} = 3.9$, $P < .001$), specifically on measures assessing level of useful employment and ability to meet own basic needs. Differences in SOFAS scores missed statistical significance ($t_{71} = 1.7$, $P < .10$). PAS scores did not differ between groups. Conclusions: Microsmic patients had poorer functional outcome than normosmics patients despite no differences in premorbid adjustment. Olfactory deficits at first episode may provide a marker of poorer outcome. Testing olfaction is a simple process and could provide clinically valuable information at first episode to identify those patients early who might benefit from more intensive biopsychosocial interventions to promote functional recovery.
ID: 554879

DISSECTING SOCIAL INFORMATION PROCESSING DEFICITS IN SCHIZOPHRENIA: CONTRIBUTION OF AFFECTIVE AND NON-AFFECTIVE COGNITIVE COMPONENTS

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Deficits in social functioning are a core feature of schizophrenia. A growing body of research on facial affect recognition in schizophrenia provides strong evidence for receptive deficits in the processing and interpretation of emotion expression in the human face. Concurrent with these findings is the body of evidence for deficits in social perspective-taking and the interpretation of meaning from verbal and non-verbal interpersonal communication. The current study was designed to investigate specific components of social information processing, on laboratory measures of facial affect recognition, and social perspective-taking, in addition to two new measures of inferential reasoning regarding interpersonal behavior in a social context. Methods: 43 adults with DSM-IV Schizophrenia or Schizoaffective Disorder and 42 Healthy Control Subjects, ages 18–65, matched for age, IQ and socioeconomic status, were evaluated on a battery of non-affective and af-fective cognitive tasks, including the Pennsylvania Emotion Recognition Task (PERT-96), a False Belief Task (FBT) to assess so-called Theory of Mind perspective-taking abilities, a new videotape equivalent of the FBT task and a newly validated Movie Clips task that taps inferential reasoning regarding the thoughts, feelings and motives of characters in selected scenes from movies. Results: Participants with schizophrenia not only demonstrated deficits in the accuracy ($P < .004$) and speed ($P < .003$) of processing facial affect, but deficits on these measures were correlated with deficits in social perspective-taking on both the videotape ($< .01$) and story version ($P < .05$) of the FBT as well as inferential reasoning regarding the thoughts, and emotions of characters in the movie scenes. A particularly interesting finding was that the ability to reflect on personal emotional response to watching the movie scene was correlated with accuracy on the objective measure of affect recognition. Findings provide promising evidence of links between specific information processing deficits and the interpretation of social behavior in a social context.
ID: 554986

21. 21. Therapeutics: Pharmacologic Probes

IDENTIFICATION OF CLOZAPINE INTERACTIONS WITH THE PHOSPHATIDYL INOSITOL 3-KINASE (PI3K) PATHWAY IN CAENORHABDITIS ELEGANS

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Clozapine has superior therapeutic efficacy and a unique side effect profile as an antipsychotic agent, but the mediators of these effects are not known. We studied behavioral and developmental effects of clozapine in the nematode C. elegans, as a model system to identify previously undiscovered mechanisms of drug action. C. elegans provides a versatile system that can be used to identify novel targets and pathways modulated by psychoactive drugs, as many gene systems of interest in psychiatric illnesses are conserved between C. elegans and mammals. In our study, we observed that clozapine induced developmental arrest in early larval stages in C. elegans in a dose-dependent manner. Larval arrest was also seen with the clozapine metabolite N-desmethyl clozapine but was not seen with other typical or atypical antipsychotic drug tested, including haloperidol, perphenazine, or olanzapine. We then screened for worms with mutations in neurotransmitter and signal transduction systems to dissect pathways involved in clozapine-induced larval arrest. Experiments with mutants deficient in neurotransmitter biosynthetic pathways showed that clozapine-induced larval arrest was not dependent on dopaminergic or serotonergic systems, which are shared targets for other antipsychotic drugs. We discovered that age-1 mutants, which have a mutation in the gene coding for phosphatidyl inositol 3-kinase (PI3K), suppressed clozapine-induced larval arrest. This result is interesting in the context of recent human genetic studies pointing to an association between the PI3K target AKT-1 and schizophrenia. It is known that PI3K plays a pivotal role in the insulin signaling pathway. We compared the effects of starvation to that of clozapine on the insulin signaling pathway, since both conditions lead to early larval arrest. We studied the nuclear/cytoplasmic localization of the transcription factor DAF-16, which is the downstream effector in the insulin signaling pathway. The DAF-16 localization results showed that starvation results in inhibition of the insulin signaling pathway, while clozapine-induced larval arrest results in activaton of the insulin signaling pathway. Our findings demonstrate a drug-specific novel interaction between clozapine and the PI3K pathway in C. elegans and hold implications for understanding the unique therapeutic and/or side effects of clozapine in humans.
ID: 542774

REASONS FOR DISCONTINUATION AND CONTINUATION OF ANTIPSYCHOTIC THERAPY FROM PATIENT AND CLINICIAN PERSPECTIVES

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The purpose of this study was to assess the reasons for discontinuation and for continuation of antipsychotic medication in the treatment of schizophrenia from patient and clinician perspectives. Two measures were developed to assess the Reasons for Antipsychotic Discontinuation/Continuation (RAD), one from patient's perspective (RAD-I) and the other from clinician's perspective (RAD-Q). These measures were administered to patients enrolled in a 12-week study of antipsychotic medication in the treatment of schizophrenia ($N = 630$). Reasons for discontinuation and reasons for continuation with the assigned antipsychotic during the study were assessed. Reported reasons were rated as being a primary reason, very important, somewhat important, or of minor importance. The top primary reasons for medication discontinuation and continuation were identified from patient and clinician perspectives, and level of concordance between patients' and clinicians' reasons was assessed. The top primary reasons for medication discontinuation differed from the top primary reasons for continuation on the medication, with a high level of concordance between patients' and clinicians' perspectives. The top 3 primary reasons for medication discontinuation were insufficient improvement or worsening of positive symptoms, medication-related adverse events, and insufficient improvement or worsening of mood symptoms. The top 3 primary reasons for medication continuation were improvement in positive symptoms, subjective perception of improvement, and improvement in level of functioning. Current findings show that medication efficacy appears to be the core driver of medication continuation and discontinuation, especially with regard to positive symptoms. Reasons for medication discontinuation differ somewhat from reasons for continuation, with a high level of concordance between patients' and clinicians' perspectives.
ID: 550806

ORAL SUPPLEMENTATION AND CONCOMITANT MEDICATION IN THE TREATMENT OF SCHIZOPHRENIA WITH LONG-ACTING ATYPICAL ANTIPSYCHOTICS

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This study aimed to assess the use of oral antipsychotics and other concomitant oral medications—psychotropics and the anticholinergic benztropine—during the 1-year open-label treatment of schizophrenia with olanzapine long-acting injection (OLAI), and to compare with previously published rates for risperidone long-acting injection (RLAI). One-year rates of concomitant oral medication use were drawn from 2 comparable open-label, single-arm extension studies of patients with schizophrenia treated with long-acting atypical antipsychotic medications: 1 for OLAI ($n = 931$), with extension of 3 OLAI clinical trials, and 1 for RLAI ($n = 371$), with extension of 2 RLAI clinical trials (based on published 1-year data—Lindenmayer et al. Eur Neuropsychopharmacol. 2007;17:138–144). Supplementation with oral olanzapine occurred in 21% of OLAI-treated patients (median duration 10 days). Oral risperidone was supplemented—beyond the first 3 weeks of treatment in 45%–83% of RLAI-treated patients (median duration not reported). Use of the anticholinergic benztropine was low among OLAI-treated patients (3%, median duration 14 days) and higher among RLAI-treated patients (31%–44%, median duration not reported). Lorazepam was used by 11% of OLAI-treated patients compared to 24%–55% of RLAI-treated patients. Zolpidem was used by 4% of OLAI-treated patients and 11%–12% of RLAI-treated patients. Atypical antipsychotic therapies in long-acting injection formulations were found in this preliminary analysis to differ on concomitant use of

oral atypical antipsychotic and other oral medications. OLAI therapy may require less oral supplementation compared to RLAI, thus offering a simpler treatment regimen. Though limited by cross-study comparisons and the need for replication, the current findings may have important clinical and economic ramifications as depot formulations are often chosen for persons previously nonadherent to oral medication regimens.
ID: 550676

NEW GENERATION ANTIPSYCHOTICS: ARE THE DOPAMINE MECHANISMS PARTIAL AGONISM OR FUNCTIONAL SELECTIVITY?

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During the past five years, the concept of receptor functional selectivity has gone from a controversial hypothesis to an accepted concept of receptor pharmacology. The demonstration of ligand-induced differential signaling has been made in dozens of receptor systems, and the involved molecular mechanisms are under intensive study. It remains unclear, however, whether functionally selective properties of drugs will be meaningful *in vivo*, and if so, how to harness this interesting phenomenon to lead to novel neuropsychopharmacological drugs. Some of the clearest examples of functional selectivity are with dopamine receptor ligands. Both dihydrexidine and its analog N-n-propyldihydrexidine bind to D2L receptors with typical shallow, GTP-sensitive curves, and inhibit adenylate cyclase (ACase) to the same degree as dopamine in a variety of preparations. Although these results would normally lead to the conclusion that these compounds are full D2L agonists, in other assays these drugs behave as pure antagonists. This functional selectivity is found in both heterologous systems expressing the D2L receptor and in physiological preparations (eg, brain or pituitary). *In vivo*, both compounds cause behavioral effects distinct from that of any known ligand that also is a full agonist at D2L-mediated adenylate cyclase. An even more compelling example is the antipsychotic drug aripiprazole (Abilify). Although commonly thought to be a simple partial agonist, aripiprazole is actually a functionally selective ligand. For example, its intrinsic activity and potency at D2L-mediated inhibition of ACase are markedly affected by the D2L receptor milieu. Moreover, sometimes aripiprazole is a pure antagonist, completely blocking some actions of dopamine or quinpirole. These data suggest that aripiprazole is functionally selective D2 ligand, not simply a partial agonist, and also explain some of its behavioral effects. Such examples of functionally selective dopamine receptor ligands provide support for hypothesis that ligands with functionally selective properties may have novel clinical effects, even when targeting "old" receptors. If one accepts this hypothesis, the scientific hurdles then become how best to differentiate potential drug candidates for novel signaling profiles, and how to select the best clinical candidates from the identified subgroup. Jumping these hurdles should be of interest and importance both heuristically and clinically.
ID: 550667

MECHANISM OF ACTION OF SERTINDOLE IN THE MODULATION OF DOPAMINE NEURON POPULATION ACTIVITY

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Antipsychotic drugs administered acutely are known to increase the population activity (ie, proportion of neurons firing spontaneously) of dopamine (DA) neurons in the ventral tegmental area (VTA). However, the mechanism by which these drugs alter DA neuron firing is not known. There are several mechanisms that can account for this effect; ie, blockade of DA neuron autoreceptors or feedback from blockade of postsynaptic

DA receptors in the accumbens. This was examined using the classical antipsychotic drug haloperidol in comparison with the 2nd generation drug sertindole. Although both haloperidol and sertindole occupy D2 receptors rapidly after administration, consistent with previous reports sertindole, unlike haloperidol, failed to block the inhibition of DA neuron firing produced by autoreceptor-selective doses of apomorphine. Therefore, it is unlikely that the change in DA neuron population activity was due to DA autoreceptor blockade. Our previous studies showed that DA neuron population activity was regulated by a hippocampus subiculum-nucleus accumbens-ventral pallidal-VTA pathway. We tested whether the increase in DA neuron population activity may be due to antipsychotic drug-induced blockade of D2 receptors in the accumbens, causing accumbens activation, inhibition of the ventral pallidum, and disinhibition of the VTA. We found that blockade of the accumbens-ventral pallidal pathway via injection of the GABA antagonist bicuculline into the ventral pallidum prevented both haloperidol and sertindole from increasing dopamine neuron population activity. Interestingly, VTA DA neuron population activity is also elevated at baseline in a developmental disruption model of schizophrenia using the mitotoxin methylazoxymethanol acetate (MAM), which we propose is responsible for DA-dependent psychosis. Therefore, we examined how sertindole affected DA neuron activity in MAM-treated rats. We found that a single dose of sertindole to MAM-treated rats caused a substantial decrease in DA neuron population activity, presumably due to induction of depolarization block. Thus, by inducing depolarization block, antipsychotic drugs are attenuating the abnormally increased DA neuron population activity proposed to underlie psychosis. Therefore, we propose that in the MAM-treated rat or the schizophrenia patient, antipsychotic drugs will produce a rapid induction of depolarization block due to the already heightened baseline state of the DA system.
ID: 550588

ATYPICAL ANTIPSYCHOTIC METABOLISM/ BIOTRANSFORMATION AND EXCRETION

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Although all atypical antipsychotics (aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) share the common characteristic of dopamine and serotonin receptor modulation, each molecule has unique pharmacodynamic and pharmacokinetic characteristics. Reviewed here are some of the pharmacokinetic differences between the atypical antipsychotics, focusing on the pathways and extent of metabolism/biotransformation, and the routes of excretion. To perform the review we used each manufacturer's radiolabeled drug ADME (Absorption, Distribution, Metabolism, Excretion) study, available in the primary literature or FDA submission documents, combined with each product's prescribing information. All atypical antipsychotics other than paliperidone require extensive biotransformation (extensive defined as ≤50% of the drug recovered unchanged). Specifically, quetiapine requires the greatest overall metabolism, with <1% of the dose recovered unchanged; in contrast, 59% of paliperidone is recovered unchanged in the urine. Hepatic CYP450 (cytochrome P450) enzymes are largely responsible for the biotransformation of atypical antipsychotics. This review delineates the extent of CYP450-mediated biotransformation of atypical antipsychotics, and the specific CYP450 enzymes involved in these reactions. After administration of a radioactive dose, fecal elimination of radioactive compounds accounted for the majority of the dose for aripiprazole (55%) and ziprasidone (66.3%). For the remaining atypical antipsychotics, the majority of a radioactive dose was recovered in the urine (>50% of recovered radioactivity, 80% for paliperidone). These findings confirm that the routes of elimination (via metabolism and excretion) of atypical antipsychotic agents

vary considerably. An understanding of atypical antipsychotic drug metabolism and excretion may permit better-informed drug and dose selection in special populations, such as patients with comorbid conditions (eg, hepatitis, substance abuse, diabetes, end-stage renal disease), those with pharmacogenetic variability, or those at risk for drug-drug interactions. The use of patient "tailored" atypical antipsychotic drug and dose-selection may result in greater treatment efficacy as well as a reduction in adverse events. Supported by Ortho-McNeil Janssen Scientific Affairs, LLC, Titusville, New Jersey, USA.

ID: 550574

UNDERSTANDING THE ROLE OF PHOSPHORYLATION IN PDE10A ACTIVITY AND IN THE REGULATION OF DOWNSTREAM SIGNALING

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Inhibition of PDE10A, a dual cAMP/cGMP phosphodiesterase located primarily in the striatum, may prove to be an effective therapeutic approach to treating the symptoms of schizophrenia. We have undertaken a biochemical approach to explore the effects of papaverine (PDE10A IC50 36nM, 9- to 277-fold selectivity over other PDEs) and MP-10 (IC50 0.18nM, >3000-fold selectivity) in rodents. MP-10 treatment caused increases in phosphorylation levels of striatal CREB(ser133), DARPP-32(thr-34), GluR1(ser845) and ERK(tyr204) by 2.6-, 3.5-, 4.1-, and 1.4-fold, respectively. Papaverine treatment resulted in a trend toward higher levels of CREB, DARPP-32 and ERK phosphorylation, particularly with the higher doses. The 10 and 54 mg/kg doses of papaverine resulted in significant increases in GluR1 phosphorylation of 2.7- and 4.6-fold, respectively. Surface biotinylation was used to determine the extent of S845-phosphorylated GluR1 on cell surfaces in MP-10-treated striatal slices. The results indicated that there is a significant increase (2.3-fold) in the levels of phosphorylated GluR1 (S845), but not total GluR1, on cell surfaces of MP-10-treated striatal slices (1 uM, 30 min) compared to vehicle control. Similar results were obtained when cultures of dissociated striatal neurons were subjected to these conditions, such that there was a 1.4-fold increase in the levels of phosphorylated GluR1 (S845) on the surface of MP-10-treated neurons (1 uM, 30 min) compared to vehicle control. In order to investigate the regulation of PDE10A itself by PKA phosphorylation, we have generated an antibody that targets phosphothreonine 16 of the PDE10A2 polypeptide (anti-pPDE10A2). Anti-pPDE10A2 specifically reacted with a GST fusion protein containing the N-terminal portion of PDE10A2 only following phosphorylation by protein kinase A (PKA). In contrast, anti-pPDE10A2 did not react with this fusion protein when it contained an alanine or glutamate mutation at position 16 (T16A and T16E, respectively), even after treatment with PKA. Using this antibody, we also confirmed by subcellular fractionation and by immunocytochemistry that the reported membrane to cytosol translocation of PDE10A2 is caused by PKA phosphorylation at Thr16 of PDE10A2. We are now trying to understand the significance of these events for the therapeutic effects of PDE10A inhibition and to understand the key regulatory signals for PDE10A activity.

ID: 550561

A PHASE 2 TRIAL OF AN ALPHA 7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONIST IN SCHIZOPHRENIA

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Nicotinic acetylcholine receptors are possible therapeutic targets for schizophrenia, based on neurobiological and molecular evidence for deficiencies in expression of alpha 7-nicotinic receptors. Patients' heavy smoking suggests attempted self-medication through this mechanism. 3-[(2,4-dimethoxy)benzylidene]anabaseine (DMXB-A) is a partial alpha 7-nicotinic agonist and can be taken orally. Thirty-one subjects with schizophrenia received DMXB-A at two different doses and placebo for periods of 4 weeks in a three-arm, two-site, double-blind, crossover Phase 2 trial. The MATRICS Consensus Cognitive Battery assessed cognitive effects, and the Scale for Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS) assessed clinical effects. Subjects continued their current antipsychotic drug during the trial and were non-smokers. There were no significant changes in the MATRICS cognitive measures compared to placebo over the three treatment arms, but the patients experienced significant improvement at the higher DMXB-A dose on SANS total score and a trend towards improvement on BPRS total score. Improvement was most notable on the SANS Anhedonia and Alogia subscales. Examination of the first treatment arm showed effects of DMXB-A on the Attention-Vigilance and Working Memory MATRICS domains, compared to baseline. Five subjects developed mild tremor, and nearly half had mild nausea on DMXB-A. DMXB-A, a nicotinic agonist that activates alpha 7-nicotinic receptors, improved clinical ratings of negative symptoms that are generally resistant to treatment with dopamine antagonist antipsychotic drugs. The clinical utility of this treatment is not yet determined.

ID: 550514

IN VITRO BINDING AND FUNCTIONAL PROFILE OF ARIPIPRAZOLE AT CLONED HUMAN DOPAMINE D3 RECEPTORS

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Background: The dopamine (DA) D3 receptor has been proposed as a therapeutic target for antipsychotic drugs. Aripiprazole is the only approved antipsychotic that behaves as a D2 receptor partial agonist, although its functional profile at the D3 receptor is less well described. The purpose of this study was to estimate the in vitro binding affinity and functional characteristics of aripiprazole at cloned human D3 receptors (hD3R) expressed in CHO cells. Methods: Radioligand binding assays were performed to estimate the binding affinity (KD) of [3H]R(+)7-OH-DPAT, density of hD3R expression (BMAX), and binding affinity (Ki and KD) of aripiprazole at the hD3R expressed on CHO-hD3R cell membranes. The in vitro potency (pEC50) and intrinsic activity (EMAX) of aripiprazole were estimated at the hD3R using upstream (forskolin-stimulated cAMP accumulation) and downstream (serine-9 phosphorylation of GSK-3β) readouts of CHO-hD3 cell signaling. Results: [3H]R(+)7-OH-DPAT bound with high affinity to a single site (KD = 2.28 ± 0.40 nM) expressed at high density (BMAX = 25.05 ± 1.63 pmol/mg protein) on CHO-hD3 cell membranes. Aripiprazole displaced this radioligand and bound to the

hD3R with high affinity (Ki = 1.62 nM). Aripiprazole potently (pEC50 = 8.23 ± 0.17) inhibited cAMP accumulation in CHO-hD3 cells, displaying lower intrinsic activity (EMAX = 27.6 ± 1.4% of 10 μM DA) than OPC-4392, (-)3-PPP and (+)terguride (EMAX = 58.0 ± 1.8%; 76.7 ± 3.2%; 77.2 ± 2.6% respectively). Aripiprazole exhibited a similar potency (pEC50 = 8.16 ± 0.31) and intrinsic activity (EMAX = 25.6 ± 4.7% of 10 μM DA) in the CHO-hD3 cell phospho-serine 9 GSK-3β assay. These effects of aripiprazole on cAMP and phospho-serine 9 GSK-3β were mediated through the D3R as they were blocked by the D3R antagonist (-)raclopride. Discussion: Aripiprazole bound with high affinity to and behaved as a potent partial agonist at the hD3R. Interestingly, aripiprazole demonstrated lower intrinsic activity in the cAMP assay than a series of other hD3R partial agonists that are clinically ineffective as antipsychotics, consistent with the rank order of intrinsic activity displayed by these compounds at cloned human D2 receptors. Moreover, aripiprazole produced D3R-mediated increases in phospho-serine 9 GSK-3β, an inactivated phosphoprotein that promotes neuronal survival and neurogenesis, which is of interest as the pathology of schizophrenia has been linked to disordered GSK-3β regulation.
ID: 550409

REPEATED DOSING OF THE SELECTIVE GLYT1 INHIBITOR, DCCCYB DOES NOT PRODUCE DE-SENSITIZATION OF GLYT1 OR NMDA RECEPTORS

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Hypofunction of NMDA receptors has been implicated in the pathophysiology of schizophrenia. Mechanisms which may lead to enhancing NMDA function are currently being pursued as novel treatments. Selective glycine transporter subtype 1 (GlyT1) inhibitors are being developed as an approach to enhance NMDA function via increasing synaptic glycine, a co-agonist for NMDA as a treatment for positive, negative symptoms and cognitive impairment in schizophrenia. DCCCyB is a potent and selective GlyT1 inhibitor. Preclinical studies with acute dosing, have demonstrated that DCCCyB produces increases in extracellular glycine levels in prefrontal cortex as measured by dialysis, however the potential for desensitization of NMDA receptors or GlyT1 after repeated dosing has not been evaluated. To address this, male SD rats were dosed with either 5 mg/kg DCCCyB or vehicle (0.5% methylcelluose) po for eight days. Rat cortex was collected 1 hour after dosing on day eight and both synaptosomal and membrane homogenates were prepared. GlyT1 functional activity was measured by [3H]-glycine uptake and density of GlyT1 was determined by saturation binding with the selective GlyT1 radioablel, [3H]-CPyPB. NMDA receptor density was measured by [3H]-MK801 binding. NMDA receptors were also localized after repeated dosing by immunocytochemistry measured with a NMDAR2 antibody in sections prepared from cortex and cerebellum. Plasma was collected at day 8 to confirm DCCCyB exposures and correlated with 65% GlyT1 receptor occupancy. Repeated dosing of DCCCyB did not result in a change in either the affinity (Ki) or the maximum rate of glycine transport (Vmax) compared to vehicle treated animals. The affinity and density of GlyT1 defined by [3H]-CPyPB was also unchanged between DCCCyB and vehicle treated groups. Repeated dosing did not affect the binding affinity for [3H]-MK801 or expression level of NMDA receptors. In addition, no evidence of significant NMDA receptor internalization was observed after repeated dosing with DCCCyB. These results indicate that neither alterations in GlyT1 function

nor expression and NMDA receptor densensitization occur after 8 days dosing with DCCCyB, a selective GlyT1 inhibitor.
ID: 549100

A SELECTIVE MGLUR2 POSITIVE ALLOSTERIC MODULATOR RADIOLIGAND DEFINES THE MGLUR2 DISTRIBUTION IN RAT, RHESUS AND HUMAN BRAIN

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Preclinical studies have shown that mGluR2/3 agonists and mGluR2 selective positive allosteric modulators exhibit anti-psychotic activity in rodent behavioral models. Based on studies with KO mice, the antipsychotic activity of mGluR2/3 agonists has been attributed to activation of mGluR2. Recently, Lilly demonstrated POC with a non-selective mGluR2/3 agonist, LY404039 showing improvements in positive and negative symptoms in schizophrenic patients, further validating the mechanism. Therefore, activation of mGluR2 is a promising, non-dopaminergic therapeutic approach for the treatment of schizophrenia. Determination of mGluR2 distribution has been difficult due to lack of subtype selective radioligands and the distribution in humans is not known. Currently, potent, nonselective mGluR2/3 radiolabeled agonists and antagonists have been utilized, however the use of these labels have been unable to definitely measure the specific contribution of mGluR2. We here report the in vitro characterization of a radiotracer developed from a potent and selective mGluR2 positive allosteric modulator TBPCOB, and its use in autoradiographic studies to localize mGluR2 binding sites in rat, rhesus and human brain. TBPCOB is a potent, selective, mGluR2 positive allosteric modulator (FLIPR mGluR2 EC50 = 29 nM; mGluR3 EC50 > 30 μM). The compound was amenable to radiolabeling with tritium and produced low nondisplaceable binding on tissue homogenates. Kd values of 1.6 and 4 nM, respectively, were determined in rat and rhesus brain homogenates and the binding fit to a one-site model. Autoradiographic studies of rat, rhesus and human brain slices with TBPOC showed high specific binding sites with a nonhomogeneous distribution. High levels of specific binding was measured in the cortex, hippocampus and caudate and was similar across species. Furthermore, GTPγ35S autoradiography employing suboptimal concentrations of the mGluR2/3 agonist, LY379268 with a selective mGluR2 potentiator revealed a similar distribution. This is the first report of the mGluR2 anatomical localization using direct radiolabel binding with a selective mGluR2 ligand and the first visualization of mGluR2 in human brain tissue.
ID: 549012

DETECTING ANTIPSYCHOTIC-LIKE COMPOUNDS WITH A DOPAMINE D3 RECEPTOR-LINKED MECHANISM OF ACTION USING PREPULSE INHIBITION OF STARTLE IN RATS

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Background: Prepulse inhibition of startle (PPI) occurs when a weak lead stimulus inhibits the response to an intense startling stimulus. PPI is impaired in schizophrenia and Tourette Syndrome (TS), among other disorders. In rats, PPI is disrupted by dopamine (DA) agonists, and this effect is blocked by both typical and atypical antipsychotics. Putative antipsychotics are commonly screened for their ability to prevent PPI deficits induced by the D1/D2 agonist apomorphine (APO). As DA D3 receptor antagonists or partial agonist might have antipsychotic properties without D2-related side effects, we developed a PPI-based screening strategy to detect such compounds. WC10, and WC44, two members of a novel panel of preferential D3-receptor compounds were tested. In *in-vitro* assays, WC10 is characterized as a D3 antagonist/weak partial agonist and WC44 as a full D3 agonist (Chu et al. 2005). The sensitivity of these compounds to prevent PPI deficits induced by the preferential D3 agonist pramipexole (PRA) vs. the D1/D2 agonist APO was used as functional evidence of D3 vs. D1/D2 selectivity, and to predict potentially novel clinical profiles for these compounds. Methods: Acoustic startle and PPI were measured in Sprague Dawley rats. First, we tested the ability of the preferential D2-receptor antagonist L741,626 (0, 1, 3, 10 mg/kg) to prevent the PPI-disruptive effects of APO (0, 0.1, 0.5 mg/kg) and PRA (0, 1 mg/kg), to confirm that D2 receptor stimulation is preferentially responsible for the PPI-disruptive effects of APO vs. PRA. Second, we tested the ability of WC10 (0, 1, 3, 10 mg/kg) and WC44 (0, 1, 3, 10 mg/kg) to prevent the PPI-disruptive effects of APO and PRA. Haloperidol (0, 0.1 mg/kg) was a positive control. In some cases, measures of drug effects on generalized motor activity were also conducted. Results: APO induced PPI deficits and HAL prevented these deficits, confirming sensitivity of the "traditional PPI assay". WC10, but not WC44 reversed APO-induced PPI deficits. In contrast, reversal of PRA-induced PPI deficits was more pronounced for WC44 than for WC10. Conclusions: The present findings confirm the feasibility of this screening strategy. The data suggests a conventional (ie, D2-antagonist-like) antipsychotic profile for WC10. In contrast, WC44 may have novel antipsychotic-like properties linked to functional D3 receptor antagonism. Supported by Tourette Syndrome Association and NARSAD Young Investigator awards to MW.
ID: 548979

THE EFFECT OF SMOKING CESSATION DRUG VARENICLINE ON AUDITORY GATING IN A MOUSE MODEL OF THE DEFICIT IN SCHIZOPHRENIA PATIENTS

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Varenicline, marketed in the US as Chantix, is an FDA approved smoking cessation drug. Because of the high incidence of smoking in schizophrenia patients as compared to the general population the utilization of varenicline in the schizophrenia population is being explored. Varenicline produces its effects via specific subtypes of nicotinic acetylcholine receptor (nAChR). Specifically, it is a partial agonist at the α4β2 nAChR, the high affinity nicotine receptor, and a full agonist at the α7 nAChR. Both subtypes of nAChR are thought to be involved, genetically and physiologically, in schizophrenia. Selective agonists for both the α7 and α4β2 subtypes produce improvements in a specific symptom of schizophrenia, the auditory gating deficit. This deficit prevents patients from filtering extraneous sensory stimuli resulting in 'sensory stimuli overload'. We utilize a mouse model, the DBA/2 mouse, which spontaneously exhibits a gating deficit analogous to the deficit of schizophrenia patients. This study assessed the effect of varenicline upon the auditory gating deficit of DBA/2 mice to determine how this smoking cessation drug may impact gating of schizophrenia patients attempting to alleviate their addiction to nicotine. Electrophysiological auditory evoked potentials (AEPs), in response to paired identical click stimuli were recorded from the hippocampal CA3 region of DBA/2 mice before and after administration of varenicline. The measure of auditory gating (TC ratio) is the ratio of the AEP produced by the second stimulus (TAMP) divided by the AEP produced by the first stimulus (CAMP). A TC ratio of >0.4 indicates deficient auditory gating while a TC ratio of ≤ 0.4 is considered normal gating. We tested four different doses (0.5, 1, 5, 10 mg/kg) of varenicline in the auditory gating paradigm. All four doses produced significant decreases in TC ratio as compared to controls. It has been proposed that control of TAMP is via the α7 nAChR while control of CAMP is in part via the α4β2 nAChR. There were significant changes in both the TAMP and CAMP at varying doses. Central administration of α-bungarotoxin with a dose of varenicline which decreased TAMP, fully blocked this effect. Taken together, these data indicate activity of varenicline at both the α4β2 and α7 subtypes. These results indicate that along with its function as a smoking cessation drug, varenicline may be useful in alleviating the auditory gating deficit in schizophrenia patients.
ID: 547916

IPTAKALIM: A POTENTIAL ANTIPSYCHOTIC DRUG WITH NOVEL MECHANISMS

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Iptakalim is a putative novel adenosine triphosphate (ATP)-sensitive potassium (KATP) channel activator. Centrally, iptakalim acts on the neuronal and astrocytic plasma membrane and/or mitochondrial KATP channels. Because it demonstrates an action on the regulation of dopamine and glutamate release in the forebrain regions, we examined its potential antipsychotic efficacy in four preclinical tests. First, we show that acute iptakalim treatment selectively and dose-dependently disrupts conditioned avoidance responding, while leaving escape response intact. Second, we show that repeated iptakalim treatment gradually loses its inhibition on avoidance responding, an effect shared only by clozapine, but not by other antipsychotics tested, such as haloperidol, olanzapine and risperidone, indicating a possible clozapine-like property. Third, we show that iptakalim is effective in reducing amphetamine- and PCP-induced locomotor activity and shows a preferential effect in reducing the PCP-induced hyperlocomotion over the amphetamine-induced one. Finally, we show that iptakalim and clozapine, but not haloperidol, preferentially induces c-fos expression in the medial prefrontal cortex and nucleus accumbens, but not in the dorsolateral striatum. These findings suggest that iptakalim may be a drug that possesses an clozapine-like antipsychotic property with a mechanism of action distinct from currently available antipsychotics. This study also suggests that neuronal and astrocytic plasma membrane and/or mitochondrial KATP channels may be a valid target for future antipsychotic drug research.
ID: 546658

DOSE-RELATED EFFECTS OF ACUTE EXPOSURE TO Δ9-THC ON BEHAVIOR, ATTENTION, MEMORY AND NEURAL SYNCHRONY IN HUMANS

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The mechanisms by which cannabinoids produce transient psychotomimetic effects and impairments in attention and memory are not clear. Perceptual, memory and attentional functions are based on distributed processes that are believed to be "bound" together by synchronous high frequency oscillatory activity. In humans, macroscopic neural synchrony can be evaluated noninvasively by entrainment of the EEG to sensory (auditory) stimuli presented of various frequencies. We are studying the dose related effects of Δ9-THC on electrophysiological indices of information processing in humans. Healthy subjects ($n = 9$) completed 3 test days during which they received (0, 0.015, 0.03 mg/kg) intravenous Δ9-THC in a double-blind, randomized design. The effects of Δ9-THC on 1) Behavior (Perceptual alterations, psychotic-like symptoms), 2) Memory (immediate verbal recall, spatial working memory and visual object recognition memory), 3) neural synchrony (steady state EEG response to auditory click trains at 20, 30 and 40 hz), and 4) event related potentials (ERPs) recorded during performance of "oddball" target detection tasks were measured. Δ9-THC induced transient psychotomimetic effects, perceptual alterations, amnestic effects and attentional impairments. Δ9-THC reduced EEG power in response to auditory click trains. Δ9-THC reduced target P3b and novel P3a amplitudes generated during the auditory oddball task even though subjects responded accurately to target stimuli. Δ9-THC appeared to affect target P3b more than novelty P3a. The reductions in target P3b amplitude may reflect Δ9-THC induced impairments in the top down allocation of attention and/or the updating of memory associated with task specific response selection as well as cognitive slowness and inefficiency.
ID: 550888

PCP-INDUCED EFFECTS UPON VOLUNTARY SUCROSE INTAKE: IMPACT OF CLOZAPINE

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Drug treatment of schizophrenia is hampered by the general lack of effectiveness of existing antipsychotic drugs against the negative symptoms and cognitive deficits. These symptoms have been correlated with dysfunctional prefrontal cortex activity. We have shown that repeated PCP treatment to rats reproduces metabolic abnormalities in the prefrontal cortex activity (hypofrontality) (Cochran et. al. 2003 Neuropsychopharmacology 28: 265–75). The aim of this study was to examine the effects of repeated PCP in a behavioural task that may mirror an aspect of negative symptoms and determine if this is modified by clozapine. The task selected was the voluntary sucrose consumption test since this is considered to relate to anhedonia. Hooded Lister rats were habituated to the sucrose drinking procedure and then received PCP (2.6 mg/kg i.p.) or vehicle according to our previous treatment regime. (Cochran et. al. 2003). Following 5 days of PCP or vehicle treatment, the effects of clozapine were determined. Measures taken daily were sucrose consumption over 30 min, water consumption in the remaining 23.5 hrs and body weight. Daily water consumption did not differ between groups either before or after treatment. The main effect observed was a reduction in sucrose intake in the groups that received vehicle/clozapine and the PCP/clozapine group. These groups also showed

parallel reductions in body weight. Taken together these results suggest that clozapine itself may produce anhedonia. The finding that PCP influences body weight in parallel with reduced sucrose intake warrants further investigation of PCP as a potential model to assess anhedonia.
ID: 551874

PSYCHOTOMIMETIC EFFECTS OF THE KAPPA OPIOID RECEPTOR AGONIST SALVINORIN A IN HEALTHY HUMANS

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Salvinorin A (SA) is the active compound derived from the leaves of the hallucinogenic plant Salvia divinorum. Salvia divinorum has been used for centuries in traditional Mexican rituals and ingestion of the leaves is reported to produce psychotomimetic effects such as depersonalization and hallucinations. SA is unique in that it does not act at any of the receptors known to be involved in psychotomimetic effects of other drugs (eg, serotonin, dopamine, glutamate etc) but only at the kappa opioid receptor (KOR), where it is a highly selective and potent agonist. Thus, the psychotomimetic effects of SA are presumably mediated via agonist effects at kappa receptors. KOR agonists and Psychosis: Studies with selective KOR agonists (including SA) in animals have demonstrated development of behaviors considered analogous to psychosis. Preclinical data suggests that KOR agonists selectively modulate the dopaminergic output from the ventral tegmental area. Further, preliminary data from our colleagues (Zhao and Gelernter) suggests that a specific single nucleotide polymorphism (SNP) in the KOR gene might be a risk locus for schizophrenia. Laboratory studies with drugs (amphetamine, ketamine, LSD) have been critical in advancing some of the better known hypotheses of psychosis. Thus, SA, a highly selective and potent agonist at the KOR that is known to be used in humans, is an ideal tool to probe this system and examine its role in the neurobiology of psychosis. While there is increasing recognition of the recreational use of SA there are no controlled studies characterizing the dose related behavioral, cognitive, physiological and endocrine effects of SA in psychiatrically and medically healthy volunteers. Pilot data suggest that SA at very small doses produces robust but transient hallucinations, perceptual alterations, synesthesias, dissociative symptoms, blunted affect and cognitive deficits. There are no significant changes in heart rate or blood pressure and no adverse effects. The onset of effects is within 30 seconds to 1 minute with peak effects lasting from 5-10 minutes and a return to baseline within 30 minutes. These data will be discussed.
ID: 551819

ATYPICAL ANTIPSYCHOTICS: FUNCTIONAL SELECTIVITY OF LIGANDS AT 5-HT2A AND 5-HT2C RECEPTORS

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Drug selectivity is generally ascribed to differential affinity for different receptor subtypes. High selectivity (ie, large difference in affinity for a target receptor vs. other receptors) is coveted, as adverse effects of drugs are attributed to actions at non-target receptors. Recent advances in understanding of receptor function indicate that drugs have more selectivity than that afforded by differential affinity for different receptor subtypes. Evidence reveals that drugs can selectively activate different cellular signaling cascades coupled to a single receptor subtype. Consequently, drugs acting

at the same receptor can produce qualitative, not just quantitative, differences in cellular activity. Importantly, differences in functional selectivity between drugs acting at the same receptor subtype may underlie differences in therapeutic efficacy and/or adverse effect liability. The serotonin2A (5-HT2A) and 5-HT2C receptor subtypes are key targets for atypical antipsychotics. Many 5-HT2A/2C ligands have been shown to be functionally selective for different cellular signaling pathways coupled to these receptors. In fact, very recently differences in behavioral actions of 5-HT2A agonists have been demonstrated to be due to functional selectivity, indicating the physiological relevance of the process. It is widely believed that antagonism at 5-HT2A/2C receptors is a prerequisite for atypical antipsychotic efficacy. However, most, but not all, atypical antipsychotics are inverse agonists at 5-HT2A and/or 5-HT2C receptors. Importantly, the pharmacological characterization of these drugs generally is based on measurement of a single cellular response (typically calcium changes in a high-throughput screening system). We have found that many inverse agonists at 5-HT2C receptors are functionally selective when a range of cellular responses is measured. Moreover, one 5-HT2C drug, SB 242084, is a strong inverse agonist for two responses (PLA2 and Gαi), but is an agonist for a third response (PLC) coupled to the receptor. Response-dependent behavior of drugs acting at a single receptor subtype suggests that we do not fully understand the mechanism of action of drugs like the atypical antipsychotics. Understanding the functionally selective characteristics of atypical antipsychotics should provide better methods for screening new drugs and may allow for drugs with greater therapeutic selectivity and improved efficacy for the treatment of schizophrenia.
ID: 551777

FUNCTIONAL SELECTIVITY OF 5-HT2C RECEPTOR AGONISTS

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Agonists of the serotonin 5-HT2C receptors offer tremendous potential for the treatment of multiple psychiatric illnesses including schizophrenia. The signaling properties and regulation of 5-HT2C receptors are highly complex due to the engagement of multiple signaling pathways and the distinct functional properties of the many RNA-edited isoforms of 5-HT2C receptors, which are subject to modulation in multiple psychiatric disorders and following pharmacological or environmental manipulation. In order to understand at a molecular level the properties of the 5-HT2C agonists that lead to therapeutic benefit, we have evaluated the impact of 5-HT2C agonists on multiple 5-HT2C receptor isoform across a broad range of signal transduction outputs *in vitro*, including measurements of effects on phosphatidylinositol and arachidonic acid metabolism, Ca2+ mobilization, ERK phosphorylation and interactions with β-arrestin2. The studies have revealed remarkable diversity in signaling patterns produced by the 5-HT2C agonists consistent with the expression of functional selectivity. The presentation will highlight recent advances in the understanding of 5-HT2C agonist functional selectivity and the potential implications for the reported therapeutic potential in psychiatric illness.
ID: 551643

THE CANNABINOID HYPOTHESIS OF SCHIZOPHRENIA: DOPAMINE-CANNABINOID INTERACTIONS AND PRE-CLINICAL EVIDENCE IN PCP-TREATED RATS

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The cannabinoid hypothesis of schizophrenia suggests that over-activity of the endocannabinoid system contributes to the etiology of psychosis. In keeping with this hypothesis, schizophrenic patients have increased expression of CB1 cannabinoid receptors in the brain and elevated anandamide in the cerebrospinal fluid (CSF), which is negatively correlated to psychotic symptoms. It is unclear, however, whether these changes contribute to the development of schizophrenia (eg, via cannabinoid-mediated alterations of dopaminergic transmission) or if they represent a compensatory adjustment to the disease. The first scenario is consistent with the observation that administration of THC increases dopamine transmission in rodents and humans. The second is supported by studies showing that activation of dopamine D2 receptors elevates anandamide in rat brain and that endocannabinoids counteract dopamine-mediated behavioral responses. To further address these questions, we studied endocannabinoid transmission in rats sub-chronically treated with PCP and monitored the development of schizophrenia-like symptoms using the following behavioral measures: (1) working memory in a variable-delayed alternation task in a T-maze (to model cognitive deficit), (2) social withdrawal (negative symptom), and (3) motor activity in response to d-amphetamine (positive symptom). Sub-chronic PCP increased endocannabinoids levels in the nucleus accumbens and amygdala, increased CB1 receptor-stimulated [35S]GTPγS binding in the anterior cingulate cortex and decreased it in the hippocampus. PCP also caused a delay-dependent impairment of working memory, increased social withdrawal and enhanced motor activity. URB597, a drug that elevates brain anandamide by blocking its metabolism, reversed PCP-induced social withdrawal, whereas it had no effect on working memory or motor activity. Pharmacological blockade of CB1 receptors by AM251 ameliorated the cognitive deficit observed in PCP-treated rats, but impaired working memory in saline-injected controls. These results indicate that: 1) PCP causes disturbances of endocannabinoid transmission; 2) elevation of endocannabinoids tone may reduce the negative symptoms of schizophrenia; 3) CB1 receptor antagonism is beneficial for schizophrenia-related cognitive deficits, but may have detrimental effects under normal conditions. Supported by NARSAD (to AG).
ID: 551415

DIFFERENT MECHANISMS UNDERLYING PARTIAL AGONISM

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In theory partial agonism should be an attractive pharmacotherapeutic principle in a variety of psychiatric and neurological conditions, which are often chracterized by imbalances of neurocircuitries rather than permanent hyper- or hypoactivities. It is thus remarkable that so few partial agonists are on the market. For example, Abilify is the only partial agonist on the market for the treatment of psychosis. Partial agonists in the classical sense are capable of binding to the same site of the receptor as the full (endogenous) agonist and can serve as either agonist or antagonist by competing or cooperating with this agonist, depending on baseline level. The compound (-)-OSU6162 is an example of an atypical partial dopamine D2 agonist, which seems to bind to two different sites of the receptor with mutually opposite actions. Judging by preclinical as well as early clinical observations such a mechanism seems to provide potential advantages compared to classical partial agonists.
ID: 551364

FUNCTIONAL SELECTIVITY OF ANTIPSYCHOTICS AT THE β-ARRESTIN 2-DEPENDENT D2 DOPAMINE RECEPTOR-MEDIATED AKT/GSK3 SIGNALING PATHWAY

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Hyperactivity of the dopaminergic system recapitulates symptoms of psychosis. Several classes of antipsychotics have been developed for the treatment of schizophrenia. Despite their complex pharmacological profiles, all clinically effective antipsychotics share the ability to interact with D2 class dopamine receptors (D2R). G protein-coupled receptors (GPCR-7TM) like the D2Rs can signal not only through the activation of G proteins but also through the ability of GPCR/β-arrestin 2 (βarr2) to scaffold intracellular signaling complexes. Interestingly, D2Rs mediate their physiological effects via both of these pathways but the role of these D2R-mediated signaling events in the actions of antipsychotics remains unclear. In mice, pharmacological or genetic activation of D2-like receptors (D2R) modulates not only the G protein/cAMP-dependent signaling pathway but also engages an Akt-GSK-3 signaling pathway through the ability of D2R/βarr2 complex to scaffold the kinase Akt and the phosphatase PP2A. Thus, in mice D2R activation leads to a dephosphorylation (inhibition) of Akt (Thr308) and dephosphorylation of GSK-3 (activation), an effect that is independent of both cAMP and Ca2+ signaling. Behaviorally, inhibition of GSK-3 inhibits dopaminergic responses. βarr2-KO mice show diminished behavioral responses to D2R activation and loose the ability of D2Rs to regulate Akt/GSK3 phosphorylation with no effects on G protein-mediated responses. Using the two cellular assays, we demonstrate that a large series of antipsychotics including haloperidol, clozapine and aripiprazole, uniformly and potently antagonize the β-arrestin 2 recruitment to D2R induced by agonists. On the other hand, these antipsychotics have complex pharmacological profiles on D2R mediated Gi/o protein/cAMP inhibition with very highly variable efficacies. The higher potency of the drugs at the β-arrestin-2-dependent D2R signaling ranges from 3 to 150 fold. Interestingly, the mood stabilizer lithium can also regulates Akt/GSK-3 signaling and related behaviors in mice by disrupting the signaling complex composed of βarr2/Akt/PP2A. These results suggest that the Akt/GSK-3 signaling pathway plays an important role in the actions of dopamine and that antagonism at the βarr2-dependent signaling is a common property of clinically effective antipsychotics. Thus, βarr2-mediated signaling complexes represent interesting novel pharmacological targets for functionally selective agents.
ID: 550919

EFFECTS OF HALOPERIDOL ON THE BEHAVIORAL, SUBJECTIVE, COGNITIVE, MOTOR AND NEUROENDOCRINE EFFECTS OF Δ9-THC IN HUMANS

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The extent to which DA D2 mechanisms play a role in the pathophysiology of Δ9-THC induced psychotomimetic effects is not known. This study evaluated whether pretreatment with a dopamine receptor antagonist, altered the effects of Δ9-THC in humans. In a 2 test day double-blind study, 28 subjects including healthy subjects ($n = 17$) and frequent users of cannabis ($n = 11$) were administered active (0.057 mg/kg) or placebo oral haloperidol in random order followed 90 and 215 minutes later by fixed order intravenous administration of placebo (vehicle) and active (0.0286 mg/kg) Δ9-THC, respectively. Consistent with previous reports, intravenous Δ9-THC produced psychotomimetic effects, perceptual alterations, and subjective effects including "high". Δ9-THC also impaired verbal recall and attention. Haloperidol pretreatment did not reduce any of the behavioral effects of Δ9-THC. Haloperidol worsened the immediate free, and delayed free and cued recall deficits produced by Δ9-THC. Haloperidol and Δ9-THCC worsened distractibility and vigilance. Neither drug impaired performance on a motor screening task, the Stockings of Cambridge task or the delayed match to sample task. Frequent users had lower baseline plasma prolactin levels and blunted Δ9-THC induced memory impair-ments. The deleterious effects of haloperidol pretreatment on the cognitive effects of Δ9-THC are consistent with the preclinical literature in suggesting crosstalk between DAergic and CBergic systems. However, it is unlikely that DA D2 receptor mechanisms play a major role in mediating the psychotomimetic and perceptual altering effects of Δ9-THC. Further investigation is warranted to understand the basis of the psychotomimetic effects of Δ9-THC and to better understand the crosstalk between DAergic and CBergic systems. Pilot data from an ongoing [11C]PHNO PET study of extrastriatal DA release induced by intravenous Δ9-THC in monkeys will also be presented.
ID: 550909

ALTERATIONS IN HIPPOCAMPAL FUNCTION IN SCHIZOPHRENIA

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Individuals with schizophrenia express manifestations of their illness in a number of symptom domains, including psychosis and cognitive dysfunction. These domains can be viewed as independent, even though the full extent of their independence is currently unspecified. One of the major areas of cognition that is affected is declarative memory, particularly in aspects of relational memory. Although the characterization of the memory defect in schizophrenia and the involvement of the medial temporal lobe (MTL) structures in that pathology has been examined for several years, the role of antipsychotic medication in modulating these cognitive alterations and hippocampal function in schizophrenia has not been examined. Thus, we have examined individuals with schizophrenia who are on-(SV-ON) and off-(SV-OFF) antipsychotic medication (APD) and report that APD medication in schizophrenia affects both performance of declarative memory tasks and fMRI BOLD activation with memory tasks in MTL structures. In summary, using the Acquired Equivalence Task or a face-house Associative Inference Task, the SV-ON perform either normally or show a modest (though significant) decrement from normals; however, the SV-OFF show significantly poorer performance than both NV and SV-ON. Using fMRI BOLD and ASL we have been able to demonstrate functional alterations, particularly in the SV-OFF, with an increase in perfusion and a decrease in activation during inferential memory tasks in MTL structures. We are in the process of localizing these alterations to hippocampal subfields and have early evidence of CA3 involvement. It is the guiding hypothesis of this investigation that changes in homeostatic plasticity mechanisms, particularly in CA3, generate increases in neuronal activity in hippocampus, associated with production of psychotic symptoms and degradation of memory process, particularly involving relational memory. Speculatively, it is the rich network of collateral feedback circuits within CA3, which provide the necessary neuronal architecture for normal associational memory, that can generate complex psychotic memories if dysfunctional.
ID: 554707

NOVEL USE OF PRECLINICAL AND CLINICAL DATA TO PREDICT THERAPEUTIC DOSE RANGES FOR ITI-007, A POTENTIAL TREATMENT FOR SCHIZOPHRENIA AND OTHER NEUROPSYCHIATRIC DISORDERS

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ITI-007 represents a novel small molecule therapeutic agent with potent 5-HT2A receptor antagonism, activity as a dopamine receptor protein phosphorylation modulator (DPPM) consistent with presynaptic D2 receptor partial agonism *in vivo*, and inhibition of the serotonin transporter (SERT). ITI-007 is being developed as a treatment for schizophrenia. As clinical development of ITI-007 progresses, we have begun to define anticipated therapeutic dose ranges based on clinical biomarkers as well as safety, tolerability, and pharmacokinetic data. Importantly, because of its high potency at 5-HT2A receptors as an antagonist relative to its potency at dopamine receptors, it is possible to fully saturate 5-HT2A receptors and then by simple dose adjustment titrate the amount of dopamine activity. With this unique profile, our hypothesis is that therapeutic efficacy should be seen at lower dopamine receptor occupancies than with other antipsychotic drugs. A single ascending dose study and multiple ascending dose study were conducted to determine safety, tolerability and pharmacokinetics of ITI-007. In a separate open-label study, dopamine D2 receptor occupancy for ITI-007 is being determined after a single oral dose in healthy male volunteers using positron emission tomography (PET). Using data from *in vitro* pharmacology assays, animal models, and early clinical studies, therapeutic dose ranges are projected. ITI-007 is safe and well tolerated in healthy volunteers over a wide range of doses thought to span low, primarily 5-HT2A receptor selective doses, and higher doses expected to have antipsychotic efficacy mediated through 5-HT2A, dopamine and SERT pharmacology. Initial data from the PET study suggest that ITI-007 penetrates brain and occupies D2 receptors. Safe and therapeutic dose ranges of ITI-007 are projected to inform the design of future clinical investigation. The present results provide a safe range of doses from which to explore the efficacy of ITI-007. It is anticipated that less than 50% occupancy of D2 receptors will be required for ITI-007 to demonstrate antipsychotic efficacy. Additionally, serotonin reuptake inhibition by ITI-007 predicts activity in mood disorders and contributes to the overall unique profile of ITI-007. Phase 2 clinical trials in schizophrenia are planned.

ID: 555224

22. 22. Therapeutics: Treatment Trials

ARIPIPRAZOLE IN SCHIZOPHRENIA PATIENTS WITH COMORBID OBSESSIVE-COMPULSIVE SYMPTOMS: AN OPEN-LABEL STUDY OF 15 PATIENTS

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Background: Approximately 15% of patients with schizophrenia also meet DSM-IV criteria for obsessive-compulsive disorder (ICD) at some point in their illness, a rate considerably high than in the general population. This study examined aripiprazole treatment of patients with comorbid schizophrenia and obsessive-compulsive symptoms (OCS) that did not meet full criteria for OCD. Method: Physically healthy adults aged 18 to 65 years with DSM-IV schizophrenia and a minimum score of 16 on the Yale-Brown Obsessive Compulsive Scale (YBOCS) were eligible to participate in this 6-week, open-label, flexible-dose trial of aripiprazole monotherapy. Patients currently taking another antipsychotic medication were concurrently down-titrated from their current antipsychotic and up-titrated with aripiprazole, starting with 15 mg/day. Coadministration of the 2 medications lasted from 7 to 14 days, until a stable therapeutic dose of 10 to 30 mg/day as reached. Subjects were recruited into the study between January 2005 and December 2006. Results: Of 15 eligible patients, 7 completed the trial. All 7 had at least minimal improvement on the YBOCS, the Clinical Global Impressions (CGI) scale, and the Positive and Negative Syndrome Scale (PANSS). At week 6, the mean CGI-Improvement scale score was 2.3 (much improved). Mean PANSS scores decreased from 75 to 56, a mean decrease of 21% ($P <$ .05) On the YBOCS, 6 or 7 completers showed a change of greater than 35% from baseline to week 6. Conclusion: These results suggest that aripiprazole monotherapy can modestly improve the outcome for some schizophrenia patients with obsessive-compulsive symptoms. Further studies with aripiprazole under controlled conditions are indicated for this patient population. Overall, even modest improvement in global functioning due to an improvement in OCS component may be clinically meaningful for the difficult-to-treat subset of schizophrenia patients.
ID: 533323

COGNITIVE REMEDIATION IN EARLY SCHIZOPHRENIA

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Background: The early application of cognitive rehabilitation approaches may afford substantial functional benefits to individuals with schizophrenia who often experience significant cognitive dysfunction. We examined the two-year effects of Cognitive Enhancement Therapy (CET; www.CognitiveEnhancementTherapy.com) in a sample of young individuals in the first years of the illness to evaluate the impact of this intervention on long-term outcomes when applied early in the course of the disorder. Methods: Stabilized, early course outpatients with schizophrenia or schizoaffective disorder were randomly assigned and treated in a two-year trial with CET ($n = 31$) or an active Enriched Supportive Therapy (EST) control ($n = 27$). CET is an integrated approach to the remediation of social and non-social cognitive deficits in schizophrenia that utilizes computer-assisted cognitive training and group-based secondary socialization techniques. EST is an individual approach that focuses on illness management and stress reduction. Structural magnetic resonance imaging and a comprehensive battery of measures were administered annually to assess treatment effects on neurobiology, cognition, functional outcome, and symptomatology. Results: Intent to treat analyses revealed significant differential effects favoring CET on composite measures of social cognition, social adjustment, and cognitive style during the first year of treatment. Strong differential effects ($d > 1.00$) on these composites remained at year 2, and extended to measures of symptomatology, particularly negative symptoms. In addition, moderate effects ($d = .46$) were observed favoring CET at enhancing neurocognitive function. Preliminary evidence from analyses of neuroanatomical change indicate a potential protective neurobiologic prophylaxis associated with CET, such that EST patients displayed significantly greater gray matter loss over the two years of study in social-cognitive networks compared to those receiving CET. Conclusions: CET is an effective approach for the remediation of social and non-social cognitive deficits in early schizophrenia that can serve to reduce disability among this population. The remediation of such deficits should be an integral component of early intervention programs treating psychiatrically stable outpatients with schizophrenia. CET may serve as an excellent adjunct to pharmacotherapy in early intervention programs.
ID: 550794

A DOUBLE-BLIND COMPARISON OF THE SAFETY AND EFFICACY OF LURASIDONE AND ZIPRASIDONE IN CLINICALLY STABLE OUTPATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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Background: Lurasidone is a new atypical antipsychotic with high affinity for D_2 and $5\text{-}HT_{2A}$ receptors, as well as for receptors implicated in enhancement of cognitive function ($5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_7$). The current study is the first to evaluate the comparative safety and efficacy of lurasidone versus ziprasidone in stable outpatients diagnosed with schizophrenia or schizoaffective disorder. Methods: Adult outpatients were recruited who met DSM-IV criteria for schizophrenia or schizoaffective disorder that was chronic (at least 6 months duration), and stable. After completing a 1-3 day single-blind, placebo run-in period, patients were randomized to 21 days of treatment with a fixed dose of lurasidone 120 mg once daily (starting dose, 80 mg for 3 days) or ziprasidone 80 mg BID (starting dose, 40 mg BID for 3 days). Results: The intent-to-treat sample consisted of 150 patients on lurasidone (mean PANSS total, 68.7) and 151 patients on ziprasidone (mean PANSS total, 68.9). The proportion of patients reporting at least one adverse event was lower for lurasidone compared to ziprasidone (57% vs. 66%; $P = .05$). The median endpoint change in weight was similar on both lurasidone and ziprasidone (-0.65 vs. -0.35 kg). Treatment with lurasidone versus ziprasidone was associated with greater reduction in triglycerides (-2.6 vs. $+22.4$ mg/dL), similar endpoint reduction in total cholesterol (-6.4 vs. -4.4 mg/dL), and similar change in glucose ($+4.7$ vs. $+4.8$ mg/dL). Treatment with lurasidone was associated with lower endpoint change in the QTcF: $+0.3$ vs. $+3.3$ msec). No patients in either treatment group had clinically significant elevations in QTcF (>450 msec in males; > 470 msec in females). Treatment with lurasidone versus ziprasidone, respectively, resulted in greater early improvement on the PANSS total score at

Week 1 (-4.1 vs. -1.6; $P = .048$), but not Week 2, (-6.0 vs. -3.7) or Week 3 (-6.2 vs. -4.5; MMRM analysis). At LOCF-endpoint, treatment with lurasidone versus ziprasidone resulted in significantly greater improvement on the PANSS negative symptom subscale (-1.3 vs. -0.6; $P = .046$). Conclusion: Treatment with lurasidone in a dose of 120 mg/d was safe and well-tolerated, and was not associated with clinically significant changes in weight, lipids or QTc. In the current study of stable patients, lurasidone had efficacy that was comparable to ziprasidone 160 mg/d, but with an earlier onset of improvement in the PANSS total score.
ID: 550774

DOUBLE BLIND, RANDOMIZED, CONTROLLED STUDY OF A PSYCHOTHERAPY DESIGNED TO IMPROVE MOTIVATION FOR CHANGE, INSIGHT INTO SCHIZOPHRENIA AND ADHERENCE TO MEDICATION

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Most patients with DSM-IV schizophrenia exhibit full or partial non-adherence to pharmacological treatment (Rummel-Kluge, 2008). Only about one-third reliably take antipsychotic medication as prescribed (Oehl, 2000). Poor adherence (ie, both complete and partial non adherence) has been found to be associated with serious negative outcomes and as such, interventions aimed at improving and maintaining adherence are of great interest to clinicians, researchers, and policy makers. Objective: To assess the efficacy of a psychotherapy based on motivational enhancement and cognitive therapies designed to improve patient's adherence to treatment and motivation to change (Listen-Empathize-Agree-Partner, or LEAP therapy; Amador, 2007). Method: 54 patients diagnosed with schizophrenia about to be discharged following inpatient treatment were included in a six month repeated measures study. Patients were randomly assigned to either the experimental or control therapies and were blind to group assignment. All patients received long acting injectable antipsychotic medications and were rated as compliant when the injection was confirmed and non compliant if the injection was refused or the appointment was missed. Insight into schizophrenia and attitudes toward treatment were assessed using the Scale to assess Unawareness of Mental Disorder, the Birchwood Insight Scale and the Drug Attitude Inventory, respectively. All assessments were made by a rater blinded to group assignment. Results show that compared to the control psychotherapy LEAP improved motivation for change, insight and adherence to treatment. Conclusion: This study found LEAP to be superior to the control psychotherapy. Strengths of the experimental design include the randomized blinded group assignment, blinded assessments of the dependent variables and near 100% reliability and validity of the adherence measure. Among the limitations of the present study was the absence of a LEAP fidelity measure and the fact that the senior author was the only therapist for all patients and as such could have biased the results by differentially treating patients depending on which therapy they were assigned to. This study should be replicated in a larger more heterogeneous sample with a longitudinal assessment of fidelity to the LEAP intervention and a therapist(s) blinded to study hypotheses. Key words: compliance; poor adherence to treatment, insight, motivation to change, schizophrenia, Long-acting injectables.
ID: 550761

LONG-ACTING RISPERIDONE FOR SCHIZOPHRENIA AND CO-OCCURRING ALCOHOL USE DISORDER

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AUD is common in patients with schizophrenia and worsens its course. Current pharmacological options to limit alcohol use in these patients are limited. While typical antipsychotics appear not to decrease alcohol in these patients, preliminary data suggest the atypical antipsychotic clozapine (CLOZ) does. We have suggested that the effects of CLOZ on decreasing alcohol use in these patients is mediated by its weak dopamine (DA) D2 receptor and potent norepinephrine (NE) alpha 2 receptor blockade, which may ameliorate a dysfunction in brain reward circuitry (Green et al. 1999). Risperidone, another atypical antipsychotic, is a potent blocker of the NE alpha 2 receptor. Studies with RISP in comorbid patients, however, have failed to demonstrate the dramatic effects seen with CLOZ. We have suggested that intramuscular LAR may be important to test in this population because: 1. patients are more likely to stay on LAR than OR 2. LAR may allow for a lower blood level of RISP with resulting less potent blocade of the DA D2 receptor than OR. Moreover, clinically, LAR may offer certain advantages over OR in minimizing extrapyramidal symptoms (EPS), prolactin elevation, and improve negative symptoms. In this "proof of concept" study conducted at 5 sites, patients with schizophrenia or schizoaffective disorder and co-occurring AUD between the ages of 18 and 65, not taking CLOZ or LAR, are currently being recruited (to achieve a sample of 100). Patients who provide consent and are eligible are randomized to either the LAR or OR treatment group and followed for 6 months. The dosage of LAR starts at 25 mg IM/ 2 weeks, with a target dose of 37.5 mg IM/ 2 weeks. OR is tapered up to a target dose of 4 mg per day. Assessments of diagnosis, symptoms, cognition and physical health are conducted at baseline. Ratings for alcohol and other substance use, psychiatric symptoms, EPS, cognition and overall functioning are performed longitudinally. Blinded independent raters review data and make a "consensus rating" of substance use at 0, 3 and 6 months. Ninety-four patients have been randomized thus far out of a target total of 100. The study population has been largely male (73.2% vs. 26.8%), with a substantial representation of African American patients (42%). We will present the full baseline dataset of this sample at the meeting and discuss key issues faced in launching such a multi-site treatment trial of patients with schizophrenia and AUD.
ID: 550725

PREDICTORS OF ATTENDANCE IN TWO METHODS OF COGNITIVE REMEDIATION

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Cognitive remediation has been shown to be an effective treatment of cognitive dysfunction in schizophrenia. However, little research has been conducted on factors effecting attendance in training. This study investigates the relationships between two cognitive remediation methods (Computer Based Training-PSS CogRehab, Bracy 1999 or Cognitive Remediation Therapy-CRT; Wykes, 2001) and initial symptom and cognitive variables. We predict that initial symptoms, most likely the emotional discomfort score, will predict the number of session attended in computer training condition, but not the CRT condition. Additionally, we hypothesized that baseline cognitive test performance will be related to the number of sessions attended in the computer condition, but not the CRT condition. Methods: Fifty (50) participants with either schizophrenia or schizoaffective disorder were randomly assigned to either CRT or Computer Based Training. Intake symptom and cognitive measures were conducted and participation rates over a 15 week course of treatment were gathered. Drop out rates were

also established (stopping participation before week 14). Analysis: Stepwise linear regressions were conducted (one for each condition with symptoms predicting the number of sessions. Symptom variables entered were the five factors (as measured by the Bell et al. 1999) from the PANSS. Additionally, stepwise linear regressions were conducted (one for each condition with baseline cognitive test scores predicting the number of sessions. Results: For participants in the Computer Training Condition symptoms were significantly predictive of the number sessions attended, but no such relationship was found between symptoms and sessions for the CRT participants. Additionally, cognitive test measures were related to attendance in both conditions. Conclusion: Symptoms interact with training methods to effect participation while cognitive abilities have a more universal effect on attendance. More specifically, symptoms reduce participation in Computer Trained group, while the individual therapeutic nature, positive reinforcement, scaffolding and interactive strategizing inherent in CRT may serve to negate the effects of symptoms on participation.
ID: 550606

DO ALL SCHIZOPHRENIA PATIENTS NEED TO USE ANTIPSYCHOTIC MEDICATIONS THROUGHOUT THEIR LIFETIMES: A 26 YEAR MULTI-FOLLOWUP

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Objectives: Multi-decade research on antipsychotic use has not been readily available to the field. A central issue in the long-term treatment of schizophrenia is whether all patients with schizophrenia need to use antipsychotic medications continually throughout their lives. The research also studied whether antipsychotic medications increase work disability. The current study of schizophrenia patients assessed 7 times over a 26-year period provides data on these issues. Method: From the Chicago Followup study, 101 patients with psychotic disorders, including 61 with schizophrenia spectrum disorders, were assessed at acute hospitalization and then followed up 7 times over 26 years. Using standardized research instruments, patients were assessed at each followup for positive symptoms, negative symptoms, depressive syndromes, cognitive impairment, work disability, and treatment. This included assessments of first and second-generation antipsychotic medications. Results: 1) A subgroup of schizophrenia patients removed themselves from antipsychotics for many years with some leaving treatment for prolonged periods. 2) Significantly more of the patients who removed themselves from antipsychotics for prolonged intervals experienced periods of recovery ($P < .01$). 3) The relatively favorable outcome of this subgroup of schizophrenia patients who stayed off of antipsychotics for prolonged periods is partly due to favorable internal characteristics of these patients, rather than their treatment status ($P < .05$). 4) Beginning at the 4.5 year followups and continuing for over 20 years there was surprisingly little work disability among the subgroup of schizophrenia patients who left treatment for prolonged periods. 5) Schizophrenia patients who were switched from first generation to second generation antipsychotics showed reductions of depressive symptoms. Conclusions: The 26 years of longitudinal data indicate that not all patients with schizophrenia need to be treated with antipsychotics continuously throughout their lives and identify specific factors which may contribute to periods of recovery. The periods of recovery in a subgroup of schizophrenia patients who leave treatment is partly due to internal premorbid characteristics and premorbid developmental achievements of these patients, rather than their treatment status. Antipsychotics, which block dopamine receptors and reduce motivational salience, may also contribute to work disability in schizophrenia.
ID: 550535

INVESTIGATOR EXPERIENCES WITH AND OPINIONS OF IRBS

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Institutional Review Boards (IRBs) oversee human subject protections in proposed research conducted, funded, or regulated by any U.S. Government agency. There is no doubt that human subjects have been mistreated in the past and that protections offered by IRBs are necessary. However, there are reports critical of IRBs where IRB "mission creep" is described as being burdensome and an obstacle to sound, ethical science. Virtually no work has been done to assess how researchers perceive IRB protections and/or burdens. Therefore, there is no empiric data on which to base a discussion of whether IRBs are satisfactorily meeting their mandate. A survey was developed to assess researcher IRB experiences. The survey was mailed first to 200 depression researchers and then to 200 schizophrenia researchers. Potential participants were identified using "depression" and "schizophrenia" as search terms in the NIH Computer Retrieval of Information on Scientific Projects (CRISP) database of funded grants. Researchers from University of Maryland were not removed from the subject pool unless the Maryland Psychiatric Research Center was their primary appointment. If, after 4 wks, there was no response to the initial mailing, participants were emailed the survey. Response rate was approximately 30%. Most respondents were Professor level with at least 15 yrs experience and over $1million in grant support. Most submitted 3 or more protocols/yr for IRB review. IRB turn-around time was 3 wks or longer 88% of the time. Protocols were returned from the IRB for subject safety concerns 46% of the time, and with bureaucracy concerns 42% of the time (format, etc). No one believed IRB paperwork was inadequate to evaluate protocols; 30% reported paperwork was excessive and discouraged scientific advancement, but most reported it was about right considering the IRB mission. Most agreed the IRB mission should involve enforcing subject privacy and policing conflict of interest, but 60% thought it was beyond the scope of the IRB to evaluate study design. Only 3–8% would not submit a controversial protocol because of difficulty dealing with an IRB. It appears that IRB review is time-consuming and time is wasted coordinating between multiple IRBs and in bureaucratic concerns. However, most researchers believe IRB paperwork is necessary, the IRB mission should include assessment of subject privacy and conflict of interest, and that IRBs do not inhibit scientific progress.
ID: 550533

EFFECT OF LURASIDONE ON DEPRESSIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

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Background: Clinically significant depression occurs in approximately 25% of individuals with schizophrenia and is associated with greater functional impairment and worse outcomes. Lurasidone is a novel psychotropic agent with high affinity for D_2 and $5-HT_{2A}$ receptors, as well as for receptors implicated in enhancement of cognitive function (partial agonist at $5-HT_{1A}$; antagonist at $5-HT_7$). The goal of this secondary analysis was to evaluate the efficacy of lurasidone in patients diagnosed with schizophrenia who were experiencing clinically significant depressive symptoms. Methods: Data for this analysis came from a 6-week, placebo-controlled study in which patients meeting DSM-IV criteria for schizophrenia were randomized to 6 weeks of double-blind treatment with a fixed dose of lurasidone 80 mg ($N = 90$; baseline MADRS score = 14.2; subgroup with MADRS >12, $N = 55$) or placebo ($N = 90$; baseline MADRS score = 14.5; subgroup with MADRS >12, $N = 58$). Results: On an ANCOVA analysis, treatment with lurasidone was associated with significantly greater LOCF-endpoint

improvement than placebo on the MADRS in the total sample (-2.72 and -0.11; $P = .026$), and in the subgroup with MADRS >12 (-6.02 vs. -2.77; $P = .04$). The Cohen's d effect size for endpoint change in the MADRS was 0.42 for the depressed subgroup. Treatment with lurasidone was also associated with significantly greater improvement than placebo in the PANSS depression item (G6; -1.03 vs. -0.30; $P < .01$). Conclusion: These exploratory findings from a double-blind, phase 2 study suggest that lurasidone is effective in the treatment of depressive symptoms associated with schizophrenic illness. Phase 3 double-blind studies are underway to fully characterize lurasidone's clinical profile and confirm its potential antidepressant benefit in patients diagnosed with schizophrenia who present with clinically significant symptoms of depression.
ID: 550473

IMPROVING OUTCOMES FOR SCHIZOPHRENIA VIA A WEB-BASED FAMILY PSYCHOEDUCATION INTERVENTION, DESIGNED FOR THOSE WITH COGNITIVE IMPAIRMENTS

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The study's purpose was to: 1) conduct usability studies to determine how to develop usable websites for persons with SMI and cognitive impairments, and; 2) use this knowledge to create a web-based intervention to provide multi-family psychoeducational therapy (M-FPE) to persons with schizophrenia and their family members via home computers. A randomized treatment and control group design was used to evaluate a web-based M-FPE intervention. Usability studies, conducted with 98 persons with SMI, revealed that standard website design guidelines produce websites that are poorly suited and confusing to persons with SMI. We identified an alternative model and set of guidelines for designing websites that was used to develop the M-FPE website for persons with schizophrenia and their family members. We found that compared to websites designed via standard guidelines, and three public mental health websites, users completed more tasks with our website ($P \leq .0002$), and completed them faster ($P \leq .000007$). The intervention website had the following components: an on-line therapy group for persons with schizophrenia, one for family members, and one for both; the ability to ask health professionals a question and receive a response; a library of previously asked and answered questions, and; educational materials. At 3 months, participants with schizophrenia in the intervention group had lower perceived stress ($P = .04$) and showed a trend for a higher perceived level of social support ($P = .06$). The average number of website page-views per person with schizophrenia was 1 080.7 (SD = 1 812.0, range = 86–6 325). At the end of one-year: the intervention group had a large reduction in positive symptoms compared to TAU, with a differential effect size of 0.90 ($P = .013$); those in the intervention group had greater knowledge of schizophrenia diagnosis, differential effect size = 0.91 ($P = .028$), and; those with more severe disease symptoms tended to use the website more ($r = .65$, $P = .005$). Persons with schizophrenia used the site significantly more than family members. Persons with SMI, and others with cognitive impairments, can and will use web-based interventions. Our experience indicates that such users can experience improved outcomes from the use of on-line treatments, if the applications are designed specifically for use by persons with cognitive impairments. This provides an opportunity to increase the receipt of evidence based treatments such as FPE.
ID: 550464

PREVALENCE OF, AND RATIONALE FOR, THE PRESCRIPTION OF HIGH DOSE AND COMBINED ANTIPSYCHOTICS IN FORENSIC PSYCHIATRY INPATIENT SETTINGS IN THE UK: A COMPARISON WITH ACUTE ADULT INPATIENT SETTINGS

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Psychiatric patients in forensic settings are characterised by psychotic illness with high levels of co-morbidity, and presentation with violence originating in complex and enduring psychiatric and social problems. Medication strategies for treatment-resistant psychosis, such as high-dose and combined antipsychotic prescriptions, might be expected to be more commonly used in forensic than acute adult inpatient settings. We used data from two quality improvement programmes to test this hypothesis. Two audit-based quality improvement programmes on prescribing of high-dose and combined antipsychotic drugs were conducted in 1. acute adult and psychiatric intensive care wards (baseline audit January 2006, re-audit January 2007), and 2. forensic wards (baseline audit March 2007, re-audit March 2008). Demographic, clinical and prescribing data were gathered for all patients prescribed antipsychotic drugs. 32 UK specialist mental health services (Trusts) participated in the first programme, submitting data for 3271 patients at re-audit. 21 Trusts participated in the second programme, submitting data for 1997 patients at re-audit. In acute adult settings, prevalence of high-dose prescribing was 34% and combined antipsychotics 39%. Corresponding figures for forensic settings were 32% and 40%. In both settings, the main reason for combined antipsychotics was to manage behavioural disturbance. In forensic settings, a quarter of patients were prescribed clozapine alone or in combination with a second antipsychotic. Almost 10% of antipsychotic combinations were prescribed for the management of persistent aggression, but few of these included clozapine. The prevalence of high-dose and combined antipsychotic prescribing was high, and similar across the two programmes; 3 out of every 10 patients were prescribed a high dose and 4 out of 10 combined antipsychotics. The clinical reasons for prescribing combined antipsychotics differed across clinical settings. Most notably, clozapine augmentation and the management of persistent aggression were more frequently cited reasons in forensic settings. The three antipsychotics most frequently augmenting clozapine were amisulpride, haloperidol and sulpiride. These drugs share potent dopamine D2 antagonism and a relatively low potential to exacerbate the metabolic side effects of clozapine, suggesting that clinicians employ a common pharmacological rationale when selecting a second antipsychotic to augment clozapine.
ID: 550405

MULTI-MODAL COGNITIVE THERAPY FOR SCHIZOPHRENIA: ADDRESSING COGNITIVE IMPAIRMENT AND DYSFUNCTIONAL COGNITIVE SCHEMAS

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The process of recovery in schizophrenia involves resolving persistent symptoms and improving functional outcomes. In large randomized, prospective clinical trials, our research group has demonstrated the efficacy of Cognitive Adaptation Training (CAT—a home-based psychosocial treatment utilizing environmental supports such as medication containers, signs, checklists and the organization of belongings to bypass deficits in cognitive functioning and cue and sequence adaptive behavior) for improving adherence to medications and functional outcomes in schizophrenia. The effect of CAT on levels of symptomatology has been mixed. Early CAT studies utilizing therapists with extensive training in psychotherapy with psychosis found significant improvements in positive symptoms. More recent randomized trials failed to replicate this finding with CAT technicians not trained in psychotherapy for psychosis. Persistent psychotic symptoms substantially impair patients' ability to adapt to life in the community. Cognitive Behavior Therapy (CBT) is an evidence-based practice in the UK for addressing persistent positive symptoms and the distress associated with them. We have demonstrated that CBT decreases symptomatology and minimizes the negative effect of persisting symptoms upon individuals with this disorder. We now describe a home delivered, multi-modal cognitive treatment (Mcog) targeting both functional outcomes and persistent positive symptoms for individuals with schizophrenia. Pilot ($n = 14$) found that those seen in CAT by therapists trained in cognitive behavioral techniques for psychosis experienced significant improvement in positive symptoms over 9 months ($n = 7$; ($t = 3.03$; $P < .03$; $t = 2.52$; $P < .05$; and $t = 1.29$; $t = 3.58$; $P < .02$; for hallucinations, delusions, and suspiciousness, respectfully). Individuals seen by CAT technicians not trained in these techniques did not improve with respect to positive symptoms (all P's >.25). By integrating CAT and CBT elements into one Multi-modal Cognitive Treatment, CAT techniques such as reviewing audio tapes of CBT conversations with the therapist can extend the reach of CBT to environments in which persistent symptoms are particularly problematic (eg, riding the bus). Moreover, because Mcog is provided on the same home visit, multiple outcome dimensions can be addressed with minimal additional costs for providing treatment.
ID: 550398

TOWARDS A COGNITIVE-EMOTIONAL TREATMENT OF INSIGHT IN PSYCHOSIS

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Goal: Insight is impaired in many people who suffer from psychosis. Limited insight has been associated with poorer social functioning, more violent behavior and poorer outcome of the disease. Therefore, we are developing a treatment module that aims to enhance insight in psychosis and thereby participation in daily life. The cognitive-emotional module is based on research findings and hypotheses regarding the role of executive function, self-evaluation and self-defense in poor insight. Methods: The treatment module encompasses several cognitive and emotional processes that are thought to play a role in insight in psychosis and exists of five submodules: introduction and explanation of the treatment's rational, self-reflection, emotion regulation, receiving feedback and perspective taking, and acceptance and goal setting for the future. The effect of the treatment module on insight, symptoms, social functioning and quality of life will be evaluated in a multicentre RCT. Results and conclusions: A psychosocial approach that targets cognitve-emotional processing holds promise for improving patients' insight in psychotic illness. We present outline and content of the treatment module, together with results of a pilot study that is currently being performed.
ID: 550389

CONTINUITY OF TREATMENT AND SUPPORTING PARENT GROUPS IN EARLY PHASE SCHIZOPHRENIA: A 5 YEAR RANDOMISED TRIAL

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The beneficial effects of early intervention in first episode schizophrenia show a return to the predominantly unfavorable course at 5 year follow-up. Objective: to evaluate the effectiveness of 5 year specialized continuity of treatment with or without parent groups in early phase schizophrenia. Methods: randomised controlled trial. Participants were consecutively admitted patients ($n = 198$) aged 15–28 years with early schizophrenia-like disorders. Interventions: Continuity of Treatment by professionals Specialized in the treatment of early schizophrenia (CST), Continuity of Specialized Treatment plus Parent groups (CST+P) and Continuity of Treatment as Usual (CTU). Outcome measures: rates of first relapse during 5 years treatment, time to first relapse after remission, suicide, psychosocial functioning, second and third relapse. Analysis: Cumulative relapse rates were estimated using life-table methods. 38 Patients changed from the assigned condition. The effect of the three interventions on time to first relapse after remission was compared using Cox regression analysing both intention to treat (ITT) and actually realized treatment (ART) grouping. Results: The relapse rate after 5 years was relatively low (0.49, 95% confidence interval 0.41–0.56). No differences between the 3 conditions were found in the ITT analysis. However, the ART analyses showed significant lower relapse rates after 5 years for CST+P (0.30, 95% CI 0.18–0.45) but not for CST (0.53, 95% CI 0.38-0.67) as compared with CTU(0.56, 95% CI 0.45 −0.67). Cox regression showed a significant positive effect in postponing relapse for CST+P condition,corrected for potential confounding factors. Continuity of treatment didn't affect the suicide rate (n:7; 3,5%). 109/190 patients started with poor social functioning: 71 patients showed improvement (65%) and 38 did not change (35%). Of the 81 patients who started with good functioning 44 deteriorated (54%) and 37 did not change (46%). No effects of ITT or ART treatment conditions were found on psychosocial functioning. Conclusion: the basic treatment design offered to all patients, including the parental educational approach was associated with a reduced relapse rate. We found no differences in effect between the treatment conditions in the ITT analysis. The favorable CST+P result underlined the importance of active participation of the parents. Psychosocial functioning improved or remained well for a significant proportion of the patients.
ID: 550291

EFFICACY OF SOCIAL COGNITIVE REMEDIATION IN SCHIZOPHRENIA PATIENTS: A META-ANALYSIS

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Objective: Increasing interest in social cognition in the last few years led to the development of several new approaches in social cognitive remediation. Initial evaluations of these approaches have been made over 20 years ago. Social cognitive remediation approaches directly intervene in individual or multiple social cognitive areas (emotional processing, social perception, Theory of Mind (ToM), social schemata and attribution style) declared by the NIMH-MATRICES-Initiative. Some of these approaches integrate social cognitive interventions with therapeutic components intended to ameliorate neuro-cognitive and social skills or with work rehabilitation. Until today no meta-analysis on the efficacy of social cognitive remediation has been presented. Method: 19 controlled studies with randomized patient

assignment were included in this quantitative analysis. The sample consisted of 961 schizophrenia patients (DSM/ICD). In 74% of the studies social cognitive remediation was compared to Placebo-Attention-Conditions and/or to standard care, in 26% of the studies it was compared to other psychotherapies. Based on the outcome variables from each study effect sizes (ES) between the compared groups were calculated. Results: Over an average length of 23 weeks a significant global therapy effect could be demonstrated (average effect size of all conducted variables). Significant effects were found in the summarized social cognitive areas and in the sub-areas of emotional processes, social perception and ToM. The summarized neuro-cognitive area showed significant evidence of amelioration compared with the control groups. The largest effects were visible in the MATRICES areas speed of information processing and planning/problem solving. The effect sizes for the verbal memory and the working memory reached the level of significance. There was however no significant effect for the visual memory. Further significant effects were found for psychopathology and social functioning. The global therapy effect could be maintained during a follow-up period at an average of 9.5 months. The setting, the control groups and the type of intervention were identified as moderators. The quantitative analysis of the results shows strong evidence that social cognitive remediation has a broad effect on various areas of functioning and symptoms relevant in schizophrenia.
ID: 550290

RELAPSE PREVENTION IN FIRST-EPISODE PSYCHOSIS PATIENTS WITH STABLE MAINTENANCE MEDICATION FOR AT LEAST ONE YEAR

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Clinically there is a strong expectation from first-episode psychosis patients and their carers to discontinue with maintenance medication after a period of remission. However, there is so far no consensus regarding how long maintenance medication should be continued. The current study aims to assess whether this point in time is reached after at least 1 year of maintenance medication. Following a first-episode of schizophrenia and non-affective psychosis (DSM-IV), patients who were remitted well and on maintenance medication for at least 12 months were randomized to receive either maintenance medication (quetiapine 400mg/day) or placebo. Relapse was defined as the re-emergence of positive symptoms. In the overall sample of 178, 83 patients relapsed during the study. Fewer patients relapsed in the quetiapine maintenance group (27 of 89, 30%) compared with the placebo group (56 of 89, 63%). The Kaplan-Meier estimate of the proportion of relapse at 11 months after randomization was 41 percent (95% CI, 29 to 53%) in the quetiapine maintenance group and 76 percent (95% CI, 66 to 86%) in the placebo group (log-rank test, $\chi^2 = 15.65$, $P < .001$). New data for relapse risks in remitted first-episode psychosis patients is provided. The risk of relapse after medication discontinuation is still substantial after receiving maintenance medication for a mean of 22 months following first-episode psychosis. Supported by investigator initiated trial award from AstraZeneca and the Research Grants Council Hong Kong (Project number: 765505).
ID: 550243

OUTCOME OF THE SERTINDOLE COHORT PROSPECTIVE (SCOP) STUDY: ALL-CAUSE MORTALITY

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Sertindole is an efficacious atypical antipsychotic with good tolerability and is currently launched in approximately 30 countries. A known dose-dependent QT prolongation gave rise to a cardiac safety concern, and therefore, a post-marketing surveillance (PMS) study, SCoP, was initiated to confirm that under normal conditions of use, sertindole is not associated with an excess mortality rate compared to other atypical antipsychotics. This was a prospective, randomised (1:1), partially blinded, active-controlled, multinational study. The primary endpoint was all-cause mortality. It was conducted under normal conditions of use and the inclusion criteria were deliberately broad to ensure patients were representative of patients to be treated with sertindole on the market. Both for sertindole and for risperidone, the titration and maintenance dosages and patient management was left to the discretion of the investigators, in accordance with the national Summary of Product Characteristics (SPCs). An Independent Safety Committee classified the events, using blinded data, and providing advice to the Independent Management Committee overseeing the study. Patients were eligible for enrolment if they had a diagnosis of schizophrenia, were >18 years, and based on the patient's clinical status, a new or a change in antipsychotic treatment was indicated. In addition, patients were only eligible for enrolment if they met all other criteria set out in the national SPCs for both sertindole and risperidone. Add-on antipsychotic therapy was allowed and patients were monitored for the entire duration of the study, including after they started add-on therapy or discontinued study drug. The SCoP study is one of the largest PMS studies ever conducted in schizophrenia research. A total of 9 809 patients were treated at 593 sites in 38 countries with approximately 15 000 patient years of exposure (PYE) accrued. The all-cause mortality rate for all patients in the study was 0.8 per 100 PYE and the estimated mortality ratio (MR) was 1.081 (90%CI: [0.801;1.458]) indicating that sertindole is not associated with an excess mortality compared to risperidone. The withdrawal rates due to serious adverse events were 2% and 1% for sertindole and risperidone, respectively, and the withdrawal rate due to lack of efficacy was 8% for both treatments. In conclusion, sertindole offers a safe and efficacious alternative to other atypical antipsychotics.
ID: 550242

RELAPSE PREDICTORS FOR DISCONTINUING AND CONTINUING MAINTENANCE MEDICATION IN REMITTED FIRST-EPISODE PSYCHOSIS PATIENTS

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After a first-episode psychosis, patients inevitably face a clinical dilemma regarding whether to continue with maintenance medication after a period of remission. This decision has to be weighed against the long-term medication side effects and the risk of relapse. In this study, we aim to identify potential predictors for relapse among patients who have continued with

maintenance medication, as well as those who have discontinued with maintenance medication. This is a double-blind randomized placebo-controlled study. Patients who were remitted from a first-episode of schizophrenia or non-affective psychosis (DSM-IV) and had remained well on maintenance medication for at least 1 year were recruited into this study. Eligible patients were randomized to either quetiapine (400mg/d) or placebo for 12 months to detect a relapse. Relapse was defined as re-emergence of definitive positive symptoms. Baseline clinical and cognitive variables were measured as potential predictors for relapse. Univariate and multivariate Cox-proportional hazards models were applied to analyze significant predictors in the maintenance medication and the placebo groups. A total of 178 patients were recruited. In the placebo group, significant multivariate relapse predictors were smoking (relative risk 4.317, 95% CI = 1.012–18.417), negative symptoms (relative risk 1.030, 95% CI = 1.008–1.053) and verbal fluency (relative risk 0.880, 95% CI = 0.807–0.960). In the medication group, significant multivariate relapse predictors were pre-morbid functioning (interest) (relative risk 1.641, 95% CI = 1.215–2.216), PANSS (general psychopathology) (relative risk 1.548, 95% CI = 1.089–2.200), logical memory at immediate recall (relative risk 0.879, 95% CI = 0.782–0.988) and neurological soft signs (disinhibition) (relative risk 3.423, 95% CI = 1.585–7.390). Importantly, predictors identified in the two groups help provide information about the characteristics of the patients who are more prone to relapse. Future intervention strategies for relapse prevention can be based on the current findings. Supported by investigator initiated trial award from AstraZeneca and the Research Grants Council Hong Kong (Project number: 765505).
ID: 550229

CLOZAPINE'S DISTINCTIVENESS IN THE TIME COURSE AND PROFILE OF EARLY SYMPTOM REMISSION IN SCHIZOPHRENIA: A QUANTITATIVE REVIEW

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In patients with schizophrenia, an early, linear response to antipsychotic treatment is generally apparent. Nevertheless, the specific response to clozapine treatment has yet to be fully elucidated despite the fact that clozapine is more efficacious than other agents in treatment-refractory schizophrenia. Therefore, we conducted a meta-analytic review of randomized, controlled clinical trials that compared clozapine to comparator antipsychotics using BPRS or PANSS outcome measures. Seventeen studies enrolling 1463 participants were retrieved. Seven of these studies enrolled refractory patients; ten studies enrolled non-refractory patients. Regression coefficients were used to estimate linear and quadratic rate of change of the per-item BPRS or PANSS scores across time, starting from the baseline and ending after four weeks of treatment. Refractory and non-refractory patient samples were combined in the analyses to maximize the robustness of the findings. Results revealed significant linear declines for both the clozapine and comparator treatments (P's < .001), with a trend towards a greater linear decline in the clozapine (M = −.400, SD = .277) relative to the comparator (M = −.302, SD = .179) arms: t (16) = −1.81, P = .09. Additionally, we detected a significant attenuation of the linear decline over time for both clozapine and the comparator (P's < .01), that did not differ between the treatments: clozapine arms (M = .041, SD = .044) versus comparator arms (M = .025, SD = .034), t_{16} = 1.58, P = .134. These results suggest that antipsychotic treatments are associated with rapid and robust symptom reduction, which significantly attenuates over time early in the course of treatment. Furthermore, there appear to be minimal differences in profile of response in patients undergoing clozapine versus comparator treatments

over four weeks of treatment. Because of a dearth of studies of refractory patients, the current meta-analytic findings are based upon combined (refractory and non-refractory) patient samples. The implications for refractory patients alone are consequently limited.
ID: 550196

ADEPT: A DEFINITIVE ESTROGEN PATCH TRIAL

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Accumulating evidence suggests estrogens may have therapeutic effects in severe mental illnesses, including schizophrenia, via neuromodulatory and neuroprotective activity. Our previous studies have indicated that women receiving 100mcg transdermal estradiol improved significantly more than women receiving placebo, in terms of positive and general psychopathology symptoms. The aim of the current study was to compare the effectiveness of adjunctive transdermal estradiol (100 and 200mcg) to adjunctive placebo in the treatment of acute psychotic symptoms. Women of childbearing age with a diagnosis of schizophrenia or schizoaffective disorder were invited to participate in this 8-week three-arm (100mcg/day adjunctive transdermal estradiol, 200mcg/day adjunctive transdermal estradiol, or adjunctive transdermal placebo) double-blind, placebo controlled study. All patients continued to receive standard antipsychotic treatment whilst in the trial. Psychopathology, mood and cognition were assessed at baseline then at weekly, fortnightly or monthly intervals using the PANSS, MADRS and RBANS. Estradiol, progesterone, and gonadotropin levels were assessed at baseline and days 28 and 56. Preliminary results indicate an improvement in psychopathology for the estradiol groups, as compared to the placebo group. The findings from this multisite 'proof-of-concept' study will determine whether estradiol can be used as an adjunctive treatment of psychotic symptoms in women with schizophrenia. This research is supported by The Stanley Medical Research Institute.
ID: 550162

COGNITIVE BEHAVIORAL THERAPY FOR PARANOIA

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Background: Studies have shown that patients' reasoning styles as well as cognitive biases underlie the formation and maintenance of paranoid beliefs. We developed the Group Cognitive Behavioral Therapy (GCBT) intervention to address specific for paranoid delusions cognitive biases and to teach patients new, more adaptive ways of processing information. The aim of this project is to conduct a preliminary controlled study to test the efficacy of Group CBT for Paranoia. Method: Twenty four paranoid patients with Schizophrenia or Schizoaffective disorder are randomly assigned to either CBT or control group with clinical/symptom assessments conducted at baseline and post-treatment by blind evaluators. Treatment as

usual (TAU) is used as a control condition. Treatment phase for the CBT group lasts 15 weeks and includes attending one individual and one group therapy sessions weekly. Individual sessions support group sessions, and are conducted by the same therapist. CBT interventions are focused on: (1) Increasing patients' cognitive flexibility and changing maladaptive methods of forming judgments by learning and utilizing meta-cognitive processes needed for making more accurate judgments; (2) Learning to identify and correct cognitive biases; and (3) Using learned methods of reasoning to analyze and replace patients' delusional beliefs with more adaptive ones. While the focus of therapeutic intervention is on helping patients learn and apply cognitive operations, principles of cognitive therapy are applied to create supportive, collaborative and empowering relationships among group members. Results: The differential treatment effects will be examined to determine whether there will be a statistically significant increase in reductions in outcome scores of the CBT for Paranoia treatment compared to control group. The initial assessment at week 8 showed that the following significant changes occurred in the CBT condition, but not in the TAU condition: reduction in delusion, suspiciousness, and poor rapport (PANNS); reduction in delusional conviction, and amount of distress (PSYRATS), increase in ability to dismiss a paranoid thought and decrease in worry (CDRS), ($P < .05$). Conclusions: These initial results suggest that paranoid patients can benefit from learning cognitive operations needed for making more accurate judgments, and applying these skills to modify their paranoid beliefs in the context of GCBT.
ID: 550049

ASSESSMENT OF ELEMENTS OF CONSENT OVER THE COURSE OF REAL CLINICAL TRIALS IN SCHIZOPHRENIA

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Informed consent is not equivalent to merely obtaining a signature and the process of consent is not complete once a signature is obtained. Ethical research requires that subjects maintain some knowledge of a study during participation. Continuing or sustained consent has received attention when progressive cognitive decline is expected over the course of a study (eg, studies in Alzheimers disease). However, little has been done on sustained consent in schizophrenia (SZ) where a relatively static cognitive insult is coupled with a fluctuating clinical state. It is unclear what elements of informed consent are lost over the course of a clinical trial in SZ and when these elements are lost. To address this issue, we followed participants with SZ enrolled in real clinical trials of 8 wks or longer and assessed their capacity to consent at set time points. Capacity to consent was assessed with the modified Evaluation to Sign Consent (mESC); a 23-item scale developed at the MPRC which measures Understanding, Appreciation, Reasoning, and Therapeutic Misconception with a maximum score of 92. Participants in the Sustained Consent Study reviewed medication trial consent forms and received a baseline mESC at wk 0 of the medication study. Participants were randomized to receive a follow-up mESC at 1, 4, and 8 wks; 4 and 8 wks; or only at 8 wks. A Brief Psychiatric Rating Scale (BPRS) was completed with each mESC. The medication trials included studies of adjunctive agents for treatment-resistant positive symptoms (risperidone added to clozapine), negative symptoms (rasagiline), and cognitive impairment (atomoxetine and others). This preliminary analysis includes 42 subjects enrolled in the Sustained Consent Study with a mean age of 42 yrs. Participants were 57% male, 40% non-white, and had an average of 12 yrs education (SD 0.37). Baseline BPRS totals averaged 32.7 ± 8.1. Baseline mESC scores were 77.5 ± 10.7. Over the course of 8 wks, there were no meaningful changes in mean mESC score (Wk 1: 75.1 ± 12.6, Wk 4: 76.4 ± 12.6, Wk 8: 79.4 ± 11.1). BPRS total did not correlate with mESC score at any time point. This result supports the idea that partici-

pants with SZ can complete clinical trials of up to 8 wks with little change in baseline capacity to consent. However, it should be recognized that this sample size is small, participants were largely drawn from a research clinic (were experienced subjects and clinically stable), and had, on average, completed high school.
ID: 550044

PILOT PROGRAM FOR MEDICATION OPTIMIZATION: SOMETIMES LESS IS MORE

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Purpose: The Optimization Program (OP) was developed as a clinical program to maximize effectiveness of pharmacological treatment in clients with severe mental illness within the VA Puget Sound Health Care System. The objectives of the OP were to: 1) identify the most efficacious agents for the treatment of specific target symptoms; 2) minimize risks to safety associated with the use of psychiatric medications; and 3) reduce the utilization of redundant and/or questionably beneficial medications. Methods: The OP enrolled clients with a psychiatric disorder who were prescribed polypharmacy (at least four psychotropic medications). The OP procedures were developed into a template followed by the client's prescriber. These procedures included a five Axis diagnosis, review of current symptoms/problems, relevant mental status findings, and overall assessment of client. Each psychotropic medication was then evaluated on a rating scale for target symptoms, tolerance, safety, compliance, and efficacy. Based on the medication evaluation, a plan was developed to optimize the pharmacological treatment of the client. Results: Assessment of 18 clients who participated in this program found that after one OP visit, the number of psychiatric medications was significantly reduced ($P < .000$) from an average of 5.3 to 4.2. During this same time, the GAF ratings remained essentially unchanged from an average of 45.6 to 46.9 ($P = .095$). Conclusion: Following a systematic approach to evaluating psychiatric medications, total number of medications were able to be reduced without apparent increase of symptoms or decompensation of the client. Eliminating unnecessary medications may decrease the risk of harm to clients and reduce overall costs to the medical center.
ID: 550022

PRELIMINARY FINDINGS FROM A COMMUNITY-BASED EFFECTIVENESS TRIAL OF SOCIAL COGNITION AND INTERACTION TRAINING (SCIT)

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Social Cognition and Interaction Training (SCIT) is a manualized, 20-week psychosocial intervention designed to improve social functioning in schizophrenia by way of enhanced social cognition. The current presentation will summarize preliminary data from an uncontrolled, pre/post effectiveness trial of SCIT conducted within a network of outpatient clinics unaffiliated with the SCIT treatment developers ($n = 48$). Outcome domains included Theory of Mind, emotion perception, and attributional bias. Preliminary results indicate that: 1) SCIT was transportable to and feasible in this environment; 2) SCIT was associated with improved performance in Theory of Mind and emotion perception; 3) SCIT was not associated with changes in attributional bias. It is concluded that SCIT holds promise as a transportable intervention, but that measurement limitations may hinder evaluation of social cognitive treatments.
ID: 549975

SOCIAL COGNITION AND INTERACTION TRAINING (SCIT): TREATMENT OUTCOMES AND POTENTIAL MECHANISMS OF CHANGE

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The current presentation will report six-month follow-up data from a previously published trial comparing Social Cognition and Interaction Training (SCIT; $n = 18$) to an active treatment control group ($n = 10$) among forensic inpatients. Initial outcome results from this study showed SCIT-related improvements in emotion and social perception, Theory of Mind, attributional style, interpersonal functioning, and neurocognition. Six-month follow-up domains included two measures of emotion perception and interpersonal functioning. At follow-up, both groups declined from post-test on these measures. However, SCIT participants remained improved relative to baseline, and were similar to non-ill controls on emotion perception measures. These results suggest that it is possible to improve social cognition and social functioning with an intervention that emphasizes metacognitive awareness and cognitive debiasing rather than neurocognitive remediation techniques.
ID: 549930

NEW RESEARCH IN PSYCHOSOCIAL INTERVENTIONS FOR ADHERENCE: PROSPECTIVE STUDIES OF THE USE OF ENVIRONMENTAL SUPPORTS VS. TREATMENT AS USUAL FOR IMPROVING ADHERENCE AND OUTCOME IN MULTI-EPISODE PATIENTS

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Cognitive Adaptation Training (CAT) is a psychosocial treatment that uses environmental supports such as signs, checklists, alarms and the organization of belongings to cue and sequence adaptive behaviors in the home. We present data from two prospective, randomized studies examining different treatments using environmental supports to target medication adherence medications. In study I, 95 outpatients with schizophrenia (SCID-DSMIV) were randomly assigned to 1) Full-CAT (CAT focused on many aspects of community adaptation including grooming, care of living quarters, leisure skills, social and role performance and medication adherence), 2) Pharm-CAT (CAT focused only on medication and appointment adherence) or 3) treatment as usual (TAU). Treatment lasted for 9 months, and patients were followed for 6 months after the withdrawal of home visits. In study II, as part of a larger treatment study, 69 outpatients were randomized to one of three treatments 1) PharmCAT 2) MM–A treatment using the Med-eMonitor™; an electronic device with the ability to store up to five different medications, cue the taking of medication, warn patients when they are taking the wrong medication or taking it at the wrong time, record side effect complaints, and through modem hookup promptly alert treatment staff to failures to take medication as prescribed. Early identification of adherence problems with the monitor was followed with rapid telephone intervention to overcome barriers to adherence; and 3) TAU. Data are available for the first 3 months of treatment for study II. For both studies, medication adherence (assessed during unannounced, in-home pill counts) and outcomes were assessed at 3 month intervals. For Study I, results of mixed effects regression models indicated that both CAT and PharmCAT treatments

were superior to TAU for improving adherence to prescribed medication ($P < .0001$). Effects on medication adherence remained significant when home visits were withdrawn. Survival time to relapse was significantly longer in both CAT and PharmCAT in comparison to TAU (.004). For study II, mixed effects regression models for pill count adherence indicated a non-significant trend for treatment group effects at 3 months. Participants in treatments utilizing environmental supports had better adherence to prescribed medications ($P < .07$). Findings suggest that supports targeting medication adherence lead to better adherence and outcomes for individuals with schizophrenia.
ID: 549888

INITIAL EFFICACY DATA ON A SOCIAL COGNITIVE SKILLS TRAINING PROGRAM

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Social cognitive deficits are promising treatment targets for new interventions to improve functional outcome in schizophrenia. This talk will present data from two studies that are evaluating a new social cognitive skills training program designed to address four aspects of social cognition (affect perception, social perception, attributional style, Theory of Mind) in stable outpatients with psychosis, a population for whom such interventions will likely be very useful. In the first study (Horan et al. in press) 31 clinically stable outpatients were randomly assigned to a social cognition skills training intervention or a time-matched control condition (illness self-management training and relapse prevention skills training), with both treatments lasting 12 sessions. Participants completed pre- and post-treatment assessments of social cognition, neurocognition, and symptoms. The social cognition group demonstrated a large improvement in facial affect perception (within group effect size = .73), which was not present in the control group (within group effect size = .15) and the between group effect was significant ($P < .05$). This improvement was independent of changes in basic neurocognitive functioning or symptoms. Results from this pilot study support the efficacy of a social cognitive intervention for community-dwelling outpatients and have led to a subsequent study. A second study is currently underway and is attempting to disentangle the effects of social cognition remediation from cognitive remediation. In this study, participants are randomly assigned to one of four types of interventions: social cognitive training, cognitive remediation, a combination of the social cognitive training and cognitive remediation, and a control condition, with each treatment lasing 24 sessions. These validation trials of a new training program for social cognition are designed to encourage further development of this treatment approach with the aim of achieving broader improvements in social cognition and eventual generalization of treatment gains.
ID: 549819

EFFECTIVENESS OF RISPERIDONE LONG-ACTING INJECTION IN THE EARLY PHASE OF SCHIZOPHRENIA: RELAPSE PREVENTION AND FUNCTIONAL OUTCOME

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Return of psychotic symptoms in the first year of treatment for schizophrenia patients is a major clinical problem. Short acting antipsychotic medication requires daily re-commitment to treatment, which is compromised by patients' poor awareness of the need for continued antipsychotic treatment. We are comparing the clinical effectiveness of the long acting injectable form of risperidone to the oral form in a 12-month randomized controlled trial in recent-onset schizophrenia patients. This is a preliminary report from Sample 4 of the project entitled "Developmental Processes in Schizophrenic Disorders" (PI: Keith Nuechterlein, Ph.D., ClinicalTrials.gov Identifier: NCT00333177), conducted at the UCLA Aftercare Research Program. Participants are also receiving individual case management, group and individual psychoeducation, assistance in returning to work or school using Individual Placement and Support, and random assignment to group training focusing on either cognitive remediation or healthy behaviors. Among patients in the risperidone long-acting injectable (RLAI) treatment group, the rate of psychotic relapse is lower, the time to first relapse is longer, and degree of independent living is higher than among patients treated with oral risperidone. The time to discontinuation of treatment with risperidone for any reason is nonsignificantly longer in the RLAI group. If these findings are confirmed in the full sample, they will support the view that RLAI, as compared to the oral form of risperidone, improves both clinical outcome and a key aspect of community functioning.
ID: 549795

THE TRAINING OF AFFECT RECOGNITION (TAR): EFFICACY, FUNCTIONAL SPECIFICITY AND GENERALIZATION OF EFFECTS

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Impairments in affect recognition are well known in schizophrenia. Such impairments have proven to be a trait-like characteristic in schizophrenia mostly unaffected by traditional treatment. Moreover they seem to play a crucial role in patients' poor social functioning. The present study should contribute to the still open question of treatment options for these impairments. A special Training of Affect Recognition (TAR) was evaluated in three consecutive studies using pre-post-control group designs with either an "active" control treatment (studies 1 and 2), a "passive" treatment as usual group (study 1), or a waiting group (study 3). The active control treatment consisted of a Cognitive Remediation Training (CRT) aiming at improvement of basic neurocognitive functioning. Outcome measures comprised facial and prosodic affect recognition, basic cognitive functioning assessed by a neuropsychological test battery, and social interaction assessed by a role play test. Analyses revealed specific training effects in the form of a double dissociation both in studies 1 and 2: the TAR improved facial and prosodic affect recognition as well as understanding of social scenes, but had no effects on memory, attention and executive functioning. Patients under CRT and those without training did not show improvements in affect recognition, though patients under CRT improved in some memory functions. Positive effects of the TAR on facial affect recognition could also be replicated in forensic schizophrenia patients (study 3) and proved to be stable for at least 4–6 weeks after the end of training (studies 2 and 3). However, an impact on social interaction could not be found (study 2). According to these results, improvements in disturbed facial affect recognition in schizophrenia patients are not obtainable with a traditional cognitive remediation program like CRT, but need a functional specific training like the newly developed TAR.
ID: 549725

EFFICACY OF A BRIEF INTERVENTION TO IMPROVE AWARENESS OF NEUROCOGNITIVE DEFICIT IN SCHIZOPHRENIA

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The majority of people with schizophrenia have neuropsychological dysfunction yet about half of them have poor insight into their cognitive impairments (Medalia and Thysen, 2008). As new treatments are developed for the cognitive problems in schizophrenia, it will be important that patients are receptive to them and understand why they require yet another intervention. We developed a brief psycho-educational intervention called Braincheck, to improve awareness of neurocognitive deficit. Braincheck involves a series of highly interactive exercises that provide multiple opportunities for participants to actively explore how cognitive functions can be assessed and changed. Braincheck begins with a brief cognitive self assessment; and then continues to psycho-educational exercises intended to improve understanding of what cognition is, and how it can be changed. The primary objective of this investigation was to determine whether Braincheck could help individuals with schizophrenia and schizoaffective disorder become more aware of their cognitive dysfunction, and more receptive to the idea that cognition can change and be treated. After a pre-assessment of cognition, insight and receptiveness to treatment, 20 adults with schizophrenia or achizoaffective disorder participated in Braincheck, and then were subsequently reassessed on the same measures. Results indicated that the participants in Braincheck made significant improvements in awareness of cognitive deficit ($P < .001$) and receptiveness to the idea that cognition is malleable ($P < .001$). These results provide the basis for an ongoing randomized controlled trial to determine if behavioral interventions like Braincheck can help improve awareness of cognitive dysfunction and receptiveness to cognitive enhancing treatments. Supported by an investigator-initiated grant from Eli Lilly (PI: A. Medalia).

Reference

1. Medalia A, Thysen J. Insight into Neuro-cognitive Dysfunction in Schizophrenia, manuscript, Schizophrenia Bulletin. 2008; doi: 10.1093/schbul/sbm144.
ID: 549691

'EXTENDED' DOSING—REDEFINING INTERMITTENT ANTIPSYCHOTIC THERAPY: A DOUBLE-BLIND TRIAL

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The numerous adverse side effects associated with antipsychotic use have fostered efforts to minimize drug exposure, as evidenced by the reduction in dose that has been documented over the last several decades. Intermittent antipsychotic treatment represents another strategy that had been tried in the past, but evidence of less favourable outcomes with this approach discouraged its use. Based on neuroimaging work, specifically positron emission tomography (PET) and dopamine D2 occupancy, we postulated that clinical response could be maintained with 'extended' dosing. In contrast with intermittent dosing, which allowed for prolonged intervals without antipsychotic exposure, extended dosing provides for intermittent but regular dosing (ie, every 2–3 days). In follow-up to a pilot project that supported such an approach, we carried out a double-blind trial in stabilized patients with schizophrenia. Subjects were randomly assigned to one of two groups: (i) their regular antipsychotic and dose, with placebo interchanged every other

day; (ii) regular antipsychotic and dose daily. The trial was 6 months in duration. Results indicated no difference in clinical outcome between groups, as measured by various clinical measures including the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression scale (CGI), and Calgary Depression Scale (CDS). Of note, no differences were noted with respect to side effects such as exptrapyramidal symptoms (EPS) or subjective response, as evaluated by the Drug Attitude Inventory (DAI). Our findings will be discussed in terms of the underlying rationale for this strategy, as well as clinical implications and practical concerns. Supported by a NARSAD Independent Investigator Award to GR.
ID: 549676

NEUROPSYCHOLOGICAL EDUCATIONAL APPROACH TO COGNITIVE REMEDIATION (NEAR) IN JAPAN

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In Japan, "Interfering Independence to People with disabilities Law" was enforced in 2006. Although, disabled persons' employment, deinstitutionalization, and socialization were promoted by this law, there are actually many people with psychiatric illness including patients with schizophrenia, who suffer from social dysfunction. It is widely accepted that cognitive dysfunction in schizophrenia plays a major role in determining social outcome. With the aim of alleviating many difficulties they encounter in their community lives, cognitive remediation therapy for patients with schizophrenia has gradually launched in Japan. After participating in the one-week clinician training of Neuropsychological Educational Approach to Cognitive Remediation (NEAR) we set up NEAR in Japan. Fifteen patients with schizophrenia participated in the study. NEAR in Japan consisted of two sessions a week, lasting one hour each. The subjects completed approximately 6 months of NEAR sessions before being assessed for the efficacy. In each session, subjects engaged in some computer tasks that involved the cognitive region according to the profile of subjects' cognitive dysfunction. In addition, a group meeting that aimed at promoting motivation and generalization of cognitive skills to daily life was held once a week. We measured efficacy by using a) Japanese version of Brief Assessment of Cognition in Schizophrenia (BACS-J) as a cognitive function scale, b) Life Assessment Scale for Mental Illness (LASMI) as a social function scale, c) Positive and Negative Syndrome Scale (PANSS) as a psychiatric symptoms scale. The findings of the present study can be summarized as follows; a) patients showed significant improvement in cognitive function, however, social function and psychiatric symptoms were not significantly improved, b) age of onset showed positive correlation with the improvement of attention, c) the improvement in executive function correlated with the improvement in the skills of daily life, d) younger patients showed greater improvement than elderly patients in terms of the skills of daily life, e) premorbid IQ negatively correlated with the social function improvement. Although the sample size in the present study was small, NEAR in Japan was moderately effective on cognition, and some potential predictors of its efficacy were found.
ID: 549654

ADD-ON D-SERINE TO ANTI-PSYCHOTICS IN SCHIZOPHRENIA: A RCT FOCUSED ON NEGATIVE SYMPTOMS AND COGNITION

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Negative symptoms and cognitive impairment are commonly observed in patients with schizophrenia, and have been hypothesized to be caused by functional under-activity of NMDA receptor-mediated neurotransmission. Previous studies on sample sizes from 30–60 subjects administered d-serine, a NMDA agonist, at doses of 2 gm/day, and showed significant improvements in negative symptoms. Based on these previous studies, the Stanley Medical Research Institute funded a large randomized, placebo-controlled trial administering d-serine to patients with schizophrenia. Between 2004–7 we randomized 195 subjects with chronic schizophrenia, stabilized on their anti-psychotic medication, to receive add-on d-serine 2 gm/d, or placebo. Subjects received double-blind medication for 4 months. The mean age of the patients was 39.3 ± 12.1, mean years of education was 10.9 ± 2.7, mean age of onset of illness was 23.4 ± 8.5 years. Mean total PANSS score was 75.5, mean PANSS negative score was 26.4. On symptoms, there were significant improvements in both d-serine and placebo groups: total PANSS scores improvement: for d-serine (+0.9 effect sizes) vs placebo (+1.0 effect sizes), $t = -0.69$, $P = .496$; SANS scores improvement: d-serine (+0.65 effect sizes) vs placebo (+.86 effect sizes), $t = -1.05$, $P = .296$. On cognition, the MATRICS composite score improved by .30 effect sizes for d-serine vs 0.24 effect sizes for placebo, $t = -0.74$, $P = .46$. Treatment was well tolerated; 75% of the subjects completed the 16 week study, and there were no significant adverse events. D-serine administered at 2 gm/day is not an effective treatment for schizophrenia. The implications for the NMDA hypothesis of schizophrenia will be discussed.
ID: 549597

NEUROCOGNITIVE EFFECTIVENESS OF HALOPERIDOL, RISPERIDONE AND OLANZAPINE IN FIRST EPISODE PSYCHOSIS: A RANDOMIZED, CONTROLLED ONE-YEAR FOLLOW-UP COMPARISON

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Context: Cognitive impairments determine general functionality in schizophrenia. The beneficial effect of second generation antipsychotics compared to first generation antipsychotics in treating these cognitive impairments has lately been questioned. Objective. To investigate the neurocognitive effectiveness of haloperidol, risperidone and olanzapine in first-episode of schizophrenia-spectrum disorders. Design. This is a prospective, randomized, open-label study. Setting. Data for the present investigation were obtained from a large epidemiological and three-year longitudinal intervention program of first-episode psychosis conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Santander, Spain. Participants. 104 patients

randomized to haloperidol ($N = 35$), olanzapine ($N = 30$) or risperidone ($N = 39$) who completed clinical and cognitive evaluations at baseline, 6 months and 1 year were included in the final analysis. 37 healthy individuals were also longitudinally assessed. Interventions. A neuropsychological battery that comprised nine cognitive domains was used. The contribution of clinical changes, concomitant medications and the severity of motor side effects to cognitive changes was controlled. Main outcome measure. Cognitive score changes at 1-year follow up. Results. The three treatment groups showed a significant improvement in cognitive scores after 1 year. The differential cognitive effectiveness between antipsychotics was insignificant. The magnitude of cognitive changes was similar in the three treatment groups and controls, although a greater improvement in Finger Tapping, Trail Making Test B and Rey Complex Figure Test was found in the treatment groups. Clinical changes, use of concomitant medications and the emergence of motor side effects did not significantly account for cognitive changes over time. Conclusions. Haloperidol, olanzapine and risperidone were equally effective in treating cognitive deficits of psychosis. The effect of practice clearly contributes to cognitive score improvements after treatment with antipsychotics. Our results provide important information regarding the practical utility of antipsychotic treatments to improve cognition, and could have implications for developing novel approaches for cognitive pharmacotherapy in schizophrenia.
ID: 549580

NEW RESEARCH IN PSYCHOPHARMACOLOGIC INTERVENTIONS FOR ADHERENCE: A PROSPECTIVE STUDY OF LONG-ACTING RISPERIDONE VS. ORAL SECOND-GENERATION ANTIPSYCHOTIC IN FIRST-EPISODE SCHIZOPHRENIA

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Background: We evaluated the potential effectiveness of long-acting route (risperidone microspheres) as an alternate approach to oral antipsychotics help address the adherence problem in first-episode patients. Methods: The study used an effectiveness approach with adherence attitude and adherence behavior as primary outcomes. Consenting first-episode subjects were randomized in a 2:1 ratio to either a recommendation of long-acting risperidone (INJ, $n = 26$) or staying on oral medication (ORAL, $n = 11$). Nonadherence behavior was defined as:1) time until a 14 day medication gap (GAP), 2) proportion of days adherent/ specific time intervals (0–12,12–36,36–52 weeks). Two Kaplan-Meier (K-M) analysis of time to GAP were conducted:Intent to Treat (ITT) and As Actually Treated (AAT). ANOVA analysis compared INJ and ORAL on proportion of days adherent. The ROMI was used for adherence attitudes with 2 subscales, ROMI-Adherence (ROMI-A; 9 items) and ROMI-Nonadherence (ROMI-NA;10 items). Data were analyzed for the 3 major assessment points (12, 36, and 52 weeks) using mixed linear models, with treatment (INJ/ORAL), time (12, 36, 52) as fixed factors, and the 2 ROMI subscales as dependent variables. Categorical analyses compared the 19 ROMI items and treatment groups at each major time point. Results: Most of the INJ patient (19/26;73%) accepted this recommendation. Most patients (68%) had at least one GAP over 52 weeks. The INJ acceptance was associated with better adherence at 12 weeks ($P < .05$), but there were no significant between-group GAP differences at 52 week K-M survival. In contrast, adherence attitudes at 52 weeks favored the INJ group, with two ROMI-NA items being significantly higher (less favorable) in ORAL; stigma (IIT) and family opposition to medication (ITT and AAT). Discussion: Almost 70% of initially adherent first-episode patients had at least one GAP within a year, and spent at least 25% of their time without medication. While adherence behavior did not differ at 1 year, adherence attitudes favored the INJ group.

The initial recommendation of long-acting antipsychotic was for the most part acceptable to first-episode patients, but the long-acting route does not, by itself, solve the adherence problem. Possible advantages of the long-acting route in first-episode patients may be associated with more favorable adherence attitudes compared to oral route, as well as the easier adherence tracking associated with the long-acting route compared to oral.
ID: 549515

A JAPANESE PROGRAM THAT ADDRESSES MOTIVATIONAL AND COGNITIVE DEFICITS IN CHRONIC SCHIZOPHRENIA

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A cognitive remediation program that targets the motivational and cognitive deficits of schizophrenia was adapted for use with chronic patients in Japan. This presentation will describe the philosophy behind the program and the techniques used to enhance intrinsic motivation and cognition. Also, results will be presented from an ongoing randomized controlled trial that has so far enrolled 15 patients (8 women and 7 men; mean age = 33.6 years [SD = 10.7] with schizophrenia or schizoaffective disorder with mean illness duration of 10.6 years. The treatment group received twice-weekly computer-based cognitive sessions and a once-weekly verbal session for six months. The treatment sites included outpatient clinics, day treatment, and inpatient units. The attendance rate, which represented a behavioral measure of motivation, was 88.0% during the first three months and 89.0% during the last three months, indicating high treatment intensity throughout the program. The average attendance rate was significantly correlated with improvements in social functioning ($r = .86$, $P < .005$), and GAF ($r = .76$, $P < .05$). The control group consisting of patients with compatible diagnoses and clinical history received outpatient milieu treatment. Data from PANSS item N4, N6 and G13 also provided measures of motivation in the two groups. Both the experimental group and control group were administered a series of tests including Brief Assessment of Cognition in Schizophrenia (BACS) as a neuropsychological measure at the start and end of the six months period. The experimental group showed significant improvement at the post- NEAR program compared to the baseline in verbal memory ($t = -3.92$, $P < .01$), working memory ($t = -3.57$, $P < .01$), verbal fluency ($t = -2.72$, $P < .05$), and executive function ($t = -2.71$, $P < .05$). The ANOVA comparing the group and treatment effect resulted in a significant group-by-treatment interaction effect in working memory ($F_{1,25} = 12.11$, $P = .05$). These findings indicate that people with chronic schizophrenia can be successfully engaged in cognitively enhancing activities, and that programs that specifically target motivation and cognition benefit even people with chronic forms of the illness.
ID: 549414

REMEDIATION OF NEURO AND SOCIAL COGNITION: RESULTS OF AN INTERNATIONAL RANDOMIZED MULTI-CITE STUDY

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Objectives: Nowadays the importance of cognitive processes for functional outcome and recovery is a main topic of interest of researchers and clinicians. It seems that neuro-cognitive domains such as attention, vigilance, memory, and executive functioning have a decisive impact and prognostic value in these areas. Social cognition (eg, emotion perception, Theory of Mind, attributional style) might be a significant mediating factor to augment this neuro-cognitive impact. The NIMH MATRICS initiative established a consensus on separate neuro-cognitive and social cognitive domains that are relevant for the treatment of schizophrenia. Against this background we developed a cognitive-behavioral group therapy program (INT: Integrated Neuro-cognitive Therapy) covering these treatment targets. INT is partly computer based and intends to restitute and compensate neuro-cognitive and social cognitive (dys-) functions. This "bottom up" and "top down" approach puts a strong focus on the patients' daily life context to promote transfer and generalization. INT additionally facilitates intrinsic motivation and resources. Methods: INT is currently evaluated in an international randomized multi-cite study in Switzerland, Germany and Austria, which is supported by the Swiss National Science Foundation. INT is compared with treatment as usual (TAU). INT patients receive 30 therapy sessions twice a week, lasting 90 minutes each. A comprehensive assessment battery comprising proximal and distal measures, is applied before and after therapy and at a 1-year follow-up. Up to now 145 outpatients participate in the study. Results: INT patients obtain medium effect sizes in neuro-cognitive and social cognitive variables, insight, negative symptoms and high ones in social functioning after therapy. The global effect size still augments at follow-up. Only the INT group shows higher significant correlations between self-rated deficits in neuro-cognition and objective psychometric test performance after the treatment phase. A SEM model supports evidence of social cognition as a mediating factor between basic neurocognition and functional outcome. Finally, a low drop-out rate of 9% of the INT patients during the study represents a high acceptance by the patients. Conclusion: Results support the significance of the MATRICS variables for psychological treatment targets. INT seems to be successful in improving functional outcome when embedded in other rehabilitation efforts.
ID: 549356

EARLY PSYCHOTIC RESPONSE INDEX FOR PREDICTING LONG-TERM GLOBAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

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Background: The delayed onset of action hypothesis for antipsychotic drugs in the treatment of schizophrenia spectrum disorders has recently been rejected. In this analysis, we assess if the combined use of early reduction in psychosis (within the first 2 weeks) and/or early side-effect measures are effective in predicting the level of long-term global functioning. Methods: The analysis data-set was based on a double-blind, 6-month study of ziprasidone and olanzapine ($N = 94$), which showed comparable efficacy between the treatment groups at all time points (2). The generalized additive model, which models the GAF change scores at Month-6 as nonparametric smoothed functions of the covariates (BPRS core score at Week-2 and/or weight change at Week-6), was used to ensure adequate control for any nonlinearities in the predictive function. A multivariate score function model was then developed to predict the likelihood of achieving >50% improvement in GAF. Results: At Week-2, the majority of ziprasidone (80%) or olanzapine (83%) patients showed greater than 20% improvement in BPRS Core symptoms. At up to 6 months of follow-up, 52 (55%) subjects met the responder criteria for 50% or greater improvement in global functioning. Early responders (Week-2) showed significantly more improvement in global functioning than early non-responders at all time points (Week-6 and Month-6) (all $P < .05$), confirming that response within the first 2 weeks of antipsychotic treatment is an indicator of continued responsiveness to treatment over at least 6 months. Application of the Generalized Additive Models revealed a nonlinear functional relationship of early weight change (6 weeks) to GAF improvement at study endpoint (Month-6) ($P < .05$), with large weight gain predicts less GAF improvement at final visit. A multivariate score function based on baseline scores, early reduction of psychotic symptoms at 2 weeks ($P < .05$), and % weight change observed at 6 weeks ($P < .05$) showed statistically acceptable predictive performances based on c-statistics (AUC ROC > 0.8; 1-specificity vs. sensitivity curve). Conclusions: Our findings suggested that very early improvement in psychotic symptoms predicts long-term global functioning. An early response score function incorporating core psychotic subscale and side-effects measures can be useful tool for predicting patient's likelihood of achieving favorable long-term treatment outcomes.
ID: 549280

SHORT-TERM IMPROVEMENT BY MINOCYCLINE ADDED TO OLANZAPINE ANTIPSYCHOTIC TREATMENT IN PARANOID SCHIZOPHRENIA

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The limited effect of current antipsychotics on the schizophrenia symptoms has led to the search for novel drugs that can potentiate the treatment of this disorder. Minocycline is an antibiotic of the tetracycline group, with efficacy in different neurological diseases. Various findings from animal and human studies suggest that minocycline has possible advantages for the treatment of schizophrenia, including case reports of beneficial effects in catatonic schizophrenia. The current study investigated the effects of minocycline as adjuvant therapy in three patients with recent onset paranoid schizophrenia in use of a stable dose of olanzapine for more than four months (15, 20 and 20 mg/day respectively). Minocycline was administered 300mg daily, divided in two doses, for a period of eight weeks. Clinical evaluation was performed fortnightly by the PANSS and CGI. In this preliminary study, olanzapine augmentation with minocycline considerably improved the positive (75, 90.9, and 100% respectively) and negative (86.36, 30, and no symptoms detected respectively) symptoms of paranoid schizophrenia. There were no significant side effects. In addition, one of these subjects was also submitted to a SPECT before and after minocycline treatment. An abnormal increase in regional cerebral blood flow was found in the posterior cingulate prior to minocycline administration, which was significantly reduced after minocycline therapy. It is noteworthy that this patient did not exhibit negative symptoms, and the reduction of the increased rCBF after minocycline treatment was observed together with improvement of the positive symptoms. Minocycline may reduce the neurotoxic consequences of N-methyl-D-aspartate receptor (NMDA-R) hypofunction implicated in the pathophysiology of schizophrenia. In fact, this agent reversed several NMDA-R antagonist symptoms in animal and human studies. It has been previously suggested that NMDA-R hypofunction may lead to glutamate, serotonin, and dopamine release in the posterior cingulate cortex. These alterations may underlie the neurotoxic effects of NMDA-R hypofunction and could be involved in the posterior cingulate overactivation during psychosis exacerbation. Thus, the neuroprotection by minocycline may be mediated by NMDA-R transmission modulation. Another possibility is that minocycline is an anti-microglial

agent, which could reduce a possible inflammatory component of schizophrenia.
ID: 549262

THE ROLE OF MOTIVATION AND ENGAGEMENT IN SUCCESSFUL COGNITIVE TRAINING WITH SCHIZOPHRENIA PATIENTS

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Schizophrenia is characterized by impairments in neurocognition that are known to contribute to decrements in psychosocial functioning in major areas of life such as work, independent living and social relationships. Treatments to target these neurocognitive impairments have typically focused on the content of the intervention, namely the cognitive task, with little regard to the way the intervention is delivered. Yet, research shows that intrinsic motivation is a significant mediator in cognitive treatment outcome. It predicts who will engage in cognitive treatment, the degree of task engagement, and persistence on the training activities. We will present results from several recently completed randomly controlled studies which examined the impact of motivational variables on neuropsychological and functional outcome. Two studies compared the degree and persistence of executive skill acquisition with and without motivational paradigms incorporated into the teaching approach ($N = 42$). Another study examined a psycho-educational intervention called Braincheck to target beliefs of cognitive malleability and awareness of neurocognitive deficit, with the premise that engagement on remediation tasks is a function of patients' expectancies of success, beliefs of neuroplasticity, and goal value ($N = 20$). Results from these trials demonstrated that (a) intrinsic motivation techniques improved executive skill acquisition ($P = .04$), attentional resource allocation ($P = .05$), task engagement ($P = .05$), and self-reported feelings of efficacy ($P = .05$); (b) although effects on neurocognitive measures dissipated over time, certain executive skills acquired through motivational learning remained intact at 132 days post-treatment ($P = .05$); (c) baseline perceptions of self competency accounted for 43% of the variance on post-test executive scores; and (d) Braincheck made significant improvements in awareness of cognitive deficit ($P < .001$) and receptiveness to the idea that cognition is malleable ($P < .001$). Overall, results provide the basis for incorporating intrinsic motivation instructions and value expectancy motivators to impact skill acquisition, duration of effects, task engagement, self-reported feelings of competency and accomplishment, awareness of cognitive dysfunction, and receptiveness to cognitive enhancing treatments.
ID: 549133

SELECTIVE ATTENTION TRAINING FOR AUDITORY HALLUCINATIONS

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An estimated 30% of individuals with schizophrenia are not responsive to antipsychotic medication and continue to suffer from distressing positive symptoms such as hallucinations. Hallucinatory experiences in this population negatively impact quality of life and daily functioning in a variety of ways including reduced ability to maintain attention and focus due to AH, chronic distress due to the often abusive nature of AH, and in some cases, serious suicide attempts in response to AH. Targeted rehabilitation of selective attention impairment has been demonstrated in several case examples to improve functioning and quality of life in schizophrenia patients with unremitting AH. The goal of the proposed work was to conduct the first treatment outcome study of selective attention training for auditory

hallucinations in schizophrenia who are receiving optimal pharmacotherapy . We examined the effects of this treatment on AH dimensions, psychosocial functioning, self esteem, psychiatric symptoms, and quality of life in 24 individuals with schizophrenia or schizoaffective disorder. Participants were randomly assigned (stratifying by age and gender) to either the selective attention training condition or supportive psychotherapy for weekly sessions totaling 24 hours of exposure. We hypothesized that individuals in the SAT condition would show significantly greater improvement in quality of life and self esteem. Results showed that those in the SAT condition showed significant improvement on the quality of life scale (World Health Organization QOL) and measures of depression. Participants across conditions showed improvement in self esteem (Rosenberg Self-Esteem scale). Findings suggest that SAT for auditory hallucinations, while not directly impacting symptoms, relates to improved quality of life. This suggests that persons with schizophrenia may use this intervention to better manage symptoms they are experience resulting in more positive feelings about quality of life. Second, participants with unremitting AH receiving either individual intervention showed significantly improved self-esteem suggesting that 1:1 attention in a community-based psychiatric rehabilitation center is important in improving self esteem. Given the small sample, this study serves as a feasibility study to further test the interpretations of these findings.
ID: 549118

CLINICAL AND SUBSTANCE USE OUTCOMES OF FIRST-EPISODE SCHIZOPHRENIA PATIENTS WITH A LIFETIME DIAGNOSIS OF CANNABIS USE DISORDERS RANDOMLY ASSIGNED TO RISPERIDONE OR OLANZAPINE FOR 16 WEEKS

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Introduction: Cannabis is the most common illicit drug used among individuals presenting with a first episode of schizophrenia. In this study, we report 16-week clinical and substance use outcomes of first-episode schizophrenia patients with a lifetime history of cannabis use disorders and treated with either risperidone or olanzapine. We focused on first-episode patients to limit the confounding effect of prior exposure to prescribed medications. Methods: Forty-nine first-episode patients with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder and a co-occurring lifetime diagnosis of cannabis use disorders were randomly assigned to treatment with either olanzapine (2.5 to 20 mg daily) ($n = 28$) or risperidone (1 to 6 mg daily) ($n = 21$). Response criteria were: a rating of 3 (mild) or less on the following SADS-C+PD items: severity of delusions; severity of hallucinations; impaired understandability; derailment; illogical thinking; bizarre behavior, and a rating of very much improved or much improved on the CGI improvement item. This level of improvement had to be maintained on two consecutive ratings. Results: Response rates of positive symptoms were 45% (95% CI: 25%, 65%) with olanzapine and 54% (95% CI: 29%, 79%) with risperidone. Survival curves did not differ between groups (log-rank test; $P < .95$). The percentage of responding subjects having a subsequent rating not meeting response criteria was higher in subjects assigned to olanzapine (60%; 95% CI: 25%, 95%) compared to subjects assigned to risperidone (20%; 95% CI: 0%, 56%) but did not reach statistical significance (log-rank test; $P < .23$). Separate RMANOVA for

delusions, hallucinations, and thought disorganization showed improvement over time but no differences between study medications. Among negative symptoms, SANS global asociality-anhedonia showed an improvement over time but no difference between study medications. Regarding rates of cannabis and alcohol use during the study, there were no differences between treatment groups for cannabis use (56% in the olanzapine group vs. 35% in the risperidone group, Chi-square test, $P < .1626$) or alcohol use (52% in the olanzapine group vs. 40% in the risperidone group, Chi-square test, $P < .4208$). Discussion: Our results suggest that olanzapine and risperidone have similar efficacy on psychotic symptoms and substance use in first-episode schizophrenia patients with co-occurring cannabis use disorders.

ID: 549115

INHALED LOXAPINE IS AN EFFECTIVE AND RAPID TREATMENT FOR AGITATION IN SCHIZOPHRENIC PATIENTS

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Agitation is a common problem in schizophrenia, often requiring drug therapy in an acute care setting. Experts in behavioral emergencies consider speed of onset as an important factor in choosing a treatment. This Phase 3 clinical trial describes the speed and effectiveness of treating agitation with inhaled loxapine. This was a multi-center, randomized, double blind, parallel group, placebo controlled study. Two doses of inhaled loxapine, 10 mg and 5 mg, and placebo were tested. Study subjects were agitated patients with schizophrenia who provided informed consent. At baseline, subjects were required to have a minimum total score of 14 for the five items of the PANSS Excited Component (PEC) including tension, excitement, hostility, uncooperativeness and poor impulse control, and a score of at least 4 (moderate) on at least one item. Subjects were excluded for recent psychostimulant use or substance dependence within the prior 2 months. Other antipsychotics, benzodiazepines and hypnotics were not allowed within 4 hours of study drug administration. The primary endpoint was the change in the PEC total score at 2 hrs. Additional endpoints included change in the PEC at 10, 20 30, 45, and 60 minutes as well as at 4 and 24 hrs, and Clinical Global Impression—Improvement (CGI-I),CGI-I responder, and ACES at 2 hrs. A total of 344 subjects were randomized to inhaled placebo ($n = 115$), inhaled loxapine 5 mg ($n = 116$) or inhaled loxapine 10 mg ($n = 113$). Mean PEC scores at entry were similar: 17.4, 17.8 and 17.6, respectively. For the PEC total score at 2 hours (11.9, 9.8, 8.9, respectively), both the 10 mg and 5 mg doses were statistically significantly different from placebo. At each post-dose time point starting at 10 minutes, the 10 mg dose was statistically superior to placebo. For CGI-I at 2 h, both the 10 mg and 5 mg doses showed statistically significant differences vs. placebo. By survival analysis, time to rescue medication over 24 hr was longer for either dose of loxapine compared to placebo. Median ACES scores were in the "normal" to "calm" range after loxapine treatment. Both doses were generally safe and well tolerated. Inhaled loxapine appears to offer a very rapid and safe alternative to injectable antipsychotics in agitated schizophrenic patients.

ID: 548921

COGNITIVE REMEDIATION WITH AND WITHOUT ATOMOXETINE IN SCHIZOPHRENIA

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Cognitive treatments have become a focus of treatment development in schizophrenia, due to the adverse effect that cognitive dysfunction has on psychosocial outcome in the illness. However, no known treatment effects have been demonstrated with drugs known to enhance cognition preclinically. Therefore, the idea has developed that the implementation of pharmacological treatments may require a cognitive remediation component in order to become manifest. Cognitive remediation is an intervention that has recently and increasingly appeared promising in improving cognitive functions in individuals with schizophrenia. Moreover, the putative treatment holds considerable face validity, especially with all that is known about the mechanisms of brain plasticity and its reliance on repetition to change function. Based on this rationale, we developed a four-cell intervention designed to test two treatments (atomoxetine and cognitive remediation) alone and together in people with stable schizophrenia and demonstrable cognitive dysfunction. We have carried out an interim analysis with an $N = 6$ in each of the four groups (atomoxetine [A] + control [Con]; A + cognitive remediation [CACR]; placebo [P] + Con; and P + CACR), to look both at symptom and cognition outcomes and at potential biomarker outcomes represented by changes in functional imaging characteristics. Here we report the outcomes of individuals with schizophrenia who have participated in cognitive remediation three times weekly (60 minute sessions) for 12 weeks using CACR-developed software.

We have done a preliminary analysis of the change in outcome measures with these treatments. This analysis has shown no significant change in any of the groups on the composite score from our cognitive battery (which is our primary outcome measure) nor on the total Birchwood SFS score. We will examine subscale scores in the future. PANSS ratings show a decrease in symptom manifestation (total PANSS score) with each treatment (atomoxetine, CACR, and CACR + atomoxetine) but not with the placebo/control task alone, although we did not test for significance yet because of the very low N. We have not predicted a reduction in psychotic symptoms, but continue to follow this outcome. We will report data from a significant number of subjects in their response to atomoxetine, cognitive remediation and both together.

ID: 548845

EFFICACY AND TOLERABILITY OF ADJUNCTIVE ARMODAFINIL IN PATIENTS WITH SCHIZOPHRENIA

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Armodafinil, the longer lasting enantiomer (R) of modafinil, improves wakefulness and long term memory in obstructive sleep apnea, shift work disorder (SWD), and narcolepsy and attention in SWD and narcolepsy. A proof-of-concept study evaluated the effect of armodafinil on cognition and symptoms in patients with schizophrenia receiving oral olanzapine, risperidone, or paliperidone. This 4-wk, double-blind, placebo-controlled study randomized 60 adult patients 1:1:1:1 to armodafinil 50 mg/d, 100 mg/d, or 200 mg/d, or placebo. Dosing began at 50 mg/d, with 50-mg titration on days 2, 4, and 6 to randomized dosage. Efficacy measures included the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (primary) and the Positive and Negative Syndrome Scale (PANSS,

secondary). Tolerability was assessed. There was no apparent improvement in measures of cognition. The 200-mg/d dose had a potentially clinical meaningful effect vs placebo on the PANSS negative scale and total scores. No evidence of worsening positive symptoms in the armodafinil groups as assessed by the PANSS positive scale scores was noted. Armodafinil was generally well tolerated. The most common adverse events vs placebo were diarrhea (5 [11%] vs 1 [7%]), headache (4 [9%] vs 1 [7%]), and restlessness (3 [7%] vs 0). Adjunctive armodafinil 200 mg/d may improve the negative symptoms of schizophrenia without worsening positive symptoms in patients receiving oral olanzapine, risperidone, or paliperidone. Armodafinil provided no apparent improvement in the MATRICS measures of cognition. Armodafinil was generally well tolerated. These findings warrant larger, adequately powered, double-blind, placebo-controlled studies. Sponsored by Cephalon, Inc.

Table. Baseline-to-Final Visit Score Change

| | Placebo ($n = 13$) | Armodafinil | | |
		50 mg ($n = 14$)	100 mg ($n = 14$)	200 mg ($n = 12$)
MATRICS composite score				
Mean change (SD)	2.2 (5.1)	1.9 (6.2)	2.8 (8.0)	2.9 (4.7)
Effect size (95% CI)		−0.04	0.09	0.15
		(−0.81, 0.73)	(−0.68, 0.86)	(−0.66, 0.95)
PANSS negative scale score				
Mean change (SD)	0.1 (1.9)	−0.3 (4.0)	−0.3 (3.4)	−3.4 (2.1)
Effect size (95% CI)		0.11	0.13	1.69
		(−0.65, 0.87)	(−0.63, 0.88)	(0.78, 2.60)
PANSS positive scale score*				
Mean change (SD)	−0.9 (1.2)	−0.7 (2.1)	0.1 (3.3)	−0.4 (2.7)
PANSS total score				
Mean change (SD)	−1.7 (4.9)	−2.5 (8.6)	−0.9 (7.8)	−6.3 (7.3)
Effect size (95% CI)		0.11	−0.11	0.73
		(−0.64, 0.87)	(−0.87, 0.64)	(−0.08, 1.54)

*From safety analysis set.
ID: 548729

PERFORMANCE AND INTERVIEW-BASED ASSESSMENTS OF COGNITIVE CHANGE IN A RANDOMIZED, DOUBLE-BLIND COMPARISON OF LURASIDONE VS. ZIPRASIDONE

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Background: Improving cognitive functioning in people with schizophrenia is a major treatment goal. The FDA has asked for a co-primary measure to demonstrate clinical relevance of any detected cognitive changes. There are few data available regarding whether co-primary measures are sensitive to treatment-related changes. Lurasidone is a new atypical antipsychotic with affinity for D2 and 5-HT2A receptors, as well as for serotonin receptor subtypes implicated in cognitive enhancement, including 5-HT7 and 5-HT1A. Methods: Adult outpatients, ages 18–70 years old, were recruited who met DSM-IV criteria for schizophrenia or schizoaffective disorder with no hospitalization or acute exacerbation of psychosis in the previous 3 months. Eligible patients were randomized to 21 days of treatment with lurasidone 120 mg once daily or ziprasidone 80 mg BID. The intent-to-treat sample consisted of 150 patients on lurasidone and 151 patients on ziprasidone. A similar proportion of patients completed the study on lurasidone and ziprasidone [67.5% ($n = 123$) vs. 69.3% ($n = 111$)]. Study participants were tested at baseline and endpoint with the MATRICS consensus cognitive battery (MCCB) and an interview-based assessment of cognitive functioning the Schizophrenia Cognition Rating Scale (SCoRS). SCoRS ratings were based on the interviewer's best judgment, after interviews with the patient and a caregiver. Results: There were no between-group differences in MCCB or SCoRS ratings, although at week 3 lurasidone was superior on the SCoRS at a trend level ($P = .058$). On the MCCB, at week 3, lurasidone demonstrated significant within group-improvement from baseline ($P = .026$) but not ziprasidone ($P = .254$). There was no significant within-group improvement from baseline on the SCoRS for the ziprasidone patients ($P = .185$), although lurasidone patients improved significantly ($P < .001$). Effect size for improvement on the SCoRS (0.43) was over twice as large for lurasidone as improvement on the MCCB (0.157). Implications: These data indicate that interview-based, "co-primary" measures of cognitive improvements are more sensitive to change compared to the MCCB. In contrast to the MCCB, ratings on the SCoRS are not performance-based, meaning that practice effects are not a viable explanation for improvements detected. In this 3-week study, lurasidone showed general trends toward improvement on the MCCB, as well as the SCoRS, and is being assessed further in ongoing clinical trials.
ID: 548350

TWO DAY TREATMENT OF AUDITORY HALLUCINATIONS BY HIGH FREQUENCY RTMS GUIDED BY CEREBRAL IMAGING

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Background: Auditory hallucinations are a common and disabling problem for many patients with schizophrenia that often fail to respond to optimal antipsychotic therapy. Repetitive transcranial magnetic stimulation (rTMS) has recently been suggested as an alternative treatment for these patients. Until now, rTMS has been used at low frequency and has been most commonly applied to the left temporoparietal cortex. In order to improve the efficiency of this treatment, we conducted a pilot study using high frequency rTMS guided by anatomical and functional magnetic resonance imaging (MRI). Methods: Eleven patients with schizophrenia (DSM-IV) were treated with high frequency (20 Hz) rTMS delivered over 2 days. The anatomical target was identified by MRI as the highest cluster activation along the posterior part of the left superior temporal sulcus from the BOLD signal contrast map of each subject (listening to French vs Tamil story). Results: A significant reduction in the global severity and frequency of auditory hallucinations between baseline and post-treatment day 12 was observed. Seven out of 11 (63.8%) patients had at least 30% improvement in Auditory Hallucinations Rating Scale scores. For 2 patients, auditory hallucinations disappeared entirely. High frequency rTMS was well tolerated in all patients. Conclusions: This is the first study reporting the successful treatment of auditory hallucinations with 20 Hz rTMS combined with anatomical and functional MRI. The high rate of efficacy, the safety and short duration of treatment present a considerable therapeutic gain compared to low frequency rTMS.
ID: 548330

ADJUNCTIVE RISPERIDONE IN CLOZAPINE TREATED PEOPLE WITH TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: Up to 50% of people adequately treated with clozapine continue to exhibit significant residual positive and negative symptoms and cognitive impairments. They represent a major therapeutic challenge, raising the question as to what treatment options are available for them. In clinical practice, a second antipsychotic medication is often used, but there is little empirical evidence to support the validity of this approach. Previous studies with adjunctive risperidone have produced mixed results. The current study was deigned to provide a comprehensive evaluation of adjunctive risperidone for persistent positive symptoms (primary outcome), negative symptoms and cognitive impairments (secondary outcomes). Methods: The study was a 16-week, placebo-controlled, parallel group, RCT of adjunctive risperidone (4 mg/day). Subjects with DSM-IV schizophrenia or schizoaffective disorder were required to demonstrate at least a minimum level of illness severity defined as a BPRS (18 item version) total score of 45 or more and a CGI severity of illness item score of 4 or more, and a minimal level of positive symptoms defined as a BPRS positive symptom total item score of 8 or more, and a score of 4 or more on any individual item. The BPRS positive symptoms items and SANS total score were used to assess change in positive and negative symptoms, respectively and a comprehensive neuropsychological battery was used to assess change in cognition. Results: Eighty-six subjects signed consent forms and 71 subjects entered the 4-week evaluation phase. Sixty-five subjects were randomized and entered the double-blind phase of the study (risperidone: 30/placebo: 35). The majority of subjects were male: risperidone group: 63.3%; placebo group: 71.4%; and Caucasian: risperidone group: 76.7%; placebo group: 62.9%. The risperidone group was significantly older: 48.3 (7.2) versus 43.6 (9.6). In September 2008, the last of the randomized subjects completed the trial. Fifty-two subjects completed all 16 weeks of the double-blind study (risperidone: 25/placebo: 27). The presentation will include complete data for intent to treat primary analyses for the primary and secondary outcome measures using mixed model analysis of variance for repeated measures. Discussion: Study results will provide a comprehensive evaluation of the efficacy and safety of adjunctive risperidone for persistent positive and negative symptoms and cognitive impairments.
ID: 547770

RECOMBINANT HUMAN ERYTHROPOIETIN: APPROACHES TO NEUROPROTECTION AND NEUROREGENERATION IN SCHIZOPHRENIA

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Mainly due to modern imaging technology, schizophrenia is increasingly recognized as developmental disease with additional neurodegenerative components, comprising cognitive decline and progressive loss of cortical gray matter. Therefore, neuroprotective/neurotrophic add-on strategies may deliver promising treatment options. Erythropoietin (EPO) is an ideal candidate compound for neuroprotection in human brain disease in general and in schizophrenia in particular, capable of combating a spectrum of pathophysiological processes operational during the progression of the disease. In the nervous system, EPO acts anti-apoptotic, anti-oxidant, anti-inflammatory, neurotrophic and plasticity modulating. EPO has been found to be neuroprotective/neuroregenerative in various different animal models of neuropsychiatric diseases. In preparation of a first trial on EPO in schizophrenia, we tested the capability of EPO to penetrate an intact blood-brain-barrier. Using indium 111-labeled EPO, we demonstrated that even in healthy subjects, EPO enriched within the brain. This accumulation was increased in schizophrenic patients as compared to healthy controls, likely explained by the higher density of EPOR expression found in frontal cortex and hippocampus of schizophrenics. Importantly, EPO is able to improve cognitive functioning in mice and to enhance hippocampal long-term potentiation and other determinants of neuronal plasticity, essential for learning and memory processes. EPO prevents the development of slowly progressing global brain atrophy in a mouse model of chronic neurodegeneration. Further, EPO reduces haloperidol-induced cell death in primary hippocampal neuronal cultures. Based on these grounds, we performed a double-blind, placebo-controlled, randomized multicenter trial. Treatment over 12 weeks with high-dose weekly EPO led to significant improvement of cognitive performance compared to placebo controls. Employing voxel-based morphometrical magnetic resonance imaging analysis, we obtained first evidence that EPO treatment delays progressive cortical gray matter loss in chronic schizophrenia. In contrast, over the three months of study duration, we did not see effects on psychopathology or social functioning. The fact that EPO is the first compound ever to exert a beneficial effect on cognition in schizophrenia should encourage further work along these lines. An EPO treatment trial including patients with first episode schizophrenia has been initiated.
ID: 546968

MODAFINIL FOR CLOZAPINE-TREATED SCHIZOPHRENIA PATIENTS. A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Rationale: Patients with schizophrenia often suffer from cognitive deficits and negative symptoms that are poorly responsive to antipsychotics including clozapine. Clozapine-induced sedation can worsen cognition and impair social and occupational functioning. Objectives:To evaluate the efficacy, tolerability, and safety of modafinil for negative symptoms, cognition and fatigue in schizophrenia patients treated with clozapine. Methods: A double-blind, placebo-controlled, flexible-dosed 8-week pilot trial was conducted, adding modafinil up to 300 mg/day to stabilized schizophrenia outpatients receiving clozapine. Psychopathology, cognition, and fatigue were assessed with standard rating scales. Results: 35 patients were randomly assigned to treatment with study drug and included in the analysis. Modafinil did not improve negative symptoms, cognition, or fatigue compared to placebo. Modafinil was well tolerated and did not worsen psychosis. Conclusions: Results of this pilot trial do not support routine use of modafinil to treat negative symptoms, cognition, or fatigue in patients on clozapine. Larger trials are needed to resolve or refute a potential therapeutic effect of uncertain magnitude.
ID: 546739

TEST-RETEST CHARACTERISTICS OF THE MATRICS CONSENSUS COGNITIVE BATTERY IN A 20-SITE SCHIZOPHRENIA CLINICAL TRIAL OF R3487/MEM3454 VERSUS PLACEBO

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Background: The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Project produced a battery of tests, the MATRICS Consensus Cognitive Battery (MCCB), designed to assess cognitive treatment effects in clinical trials of patients with schizophrenia. In validation studies, the MCCB demonstrated excellent reliability, minimal practice effects and large correlations with measures of functional capacity. It has been an empirical question whether the MCCB would demonstrate these favorable characteristics when administered in the context of the type of large multi-site industry trial for which it was designed. Methods: Patients with schizophrenia maintained on a stable dose of a second generation antipsychotic therapy were enrolled into a randomized, double-blind, placebo-controlled trial of R3487/MEM3454. Testers from 20 sites were trained and certified, and all MCCB data were reviewed and re-scored centrally. The MCCB was administered at screening and 7–14 days later at baseline. A measure of functional capacity, the UCSD Performance-based Skills Assessment (UPSA) was also measured at baseline. The MCCB generates a composite score and cognitive domain scores standardized to a normative population with mean $(T) = 50$ and $SD = 10$. Results: Baseline T-scores for the 7 MCCB cognitive domains and a composite score were determined for 62 male and 21 female subjects, mean age 39.0 years $(SD = 8.8)$, mean PANSS total score 57.7 $(SD = 9.6)$ and mean UPSA-2 total score 84.9 $(SD = 15.3)$. Only 7 test scores were missing out of a total of 1800 test assessments for the 10 MCCB tests performed in 90 subjects at 2 occasions (99.6% complete). All 90 (100%) patients had sufficient data for computing a composite score according the MCCB criteria. The mean MCCB composite score was 28.1 at screening and 30.2 at baseline, with identical SDs of 11.5 at both time points. The test-retest reliability for the MCCB composite score was very high $(ICC = 0.88)$. Construct validity was also strong, as the MCCB composite score demonstrated a large correlation with the UPSA composite score $(r = .59, df = 82, P < .001)$. The practice effect on the composite score was small $(z = 0.17)$. Discussion: In the context of a 20-site clinical trial in stable patients with schizophrenia, the MCCB is sensitive to cognitive deficits in all domains, demonstrates excellent test-retest reliability and construct validity, and small practice effects.
ID: 546725

OPEN LABEL, PILOT STUDY OF ADJUNCTIVE SODIUM OXYBATE FOR THE TREATMENT OF SCHIZOPHRENIA AND ASSOCIATED SLEEP DISTURBANCES

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Subjective and objective sleep is abnormal in schizophrenia, and associated with significant distress and cognitive deficits. Gamma-hydroxybutyric acid (sodium oxybate), a GABAB and GHB agonist, improves deficits in subjective and objective sleep in narcolepsy and fibromylagia, and multiple lines of evidence link modulation of the dopaminergic system with the GABAB receptor. We report interim results of an ongoing, four week open label, 8-patient trial of adjunctive sodium oxybate in patients with schizophrenia and insomnia related to schizophrenia. 5 patients with a mean baseline Epworth Sleepiness Scale (ESS) of 9.8, Pittsburgh Sleep Quality Index (PSQI) of 10.6 and PANSS of 93 have completed. Exclusion criteria includes: (1) Restless leg syndrome or obstructive sleep apnea (2) History of alcohol dependence (3) Persistent need for other sedative hypnotics. After tapering previous sedative-hypnotic and baseline evaluations, patients receive 4 weeks of adjunctive sodium oxybate at night, beginning at 4.5 g and increasing by 1.5 g/night/week to 9 g (in divided doses of ½ at bedtime and ½ four hours later). A two-week taper of sodium oxybate followed. Treating psychiatrists were encouraged to keep antipsychotic dosage stable. Primary outcome was subjective sleep (ESS and PSQI), with clinical/cognitive scales (PANSS, CGI and MATRICS) and objective sleep (polysomnography/actigraphy) secondary. Safety measures included several EPS scales and weekly vital signs. Through 5 patients, improvements were noted in the primary subjective outcomes— PSQI $(P = .04;$Cohen's $d = 1.34)$ and the ESS $(P < .05;$Cohen's $d = 1.29)$. In an interim analysis, a majority of polysomnography $(n = 3)$ and actigraphy $(n = 4)$ comparisons normalized from baseline to study end, particularly in stage III/IV sleep and REM latency (with increase in total REM) and decreased daytime napping. No changes were noted on the other clinical, cognitive or safety measures. Despite no change in objective symptoms, two days before final ratings, one patient's antipsychotic was changed from perphenazine to quetiapine by the treating psychiatrist for subjective worsening of psychosis. The improvement in ESS remains $(P < .05)$ even with exclusion of this patient, but the PQSI change is reduced $(P = .11)$. The interim results of this study of sodium oxybate in schizophrenia associated insomnia demonstrate large effect size improvement in subjective sleep without significant changes in general psychopathology.
ID: 546447

ATOMOXETINE AND GROUP SUPPORT FOR TREATMENT OF WEIGHT GAIN IN SUBJECTS TAKING OLANZAPINE OR CLOZAPINE

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Weight loss interventions for those on second generation antipsychotic medications have demonstrated varying success. We attempted to determine if atomoxetine, a structured support group, and exercise would result in significant benefits for this population. The study was a randomized, parallel group, double-blind comparison of adjunctive atomoxetine or placebo. Subjects with schizophrenia or schizoaffective disorder, taking either olanzapine or clozapine, who had gained at least 7% of their pre-clozapine or olanzapine weight were eligible. A weekly diet support group and exercise program, implemented during a 2-week evaluation period, continued during the 24 week double-blind treatment period. Of the 44 subjects who signed consent, 36 entered treatment and 26 completed the study. Atomoxetine did not effect weight loss $(F = 0.05, df = 1,28.2, P = .82)$: both treatment groups showed modest trends in weight loss, averaging about 2 kg $(F = 3.77, df = 1, 28.2, P = .062)$. There was no significant evidence that gender or baseline antipsychotic modified treatment effects (time x gender x treatment, $F = 0.96, P = .34$; time x antipsychotic x treatment, $F = 2.16, P = .15$). Secondary outcomes evaluated included neuropsychological assessments, symptom assessments (BPRS, SANS) and safety assessments . Among individual neuropsychological tests, only the Gordon distractibility test scores were nominally statistically significant (Wilcoxon permutation test p-value = 0.041, unadjusted for multiple comparisons), although this difference partly reflected worse performance in the placebo group. Only one of 26 laboratory measurements, blood C02, showed a nominally significant $(P = .019,$ unadjusted for multiple comparisons) reduction (approx 6%) in atomoxetine versus placebo. Of the symptom and safety assessments, only one side effect, tremor, showed nominally significant $(P = .018)$ differences in incidence of new or worsened symptoms (almost all "mild") between atomoxetine (28%) and placebo (71%). Six placebo and three atomoxetine subjects achieved exercise levels consistent with current weight loss recommendations, but this number was too small to evaluate for significance. Results indicate that adjunctive atomoxetine is not effective for weight loss in this population, but both olanzapine and clozapine subjects can lose weight with structured group support and exercise. Motivation to exercise poses the biggest challenge. Supported by Eli Lilly and Company and an ACISR pilot project grant.
ID: 546250

PSYCHIATRISTS' ATTITUDES TO FIRST AND SECOND GENERATION ANTIPSYCHOTIC LONG-ACTING INJECTIONS: COMPARISONS OVER FIVE YEARS

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Background: Previously, when only first generation antipsychotic depot long-acting injections (LAIs) were available, some clinicians perceived LAIs as having an "image" problem despite them being associated with reduced rates of rehospitalisation when compared to tablets. This study investigated psychiatrists' attitudes and knowledge concerning depot long-acting injections (first and second generation antipsychotics) and whether they had changed over time. Method: Cross-sectional postal survey of consultant psychiatrists working in NorthWest England. A pre-existing questionnaire on clinicians' attitudes and knowledge regarding LAIs was updated. Results were compared with a former sample (South-East England, 2001: $N = 143$). Results: The sample comprised 102 consultant psychiatrists (response rate 71%). LAI use over the past 5 years had: decreased (50%), not changed (27%), increased (23%). Most regarded LAIs as associated with better compliance (89%) than tablets. A substantial proportion believed that LAIs could not be used in first-episode psychosis (38%) and that patients always preferred tablets (33%). Psychiatrists with decreased LAI use had significantly lower scores for the side effects knowledge subscale than those who had unchanged or increased rates of LAI use (mean 51.5% vs 54.8%, $P = .029$). When compared to psychiatrists sampled five years previously, our current participants scored more favourably on a patient-focused attitude subscale had more favourable patient-focussed attitudes (63.5% vs 60.4%, $P = .034$); other subscales did not differ. Item-by-item analysis revealed specific differences between the two samples including significantly fewer current participants regarding LAIs as: (i) compromising patient autonomy (mean 0.99 vs 1.28, $P = .036$); being stigmatising (1.88 vs 2.42, $P = .002$); being old fashioned (1.49 vs 2.04, $P = .002$). Conclusions: During the period that a second generation antipsychotic LAI has been available, and LAI prescribing rates have reduced, most attitudes and knowledge have remained fairly stable and consistent in the UK, except for attitudes regarding the patients who are prescribed LAIs which improved. Concerns about stigma and autonomy with LAI use have decreased. However, concerns about patient acceptance continue as do negative views about some aspects of LAI use; these may compromise medication choices offered to patients.
ID: 546172

EXPLORING PLACEBO RESPONSE IN RECENTLY CONDUCTED VS. EARLIER TRIALS OF PATIENTS WITH SCHIZOPHRENIA

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Research suggests that the placebo-adjusted effect of antipsychotic treatment in acute schizophrenia trials has diminished over the past several decades. This may be partly due to an increasing placebo response, which was the focus of these post-hoc analyses. The analyses were performed using placebo-arm data from available acute schizophrenia trials that were denoted as Earlier Trials (late 1980s-mid 1990s: RIS-USA-1, RIS-INT-3 [CR006067], RIS-USA-72) and similarly-designed Later Trials (2004–2005: CR003379, CR004378, CR004375). PANSS and CGI-S at week 6 (completers) and endpoint (LOCF) were examined. Regression models assessed the relationship between placebo response ($\geq$20% or $\geq$30% reduction in PANSS total score) and: country, age, gender, illness duration, baseline PANSS and CGI-S, and enrollment in Later vs. Earlier trials. Results of the analyses included that the distribution of percentage change in total PANSS scores over time shifted towards greater improvements with placebo in Later vs. the Earlier trials at week 6 ($P = .012$), but not at study endpoint. Multiple logistic regression models identified "Later vs. Earlier Trials" as the only variable significantly associated with placebo response. Placebo-treated patients in Later vs. Earlier Trial were 4.3-times (95% CI, 1.89–9.58, $P \leq .001$) and 4.7-times (95% CI, 1.58–13.94, $P = .0054$) more likely to experience a $\geq$20% and $\geq$30% reduction, respectively, in PANSS at week 6. In conclusion, placebo-treated patients with schizophrenia enrolled in more recently-conducted trials are more likely to exhibit a reduction in PANSS at week 6 than those in earlier-conducted trials. None of the tested variables were significantly associated with this response, suggesting that factors not considered (ie, associated with study conduct/other patient characteristics/etc.), or hidden biases, may underlie this phenomenon.
ID: 543442

INSIGHT AND ITS RELATIONSHIP TO BASELINE CHARACTERISTICS OF SCHIZOPHRENIA PATIENTS RANDOMIZED TO LONG-ACTING INJECTABLE RISPERIDONE OR ORAL ATYPICAL ANTIPSYCHOTICS: RESULTS FROM THE PROACTIVE STUDY

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a) While the use of long acting antipsychotics is often recommended to increase medication adherence, the relationship between atypical long acting antipsychotics and relapse is not well established. The purpose of PROACTIVE (Preventing Relapse in schizophrenia: Oral Antipsychotics Compared To Injectables: eValuating Efficacy) study is to compare the relapse rates of patients receiving the first line oral atypical antipsychotics vs. the long acting atypical risperidone. A secondary aim is to evaluate the role of insight in adherence and relapse. This study presents baseline data on the level of insight, patient presenting symptomatology and previous relapses. b) The primary outcome variable in this analysis is the level of insight measured by the modified Scale to Assess Unawareness of Mental Disorder (SUMD) at baseline. Inclusion Criteria: 1. Schizophrenia and schizoaffective disorder patients. 2. Exacerbation in the last 12 months. Exclusion 1. First episode patients. c) To date, baseline data have been analyzed for 78 subjects. The number of patients with good insight = 45 (males = 33, females = 12), with limited insight = 33 (males = 24, females = 9). The age of patients with good insight (mean = 39.13, SD = 10.44), with limited insight (mean = 34.97, SD = 12.02). Adherence with good insight = 39 (good = 33, poor = 6), with limited insight = 32 (good = 24, poor = 8). The number of hospitalizations in patients with good insight (mean = 12.38, SD = 17.75), number of hospitalizations in patients with limited insight (mean = 6.43, SD = 8.76). BPRS with good insight (mean = 2.60, SD = 1.03), BPRS with limited insight (mean = 2.93, SD = 1.31). SANS with good insight (mean = 2.34, SD = 0.54), SANS with limited insight (mean = 2.45, SD = 0.57). d) There were no statistically significant differences between those with good and limited insight on sociodemographic variables or measures of psychopathology. The only variable that correlated with insight was the previous number of

hospitalizations; those with good insight had a higher number of prior hospitalizations. This result offers several possible interpretations: first that with greater experience in treatment patients develop more insight about the illness. However, it could mean that those with insight at the start of their illness seek help and utilize resources while those without insight avoid treatment. Funding from National Institute of Health, Grant No. 5U01MH070008-03.
ID: 540493

TRAJECTORIES AND ANTECEDENTS OF TREATMENT RESPONSE OVER TIME IN EARLY EPISODE PSYCHOSIS

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Background: Little is known about the extent of heterogeneity of symptomatology in treated early onset psychosis. The current study aims to quantify the extent of heterogeneity in trajectories of treated symptom severity in early episode psychosis and their antecedents. Methods: Data were from 491 persons with early episode psychosis from a clinical trial of haloperidol and risperidone. Positive and Negative Syndrome Scale (PANSS) administrations were used to measure symptom severity trajectories for: (a) rapid treatment response scores over 4 weeks, and (b) medium-term course over 24 weeks. Baseline antecedents included: sex, DSM-IV diagnosis, age of onset, the Premorbid Adjustment Scale, and a cognitive test battery. Symptom severity trajectories were calculated with mixed mode latent class regression modeling from which groups were derived. Results: Five groups based on PANSS scores over time were identified. Over 4 weeks three groups with varied baseline PANSS scores (54 to 105) did not surpass 30% PANSS improvement. Another group improved and then was stable ($n = 76, 15.3\%$) and another showed marked improvement ($n = 94, 18.9\%$). Logistic regression showed that membership in the best response trajectory was associated with not having a diagnosis of schizophrenia, good premorbid functioning and higher cognitive functioning, whereas membership in the poor response trajectory was associated with earlier age of onset and poorer cognitive functioning. Conclusion: Amelioration generally characterizes treated symptom severity. Age of onset, diagnosis, cognitive functioning and premorbid functioning have prognostic value in predicting treatment response trajectory.
ID: 537757

PRIOR PARTICIPATION IN CLINICAL TRIALS IN SCHIZOPHRENIA: DOES THE DESIGN OF THE CLINICAL TRIAL HAVE AN IMPACT?

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Background: As documented in a recent article[1], there has been a historical reduction in the drug-placebo difference in multicenter trials of antipsychotic medications in schizophrenia. Many possible explanations for this finding have been raised, including the fact that clinical trial subjects may have different characteristics. One possible difference between subjects entering clinical trials now and those who entered earlier clinical trials may be prior participation in a clinical trial examining a treatment for schizophrenia. We examined data obtained from two global clinical trials in schizophrenia to determine whether protocol design might influence recruitment of subjects with prior participation in clinical trials. Methodology: Trial 1 was a 6-week placebo controlled double blind clinical trial in patients with an acute exacerbation of the symptoms of schizophrenia. It excluded subjects who had participated in a trial within 6 months of screening. Trial 2 was a 6-week, outpatient trial in patients with schizophrenia, who had suboptimal response or adverse events to current therapy. It excluded subjects who had participated in a clinical trial within 12-months of screening. Results: Table 1. Percentage of Subjects with Prior Trial Experience in Region. Conclusions: This data demonstrates that prior trial experience of subjects is multifactorial and is impacted significantly not only by geographical region but also by the trial design, as well as factors not examined in this study.

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ID: 550812

CHANGES IN ADIPOSITY, INSULIN SENSITIVITY AND LIPID METABOLISM DURING RANDOMIZED ANTIPSYCHOTIC TREATMENT IN SCHIZOPHRENIA

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Background: Antipsychotic medication treatment can increases or decrease body weight, as a function of individual medication effects and pretreatment conditions. Interest in treatment effects on body weight is related to hypothesized changes in adiposity, and glucose and lipid metabolism, relevant to risk for cardiovascular disease and diabetes. However, few studies to date have quantified medication effects on direct measures of adiposity, versus weight or surrogate measures like body mass index. Complicating measurement of medication effects, pre-treatment conditions can influence treatment response. However, no studies to date have balanced pre-treatment conditions across randomized treatment groups. Methods: Schizophrenia patients were randomized to 12 weeks of treatment with olanzapine, quetiapine, risperidone, or ziprasidone, balancing prior treatment conditions and baseline adiposity across treatment groups. Detailed metabolic measurements, including dual energy X-ray

Table 1.

Number of Subjects with Prior Trial Experience in Region	U.S.	Ukraine	Russia	India	All Subjects		
Trial 1	45/86 (52%)	2/49 (4%)	16/75 (21%)	1/60 (2%)	64/270 (24%)		

	U.S.	Ukraine	Argentina	Colombia	Slovak Republic	Czech Republic	All Subjects
Trial 2	53/101 (52%)	9/13 (69%)	12/35 (34%)	2/11 (18%)	1/20 (5%)	8/25 (32%)	85/205 (41.5%)

absorptiometry (DEXA), magnetic resonance imaging (MRI), hyperinsu-linemic, euglycemic clamps, and fasting plasma measurements were used to quantify whole-body and regional adiposity, insulin sensitivity, and plasma lipid levels. Results: Preliminary analysis of final results from this study indicate that significant treatment group-related differences are observed treatment-related changes in DEXA and MRI-measured adiposity, fasting plasma triglyceride, fasting cholesterol, and fasting LDL. For example, sig-nificant time x treatment condition effects are observed on DEXA-mea-sured total body fat, MRI Visceral Surface Area, MRI Subcutaneous and Visceral combined, fasting plasma triglyceride, fasting plasma choles-terol, and fasting plasma LDL, with pretreatment conditions contributing to differential outcomes in some treatment groups. Discussion: Antipsy-chotic medications can produce differential effects on direct measures of adiposity, as well as clinically available measurements relevant to cardio-metabolic risk. The results are relevant to understanding opportunities to reduce risk in persons treated with antipsychotic medications. Supported by MH63985.
ID: 551876

SUBJECTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER AND HEPATIC ILLNESS: BASELINE CHARACTERISTICS FROM A TRIAL OF PALIPERIDONE EXTENDED-RELEASE

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Management of patients with schizophrenia or schizoaffective disorder (SCH/SCA) is often complicated by comorbidities, including hepatic illness (HI). This large prospective study of these patients was undertaken to eval-uate the effects of paliperidone extended-release (ER), which undergoes limited hepatic metabolism. Interim baseline data from a 9-week, open-label, single-arm, crossover study of outpatients with stable SCH/SCA and HI were reviewed to assess the distribution of HI, by etiology and stage, in the study population. The inclusion criteria were Child-Pugh scores reflect-ing well-compensated (Class A) to functionally compromised (Class B) HI and liver tests (LTs) ≤3x the upper limits of normal (ULN). In this pre/post comparison, subjects receive treatment as usual for 4 weeks, a 1-week cross-titration, and paliperidone ER for 4 weeks. The study endpoints were ad-verse events (primary), laboratory tests, movement disorder scales, Positive and Negative Syndrome Scale (PANSS), quality of life, and alcohol use. Study identification number: CR014341. A total of 69 US subjects enrolled; 57 (82.6%) subjects had a diagnosis of schizophrenia and 12 (17.4%) sub-jects had a diagnosis of schizoaffective disorder. The mean (±SD) age was 48.2 (±7.5) years. Most subjects were male 69.6% ($n = 48$), black 63.8% ($n = 44$), with ≤high school education 72.5% ($n = 50$), unemployed 88.4% ($n = 61$); 44.9% ($n = 31$) lived in supported housing. The most common etiology of liver disease was viral hepatitis (95.7%, $n = 66$). Most subjects had a Child-Pugh rating of A (82.6%, $n = 57$). LTs (alanine and aspartate aminotransfer-ase) were just above ULN (44.7 ± 23.90 U/L and 39.2 ± 17.09 U/L, respec-tively). The mean (±SD) PANSS total score was 73.8 (±12.6). Most subjects had used tobacco (95.7%, $n = 66$), alcohol (91.3%, $n = 63$), marijuana (68.1%, $n = 47$), and cocaine (66.7%, $n = 46$); 43.5% ($n = 30$) had used heroin. Thus far, most subjects have mild HI due to viral hepatitis, possibly related to prior substance abuse. The effects of paliperidone ER in this important patient population are currently under study. Supported by Ortho-McNeil Janssen Scientific Affairs, LLC.
ID: 551875

EARLY ANTIPSYCHOTIC RESPONSE AS A PREDICTOR OF LATER RESPONSE IN FIRST EPISODE SCHIZOPHRENIA

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Objective: Few studies have examined the time course of response in schizo-phrenia. Studies with multi episode patients suggest that lack of response early in treatment predicts longer term non-response. Correll et al. (2003), in an open label study with multi episode patients found high predictive power for non-response at 2 weeks to predict non-response at 4 weeks. Kinon et al. (2008) and Leucht (2007) showed the non-response to antipsy-chotics early in treatment (1–2 weeks) is predictive of non-response later in treatment (4–12 weeks). However, Emsley et al. (2006) analyzed data from 522 first episode patients treated with risperidone or haloperidol and found that time to response varied widely with many patients responding during the first two weeks but with a significant number of patients responding after week 8. Given this inconsistency in time course of response between first episode and chronic patients data which can help to resolve this ques-tion, would be very valuable. This study examined time course of response of first episode patients treated with the widely used second generation anti-psychotics olanzapine or risperidone. Methods: Post hoc analysis of two different randomized controlled trials in patients with a first episode of schizophrenia. Prediction models were utilized, using survival analysis, re-ceiver-operated analysis and sensitivity-specificity models. Results: In an analysis of data on 225 first episode patients participating in a randomized controlled trial, early response/non-response at 2 weeks predicted subse-quent response/non-response at 12 weeks. Early responders achieved a sig-nificantly greater level of symptom improvement than the early non-responders at all time points. In a separate 16 week trial, 112 first episode patients were also evaluated regarding time course of response. We did not see the same degree of predictive power based on early response in this cohort. Differences between these cohorts in terms of length of prior treat-ment, etc., which might impact the results will be discussed. Conclusions: Response patterns may differ in patients with a first episode of schizophre-nia compared to more chronic patients. These data are important in inform-ing treatment decisions as well as providing a framework for biologic and pharmaco genetic studies.
ID: 551856

LONG-TERM TOLERABILITY AND SAFETY OF ARIPIPRAZOLE IN THE TREATMENT OF PEDIATRIC PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR I DISORDER

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Background: There is limited published long-term clinical trial safety data upon which to guide treatment decisions and expectations in pediatric

patients with schizophrenia or bipolar disorder. Method: This is a combined safety analysis from double-blind and open-label studies which assessed the short- and long-term safety and tolerability of aripiprazole (2–30 mg) in 514 child and adolescent patients (281 schizophrenia and 233 bipolar I mania) over a treatment period of up to 32 weeks. Pooled data in this analysis was attained from subjects who had participated in either double-blind parent study: a 6-week, double-blind study in schizophrenia (ages 13–17 years), or a 30-week (4-week acute + 26-week continuation) double-blind study in bipolar I disorder (ages 10–17 years). Also included were tolerability and safety data from subjects who qualified for and participated in a 6-month, open-label extension study with a combined patient population. Assessments for each patient population included frequency and severity of adverse events, discontinuation due to adverse events, blood chemistries, ECG, and metabolic parameters, including body weight and BMI. Results: AEs were generally mild to moderate in severity. Over the course of more than 26 weeks of treatment, 7.2% of patients discontinued due to AEs (6% and 8.6% in the schizophrenia and bipolar disorder samples, respectively). The most prominent AEs in the combined sample included somnolence (23.2%), extrapyramidal disorder (21.6%), headache (17.7%) and akathisia (12.3%). There were 4 cases of suicidal ideation, with no completed suicide. Body weight shift table analysis showed that 19 subjects had a shift in weight from normal at baseline to abnormal at the last visit. Mean change in weight z-score was not clinically significant over >32 weeks of treatment (<0.5 SD). Conclusions: Aripiprazole was well tolerated, in general, over a treatment period of up to 32 weeks in pediatric patients with schizophrenia or bipolar disorder. Incidence and severity of AEs were consistent with respective short-term, double-blind parent studies. Relative to the normal rate of growth in these patient populations, mean weight gain observed in the aripiprazole groups was not clinically significant.
ID: 551855

PREDICTORS OF REMISSION WHEN LONG-ACTING RISPERIDONE IS ADDED TO STANDARD CARE IN PATIENTS WITH BIPOLAR DISORDER WHO RELAPSE FREQUENTLY

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Patients with bipolar disorder who relapse frequently can be a challenging population to treat. Predicting which patients are more likely to achieve remission may optimize their therapy and improve long-term outcomes. This analysis examined whether specific patient characteristics at baseline were associated with achieving remission in symptomatic patients with bipolar disorder who relapse frequently. Post-hoc analysis was conducted of the OL phase of an international study (United States and India) that assessed risperidone long-acting injectable therapy (RLAT) or placebo as adjuncts to treatment as usual (TAU) for bipolar disorder in delaying time to relapse. During the 16-week, OL stabilization phase, RLAT (25, 37.7 or 50 mg intramuscular every 2 weeks) was administered adjunctively with TAU (mood stabilizers, antidepressants and anxiolytics). Patients with symptoms of depression (MADRS >10) or with manic or mixed symptoms (YMRS>10) at baseline were analyzed. Remission was defined as MADRS ≤10, YMRS ≤10 and CGI ≤3 at the end of the OL stabilization period (week 16). Subjects were stratified by patients who remitted vs patients who did not remit. Statistical significance was determined using Fisher's exact test (categorical variables) and t test (continuous variables).

Predictors of remission were explored using univariate logistic regression models. Study identification number: CR004693. Of 275 enrolled patients, 177 (64.4%) were not in remission at OL baseline. At the end of the 16-week, OL stabilization phase, 100 of these 177 patients completed the 16-week, OL phase and remitted (56.5%). A higher percentage of patients from India vs the United States remitted (70.9% vs 32.8%; OR: 5.0, 95% CI: 2.6–9.6; $P < .0001$), and a lower percentage of females vs males remitted (35.2% vs 70.8%; OR: 0.23; 95% CI: 0.12-0.43; $P < .0001$). Patients without substance abuse were more likely to remit than those with substance abuse (62.5% vs 40.8%; OR: 2.4, 95% CI: 1.2–4.7; $P = .01$). Patients who remitted had a lower baseline CGI-BP-S score than patients who did not remit (3.9 vs 4.2; OR: 0.68; 95% CI: 0.48-0.94; $P = .02$). These analyses identify several demographic and baseline clinical characteristics associated with achieving remission after treatment with RLAT when used adjunctively with TAU in symptomatic patients with bipolar disorder. Additional analyses are necessary to clarify these relationships. Supported by Ortho-McNeil Janssen Scientific Affairs, LLC.
ID: 551841

PATIENT ASSESSED QUALITY OF LIFE (PQ-LES-Q) VS. CLINICIAN ASSESSMENT (PANSS, CGI) IN A TRIAL OF ARIPIPRAZOLE IN ADOLESCENT PATIENTS WITH SCHIZOPHRENIA: TREATMENT ARM ANALYSIS

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Background: The self administered Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q(T)) is made up of 14 items that assess aspects of quality of life and a 1 item overall (O) assessment. We previously showed a strong correlation between physician and patient assessment in treatment improvement. The purpose of this post hoc analysis was to assess the same correlations by treatment arm. Methods: 302 children (age 13–17) with schizophrenia participated in a 6-week, multicenter, randomized trial. It examined 2 fixed doses of aripiprazole (10 and 30 mg/day) vs. placebo. The primary measure was mean change on PANSS Total score (LOCF). Secondary measures included: mean changes on CGI-S and PQ-LES-Q(T) and (O). Descriptive statistics of change from baseline in PQ-LES-Q(T) and (O) score were summarized by category of change in PANSS and CGI-S. Trend analysis explored the relationship between the PQ-LES-Q(O) and CGI-S score using the a Cochran-Mantel-Haenszel correlation. Results: Aripiprazole showed significant improvements over placebo in PANSS, CGI-S, and PQ-LES-Q(O) (week 6; $P < .05$; LOCF). Strong correlation was found between all measures when treatment arms were combined. This includes PQ-LES-Q(T) vs. PANSS Total and PQ-LES-Q(O) vs. CGI-S ($r \le .37$; $P \le .01$). Analysis by treatment arm (10mg, 30mg and placebo) showed strong correlation between change in PQ-LES-Q(T) vs. change in PANSS(T) in the 10mg, 30mg, and placebo groups ($r \ge -0.269$; $P < .011$; LOCF). Correlation between change in PQ-LES-Q(O) vs. change in CGI-S was significant in the 10mg group ($r = -0.277$; $P = .0063$; LOCF) but not for the 30mg and placebo

groups ($r \geq -0.084$). When the 3 treatment arms were combined and CGI-S improvement was put into 4 categories (no improvement in CGI-S Score; improvement of 1; improvement of 2; improvement of ≥ 3), change in PQ-LES-Q(O) correlated with CGI-S change from baseline ($P = .0037$; LOCF). When separated by treatment arm, correlation in the 10mg arm remained significant ($P = .002$) while the 30mg and placebo arms were not. Conclusions: There is significant correlation between improvement in patient assessment (PQ-LES-Q(T)) and clinician disease state assessment (PANSS Total score). It is seen both when treatment arms are combined or analyzed separately. There is significant correlation between improvement in patient assessment (PQ-LES-Q(O)) and clinician global assessment (CGI-S) for 10mg arm and for treatment arms combined.
ID: 551758

A CLINICAL RESEARCH PROGRAM FOR THE TREATMENT OF SCHIZOAFFECTIVE DISORDER

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Although treatment of schizophrenia and bipolar disorder has been the focus of extensive clinical research, schizoaffective disorder (SCA) remains understudied. We present key design elements from the first registration program in SCA, as well as the demographic and clinical characteristics of this population at study entry. The registration program consisting of two international, double-blind, placebo-controlled studies assessed paliperidone ER in patients with SCA. Included subjects met SCID-confirmed DSM-IV criteria for SCA; PANSS total score ≥ 60, a score of ≥ 4 on at least two of the PANSS items of hostility, excitement, tension, uncooperativeness and poor impulse control and prominent mood symptoms (≥ 16 on YMRS and/or on HAM-D-21). Concomitant antidepressants and/or mood stabilizers were permitted, if given at stable dose within 30 days of screening. The primary endpoint was the PANSS total score change at endpoint for paliperidone ER vs placebo. Secondary efficacy measures: the novel CGI-Severity for Schizoaffective Disorder (CGI-S-SCA) and -Change (CGI-C-SCA) scales, the YMRS and the HAM-D-21 scales. 614 patients were in the combined ITT population; 40.4% were from the US and 59.6% were ex-US. Mean age was 37.4 years (range 18–61); 60.4% were male and 48.9% were Caucasian. Mean ages at first psychiatric and first schizoaffective diagnoses were 25.2 (range 4–56) and 31.7 (range 3–61) years, respectively. Approximately 45% of patients were taking concomitant antidepressants and/or mood stabilizers. 68.9% of patients were diagnosed with bipolar subtype of schizoaffective disorder and 31.1% were diagnosed with depressive subtype. 31.4% of patients had attempted suicide in their lifetime; 47.9% of those patients made at least two or more attempts. Mean (SD) baseline PANSS total score was 92.8 (12.9) and mean (SD) baseline CGI-S-SCA score was 4.6 (0.6). The percentages of patients with YMRS ≥ 16 or HAM-D-21 ≥ 16 at baseline were 79.5% and 66.9%, respectively. The percentage of patients with both YMRS and HAM-D-21 ≥ 16 at baseline was 46.4%. To our knowledge, this clinical program represents the first registration trials focused specifically on SCA. Baseline features reflect the prominence of psychotic and affective symptoms distinctive of this disorder. This database will provide valuable information regarding the characteristics and treatment of this understudied patient population. Supported by Ortho-McNeil Janssen Scientific Affairs, LLC.
ID: 551755

"TIME COURSE FOR RESPONSE TO OLANZAPINE AND RISPERIDONE IN FIRST-EPISODE SCHIZO-PHRENIA"

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Objective: Few studies have examined the time course to response in schizophrenia. Studies with multi episode patients have attempted to identify subjects who will ultimately not meet study response criteria based upon response during the first weeks of the trial (Correll 2003, Kinon 2008, Leucht 2007). Very few studies have examined treatment response with a first episode population. Emsley et al. (2006) analyzed data from 400 first episode patients who responded within 12 weeks to treatment with either risperidone or haloperidol. Their finding that time to response varied widely and that 11.5 % of responding patients improved first after week 8 suggests that first episode patients may have different response patterns than multi-episode patients. To further knowledge about response patterns of first episode patients, we examined time to response over a 16 week period to treatment with the widely used second generation antipsychotics olanzapine or risperidone. Methods: 112 subjects (70% male; mean age 23.3 years) with first-episode schizophrenia, schizophreniform disorder or schizoaffective disorder were randomly assigned to olanzapine (2.5 to 20 mg daily) or risperidone (1 to 6 mg daily). Two different response criteria models were examined: 1) A model based on absolute criteria, which required ratings on 2 consecutive visits of mild or better on the SADS-C+PD psychosis items plus a rating of much or very much improved on the CGI; 2) A model based on a reduction of more than 20% on the SADS-C+PD. To allow for comparison with prior studies, the SADS-C+PD items that correspond to the BPRS items were chosen for this analysis. Different models of hazard function models (exponential, weibull, lognormal) were used to analyze time course to response. Results: 49% (95% CI: 39%, 60%) of patients met response criteria based on the absolute response criteria at the end of week 16. The cumulative response rate at week 16 based on a 20% reduction was 93% (95% CI: 87 to 99%). Based on graphical methods and examination of the Pearson correlation coefficients, the exponential model compared to the Weibull and Lognormal models provided the best fit. Conclusion: Time to treatment response to atypical antipsychotics differ between first episode and multi-episode patients. The exponential model provided the best fit to describe treatment response in this study. Our data suggests that treatment trials with first episode patients should last at least 16 weeks.
ID: 551739

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF FLEXIBLE-DOSE PALIPERIDONE ER IN THE TREATMENT OF PATIENTS WITH SCHIZOAFFECTIVE DISORDER

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Schizoaffective disorder (SCA) is a common mental illness with no established treatment guidelines. Although antipsychotics are the cornerstone of

treatment for these patients, their use has not been systematically evaluated in clinical trials either alone or in combination with other psychotropic agents. Data are presented from one of two registration trials of paliperidone extended-release (ER) in patients with schizoaffective disorder. A randomized, 6-week, international, double-blind, placebo-controlled study enrolled SCA subjects experiencing acute exacerbation. Inclusion criteria: SCID-confirmed DSM-IV diagnosis of SCA; PANSS total score ≥ 60; score ≥ 4 on two or more PANSS items of hostility, excitement, tension, uncooperativeness or poor impulse control; and prominent mood symptoms (≥ 16 on YMRS and/or on HAM-D-21). Stable doses of antidepressants/mood stabilizers were permitted. Patients were randomized in a 2:1 ratio to 6 mg/day paliperidone ER or placebo. Dosages could be adjusted (3-12 mg/day) up to day 15; no adjustments could be made thereafter. Primary endpoint: PANSS total score change at endpoint for paliperidone ER vs placebo. Secondary endpoints: YMRS and HAM-D-21 scores and adverse events (AEs). Study identification number: CR013099. 311 subjects were randomized to paliperidone ER ($n = 216$) or placebo ($n = 95$); 52.1% received concomitant antidepressants and/or mood stabilizers. 63.5% of paliperidone ER and 55.9% of placebo patients completed the study. Mean (SD) modal dose of paliperidone ER was 8.6 (2.5) mg/day. There was significant improvement with paliperidone ER vs placebo on mean (SD) PANSS total change score (-20.0 [18.9] vs -10.8 [18.7.4]; $P < .001$) and on all five PANSS factor scores ($P < .05$). Among patients with prominent manic or depressive symptoms, paliperidone ER showed significant improvement vs placebo on mean (SD) YMRS (-10.6 [10.8] vs -5.7 [10.0]; $P = .001$) and HAM-D-21 (-10.2 [8.7] vs -6.2 [8.6]; $P < .001$) change scores. Most common AEs (≥ 5%) for paliperidone ER vs placebo: headache (15.0% vs 12.6%), akathisia (6.1% vs 1.1%), dizziness (8.4% vs 5.3%), insomnia (6.5% vs 5.3%) and dyspepsia (5.6% vs 5.3%). This study demonstrated the efficacy and effective dosing of flexible-dose paliperidone ER in this understudied population with no unexpected tolerability issues. These findings were consistent with another similarly designed registration study of paliperidone ER in SCA. Supported by Ortho-McNeil Janssen Scientific Affairs, LLC.
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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF TWO DOSE RANGES OF PALIPERIDONE ER IN THE TREATMENT OF SUBJECTS WITH SCHIZOAFFECTIVE DISORDER

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Schizoaffective disorder (SCA) is common among patients with mental illness. Although antipsychotics are widely used, they have not been systematically studied in this population, and no treatment is specifically indicated for this disorder. Data are presented from one of two registration trials of paliperidone extended-release (ER) in patients with SCA. A randomized, 6-week, international, double-blind, placebo-controlled study enrolled SCA subjects experiencing acute exacerbation. Inclusion criteria: SCID-confirmed DSM-IV diagnosis of SCA; PANSS total score ≥ 60; score ≥ 4 on two or more PANSS items of hostility, excitement, tension, uncooperativeness or poor impulse control; and prominent mood symptoms (≥ 16 on YMRS and/or on HAM-D-21). Stably dosed antidepressants/mood stabilizers were permitted. Patients were randomized to placebo, paliperidone ER 6 mg/day (lower dose) or 12 mg/day (higher dose). Doses could be reduced to 3 mg/day and 9 mg/day, in the lower- and higher-dose groups, respectively, with optional increases to initially assigned dose; no adjustments after day 15. Primary endpoint: PANSS total score change at endpoint for each paliperidone ER group vs placebo. Study identification number: CR010498. 316 subjects were randomized to 6 mg/day

paliperidone ER ($n = 109$), 12 mg/day paliperidone ER ($n = 100$) or placebo ($n = 107$); 38.9% received concomitant antidepressants and/or mood stabilizers. Completion rates were 68.6%, 78.6%, and 59.4%, respectively. Mean (SD) modal daily doses in the lower- and higher-dose groups were 5.7 (0.9) and 11.6 (1.0) mg/day, respectively. Mean (SD) PANSS total score was significantly improved with higher-dose paliperidone ER vs placebo (-30.6 [19.1] vs -21.8 [21.4], $P = .003$). Change with lower-dose paliperidone ER (-27.4 [22.1]) was similar to placebo ($P = .200$). Higher-dose paliperidone ER was significantly better than placebo on most secondary efficacy endpoints. Similar findings were observed for mania and depression scores in patients with prominence of these affective symptoms. Most common AEs: headache (placebo 16.8%, lower-dose 13.9%, higher-dose 13.3%) and tremor (3.7%, 12.0%, 11.2%, respectively). This study demonstrated the efficacy, safety, and effective dosing of paliperidone ER in this understudied population. Improvement was consistently observed for higher-dose paliperidone ER vs placebo. Similar findings were observed in a second, flexible-dose study. Supported by Ortho-McNeil Janssen Scientific Affairs, LLC.
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EVALUATION OF THE EFFECTS OF AL-108 ON NEUROCOGNITION IN SCHIZOPHRENIA: INITIAL TURNS STUDY RESULTS

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Background: Persistent neurocognitive dysfunction is a primary predictor of impaired long-term outcome in schizophrenia. At present, no treatments are specifically approved for treatment of cognitive impairments in schizophrenia. TURNS (Treatment Units for Research on Neurocognition and Schizophrenia) is an NIMH-funded multicenter consortium focused on identifying and evaluating promising new treatments for persistent neurocognitive dysfunction. AL-108 is an intranasal drug product containing NAP, an 8 amino-acid peptide (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln; NAPV-SIPQ, MW = 824.9) fragment of the much larger Activity-Dependent Neuroprotective Protein (ADNP), which participates in neurodevelopment and neuroprotection. AL-108 acts, in part, by stabilization of microtubular structure. AL-108 is active in rodent models of neurodegeneration and was originally developed for treatment of neurocognitive dysfunction in Alzheimers disease and mild cognitive impairment. This poster will report initial results of a multicenter study of AL-108 in schizophrenia. The study is due for completion in 2/2009, with initial statistical analysis scheduled for 3/2009. Study design: The study consists of a 12-week, parallel group randomized clinical trial of 2 doses of AL-108 (4 and 30 mg/d intranasally) vs. placebo. Subjects are 18–60 yr old male and female patients with DSM-IV diagnosis of schizophrenia being treated with oral second generation antipsychotics or first generation injectables with controlled positive and negative symptoms. The primary outcome measure consists of the composite score of the MATRICS Consensus Cognitive Battery (MCCB). Secondary outcome measures include BPRS and SANS symptom rating scale scores, functional capacity scores and safety assessments. Targeted n is 60 subjects. Results: As of August, 2008, 50 patients had been randomized. The treatment was well tolerated with no medication related SAEs observed across subjects. The study is projected to complete in 2/2009, with initial statistical analysis to be performed in 3/09. Study results will be presented. Discussion: AL-108 is a novel peptide being investigated for treatment of AD. This

report will provide the first assessment of its clinical effectiveness in schizophrenia.
ID: 551596

ALL SOURCE VERIFICATION: A NEW TOOL FOR MEASURING ADHERENCE IN SCHIZOPHRENIA CLINICAL TRIALS

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Plasma concentrations and electronic monitoring are the gold standard in determining adherence to medication but are impractical in many settings. Other assessment techniques include patient questionnaires, pill counting, clinician judgments based on patient and caregiver reports and review of pharmacy records. Each method has limitations and advantages. We have developed a method—All Source Verification (ASV) that integrates multiple sources of information. Methods: The ASV includes prescriptions, pharmacy records, other medication sources (eg, samples) the Treatment Compliance Interview (TCI), based on patient report, clinician and family/caregiver judgments. An integrated rating is based on all available information. The ASV was used in a randomized clinical trial—PREFER (PREventing First Episode Relapse—that compared long-acting injectable risperidone microspheres to oral antipsychotics in first episode schizophrenia patients in the community. Adherence was assessed over 52 weeks for all randomized subjects. Non-adherence was defined by the first 14-day medication gap. The TCI was administered at weeks 12, 36 and 52. We compared the TCI report of adherence with the ASV judgments to determine whether ASV added information regarding non-adherence. Results: There were thirty seven subjects in the trial. At week 12, 2 (5.4%) had a gap according to TCI compared to 10 (27%) according to ASV ($\chi^2 = 5.71$ df1, $P < .01$. By week 52, the percentages were 29.7% and 70.3% respectively (χ^2 6.62 df 1, $P < .01$. Discussion: To our knowledge, this is the first clinical study to use a multi-pronged approach that includes pharmacy records to assess adherence behavior. In addition to the overall adherence judgment, the ASV permits comparison of estimate based on each source. In the present study, ASV significantly increased estimates of non-adherence compared to patient report. This is consistent with other studies that suggest that patient report may underestimate non-adherence. Limitations of this study include its small size, the fact that ASV ratings were made by a non-blind rater and involved consensus judgments. At present, the method is labor-intensive and will not be suitable for clinical use or very large RCTs. However, ASV emphasizes the value of multiple sources of information. It further underscores the high risk for non-adherence of first episode patients and the degree to which they fail to report this to clinicians.
ID: 551580

CLOZAPINE VS. RISPERIDONE FOR PEOPLE WITH FIRST EPISODE SCHIZOPHRENIA AND CO-OCCURRING CANNABIS USE DISORDER

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Schizophrenia (SCZ) with comorbid substance use disorder is associated with increased morbidity and mortality. Early in the course of SCZ, cannabis is one of the most commonly abused substances. Patients with SCZ who use cannabis have an earlier age of onset, higher rate of relapse and a poorer outcome than those without cannabis use disorder (CUD); and continued use after anti-psychotic treatment is associated with an even worse outcome. Repeated relapse has been associated with progression

of SCZ to a more chronic and treatment resistant illness. Clozapine is the most effective antipsychotic and has been shown to increase time in remission for first episode patients (relative to chlorpromazine), and to decrease cannabis use in patients with schizophrenia. Thus, patients with first episode SCZ and co-occurring CUD may be appropriate candidates for the use of clozapine, in an attempt to improve the long-term course of this disorder. This pilot study is assessing whether treating patients with first episode SCZ and comorbid CUD with clozapine will lead to increased abstinence from cannabis as compared to those treated with risperidone over 24 weeks of treatment. As a secondary objective, the study is assessing whether patients treated with clozapine will have improved global functioning, clinical symptoms, psychosocial functioning and neurocognitive functioning, as compared to those receiving risperidone. The study population (an eventual sample of 21) includes patients between the ages of 17–45 who are in their first episode of SCZ and have a comorbid CUD. Participants are randomized to clozapine or risperidone for 24 weeks and medication drop-outs are followed in intent-to-treat fashion. Participants are assessed for: (a) continued cannabis and other substance use each week using a Time Line Follow Back interview; (b) clinical symptoms every 4 weeks using the BPRS, SANS, and CGI; (c) psychosocial functioning every 4 weeks using a structured interview; and (d) neuropsychological functioning every 12 weeks using the BACS. We will present preliminary data on sample demographics, baseline characteristics, and treatment parameters.
ID: 551539

TRAJECTORIES OF ANTIPSYCHOTIC RESPONSE: MOVING BEYOND THE RESPONDER/NON-RESPONDER DICHOTOMY

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Objective: When clinical trials are analyzed in groups with a focus on end-of-trial outcomes, ie, drug versus placebo resulting in responders versus non-responders, it obscures the tremendous inter-individual variation across patients. We hypothesized that an approach based on individual trajectories through the trial, rather than an end-point analysis, would provide a statistically superior and clinically more meaningful way for conceptualizing response. Method: We examined data on 420 patients with schizophrenia treated for six weeks in two double-blind placebo-controlled trials using haloperidol and olanzapine. Their weekly response data were examined using conventional methods and growth mixture modelling to identify the optimal number of response trajectories. We examined if these trajectories were similar across drug and placebo and across different symptom dimensions. Results: Positive symptoms respond along four distinct trajectories: the two most common trajectories were the 'partial responder' (48%) and 'responder' (22%), to which drug-treated and placebo-treated patients contribute equally. The most striking drug-placebo differences were in the 'dramatic responders' (10%), who are exclusively drug-treated patients, and the 'non-responders' (20%), who are predominantly on placebo. The response of negative symptoms was more modest and did not show such distinct trajectories. Conclusions: Four distinct trajectories of response, rather than simple responder/non-responder models, provide a much better statistical and heuristic understanding of how antipsychotics work. The data show that there are no simple "drug response type" versus "placebo response type", thought the most striking responses are observed only in the drug-treated. Since this approach is data driven and does not make any apriori categorizations, we hypothesize that groups defined by such trajectories are much more likely to correlate to underlying genetics and biology than simple dichotomous categorizations.
ID: 551471

DOES CATATONIC SCHIZOPHRENIA IMPROVE FASTER WITH ELECTROCONVULSIVE THERAPY THAN OTHER SUBTYPES OF SCHIZOPHRENIA?

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Treatment guidelines recommend the use of electroconvulsive therapy (ECT) for catatonic schizophrenia. In the Indian setting, many non-catatonic schizophrenia patients also receive ECT. In this study, we compared the response to ECT of catatonic schizophrenia versus other subtypes of schizophrenia. Consecutive schizophrenia inpatients ($n = 53$) referred for ECT within three months of starting antipsychotic treatment were studied. This included 19 with catatonic schizophrenia (Bush Francis Catatonia Rating Scale ≥ 2) and 34 with non-catatonic schizophrenia. Behavioural observation was assessed using Nurse's Observation Scale for Inpatient Evaluation (NOSIE-30) by a trained rater. ECT was administered thrice weekly and assessments were done at baseline, at the end of 2nd, 4th, 6th, 8th, 10th, 12th and 14th ECT sessions. The treating psychiatrists decided to terminate ECT and the total number of ECTs required to achieve clinical response was taken as an indirect measure of speed of response. Changes in NOSIE-30 scores between the groups were compared using repeated measures analysis of variance. The total number of ECTs administered in each group was compared using survival analysis. Table shows change of NOSIE scores during the first two weeks of treatment. There was a significant group X occasion effect in NOSIE total patient asset scores, suggesting faster response to ECT in the catatonia group ($F = 5.42$; $df = 3, 150$; $P = .001$). Survival analysis suggested that patients with catatonic schizophrenia required significantly fewer ECTs (one less ECT session on an average) to achieve clinical improvement (Log-rank statistic = 5.31; $P = .02$). Catatonic schizophrenia patients show faster response to ECT than non-catatonic schizophrenia patients. However, the magnitude of the difference is modest.

Table. Comparison of NOSIE total patient asset score across time. Figures are in mean (SD)

Assessment Time	Catatonic Schizophrenia ($n = 19$)	Non-catatonic Schizophrenia ($n = 34$)
Baseline	65.2 (12.0)	83.3 (17.4)
After 2nd ECT	100.3 (9.7)	105.1 (17.7)
After 4th ECT	132.8 (14.1)	125.5 (17.5)
After 6th ECT	166.3 (14.8)	142.9 (17.3)

For this analysis, data was taken only from the first 2 weeks, as very few patients received ECT beyond this time.
ID: 551381

AMISULPRIDE IMPROVES OBSESSIVE-COMPULSIVE SYMPTOMS IN SCHIZOPHRENIA PATIENTS TAKING ATYPICAL ANTIPSYCHOTICS: AN OPEN-LABEL SWITCH STUDY

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Objective: Atypical antipsychotics with a 5-HT2a antagonist effect have been reported to induce or exacerbate obsessive-compulsive symptoms (OCS) in patients with schizophrenia. We aimed to evaluate the effect of amisulpride on OCS that occurred in patients with schizophrenia, who were taking atypical antipsychotics. Methods: Subjects with a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of 10 or greater and taking atypical antipsychotics were recruited. Their OCS were observed for changes 12 weeks after their antipsychotic medications were changed to amisulpride, which is a selective dopamine D2/D3 receptor antagonist with a negligible affinity for the 5-HT2a receptor. Results: Thirteen patients taking risperidone and three patients taking aripiprazole were enrolled and fifteen patients completed the study. Improvements in the YBOCS scores were statistically significant. Twelve of the sixteen patients showed 50% or greater improvement in the YBOCS total score. The scores of the Positive and Negative Syndrome Scale (PANSS) also significantly decreased following the switch to amisulpride, but there was no significant relationship between the changes of the YBOCS and PANSS scores. Conclusion: In conclusion, amisulpride was effective at improving OCS related to the use of risperidone or aripiprazole. This case series supports the hypothesis that switching from antipsychotics antagonizing 5-HT2a receptors, which have the potential to induce or exacerbate OCS, to amisulpride, which has a negligible affinity for the serotonin 5-HT2a receptor, may be a good treatment option for the management of OCS in patients with schizophrenia.
ID: 551342

EVALUATION OF THE EFFECT OF ARIPIPRAZOLE ON COGNITIVE FUNCTION AND WEIGHT CHANGE IN SCHIZOPHRENIA: AN OPEN-LABEL STUDY

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Secondary outcomes related to cognitive function from a 12 week multicenter open-label naturalistic study (1) examining the effectiveness of aripiprazole in patients with schizophrenia (DSM-IV) are reported here. Aripiprazole was started at 15 mg/day and dosing adjustments were allowed as per clinical judgement in the range of 10-30 mg/day. Cognitive functioning was measured by the California Verbal Learning Test (CVLT) indexes and the letter and category Verbal Fluency (VF) tests. Mean change in cognitive test scores and in body weight from baseline to Week 12 were calculated (LOCF) using descriptive statistics with 95% confidence intervals. A total of 361 patients were treated in the study. At the study endpoint (Week 12) patients showed improvements in all CVLT indexes and VF tests. The average change in baseline body weight at Week 12 (LOCF) was -1.5 Kg (95% CI: -1.94, -0.97) $n = 328$. Aripiprazole was well tolerated with the most common treatment related adverse event reported being insomnia 14.13% $N = 51/361$. Schizophrenia patients treated with aripiprazole in a naturalistic setting revealed modest improvements in list learning and word generation measures of cognitive function. More rigorous, controlled trials are needed to determine the nature and extent of potential cognitive improvement with aripiprazole.

Reference

1. Peuskens, et al. Poster presented at the European College of Neuropsy-chopharmacology, 2008, Barcelona, Spain.

Table.

		Baseline [(BL) , n]	Week 12 (LOCF) [Mean change from BL 95% CI, (n)]
Verbal Fluency	Letter fluency	20.2, $n = 345$	+2.9 (2.04, 3.81), $n = 301$
	Category fluency	27.2, $n = 345$	+1.7 (0.83, 2.56), $n = 301$
CVLT indexes	Free recall	42.2, $n = 343$	+9.4 (8.18, 10.60), $n = 297$
	Short delay free recall	8.3, $n = 346$	+2.0 (1.62, 2.35), $n = 297$
	Short delay cued recall	9.4, $n = 345$	+ 2.2 (1.85-2.53), $n = 297$
	Long delay free recall	8.8, $n = 345$	+1.9 (1.59, 2.30), $n = 297$
	Long delay cued recall	9.7, $n = 346$	+2.1 (1.72, 2.40), $n = 295$
	Semantic clustering index	1.3, $n = 167$	+0.3 (0.15, 0.43), $n = 122$
	Discriminability	89.7, $n = 346$	3.3 (2.30-4.22), $n = 296$

ID: 551284

NEUROSTEROIDS AS NOVEL THERAPEUTIC AGENTS IN SCHIZOPHRENIA AND PTSD

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Background: Many neurosteroids demonstrate pronounced neuroprotective, anxiolytic, and cognition-enhancing actions in rodents, properties that suggest therapeutic potential for schizophrenia and PTSD. Furthermore, clozapine and SSRIs markedly elevate brain neurosteroid levels to physiologically relevant concentrations. Brain neurosteroids are also altered in patients with schizophrenia and reductions in peripheral neurosteroid levels are associated with PTSD symptomatology. In addition, certain neurosteroids are positive NMDA receptor modulators and may potentially ameliorate NMDA receptor hypofunction in schizophrenia. We therefore conducted two pilot randomized controlled trials (RCTs) utilizing adjunctive pregnenolone (PREG) in patients with 1.) schizophrenia, and 2.) PTSD. Methods: Both proof-of-concept investigations randomized patients to 8 weeks of adjunctive PREG (fixed escalating doses), or placebo, following a 2-week placebo lead-in phase. Outcomes not reported previously include the Clinical Global Impressions-Improvement (CGI-I) Scale, the Heinrich-Carpenter Quality of Life (HC-QOL) Scale, lipid profiles, and baseline neurosteroid levels in relationship to MATRICS and BACS assessments, among others. Results: 1) Schizophrenia RCT ($n = 18$; 9 per group): Patients receiving PREG demonstrate significant improvements in the CGI-I scale at study completion compared to the placebo group. The HC-QOL Scale scores were improved by 5.27 points in the PREG group. Baseline neurosteroid levels are positively correlated with cognitive improvements, as assessed by MATRICS composite scores. LDL and cholesterol levels (non-fasting) are significantly decreased post-treatment in patients receiving PREG. 2) PTSD RCT ($n = 17$; 10 placebo / 7 PREG): Effect sizes comparing the PREG and placebo completer groups for the Beck Depression Inventory-II and the Connor-Davidson Resilience Scale are 0.36 and 0.48, respectively. Increases in serum pregnanolone levels are correlated with cognitive improvements in BACS composite scores. LDL levels (non-fasting) are decreased in 6 of the 7 patients receiving PREG. PREG was well-tolerated in both RCTs. Conclusions: Neurosteroids may demonstrate promise as mechanistically novel therapeutic agents in schizophrenia and PTSD. Pregnenolone was well-tolerated and associated with reductions in non-fasting serum LDL levels post-treatment. These molecules may also have biomarker utility for the assessment of clinical response. ID: 551242

OUTCOME EVALUATION OF SOLUTIONS FOR WELLNESS AND TEAM SOLUTIONS PROGRAM IN PATIENTS WITH SEVERE MENTAL ILLNESS

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Aim: Obesity is increasing at an alarming rate in the US especially in patients with schizophrenia. Our study was designed to evaluate retrospectively the outcome of the effectiveness of the Solutions for Wellness and Team Solutions programs in a large, non selected inpatient sample. Method: 275 inpatients with DSM-IV mental illness, at a tertiary care psychiatric facility, were included in the 36-week comprehensive and manualized educational programs that encourage healthy lifestyles for people with chronic mental illness. Each of the eleven 12-week modules was tested before and after by 30 knowledge questions and levels of metabolic markers, weight and BMI were recorded at three time points. Results: Of the 275 patients, significant increases in scores were observed for seven of the eleven knowledge assessment modules. The greatest improvements in scores were observed for the "Discharge Preparation (Avoiding Crisis Situations)", "Understanding Your Treatment" and "Fitness and Exercise". A significant weight loss of 4.88 lbs was observed and a decrease in BMI. Significant reductions were observed in glucose and triglycerides ($P < .05$), but not in cholesterol levels controlling for patients on cholesterol medications. 26.18% presented with DM II, impaired fasting glucose, and/or impaired glucose tolerance at baseline. Patients with impaired glucose tolerance showed a significantly greater decrease in glucose level ($P = .000$). Group differences were also observed for change in weight, with the DMII group showing a slightly greater reduction of 5.98 lbs. 10 year CHD risk was computed and 33.3% ($n = 23$) of patients with Metabolic Syndrome (MetS) at baseline were at significantly greater risk (>5%) for developing a CHD event as compared to those without MetS (21.78%, $n = 44$) (risk ratio = 1.64). Conclusion: Participants gained a significantly greater understanding of healthy lifestyles with decreases in weight, BMI and key metabolic markers, which may point to a possible interactive effect, whereby better understanding of key parameters such as medications and symptoms may support healthy lifestyles. A structured, manualized program on wellness and psychoeducation can be successfully implemented in a large psychiatric naturalistic inpatient setting. Results may help both clinicians and hospital managers to implement similar programs or to include successful components in existing programs addressing weight and metabolic abnormalities. ID: 551202

PATTERNS AND PREDICTIVE VALUE OF EARLY TREATMENT RESPONSE IN ADOLESCENTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: In acutely exacerbated patients with chronic schizophrenia, the majority of symptomatic response occurs early on in treatment and early non-response seems to be a reliable marker of later treatment non-response. However, it is unknown whether these findings extend to adolescents with schizophrenia. Methods: We examined time course and predictive power of early response in 1) a 3-month, observational study of atypical antipsychotics; and 2) an industry sponsored, 6-week, placebo-controlled trial (RCT) of aripiprazole. In the "real-world" sample, we assessed time course of CGI-S and GAF scores, and the prediction of presence/absence of a CGI-I score of much/very much improved for later/sustained response status. In the RCT, we assessed the prediction of a >20% total PANSS score reduction at week 1 and 2 for response or remission at endpoint. Analyses included survival models, sensitivity and specificity analyses, and Receiver Operating Characteristics (ROC). Results: In 80 adolescents (15.2 years) with first episode schizophrenia ($n = 32$) or psychosis NOS ($n = 48$) treated openly for 3 months(mean prior antipsychotic exposure: 2.2 ± 3.9 months, 58.4% antipsychotic naïve), CGI-S and GAF score reductions were significantly more pronounced in the first 4 weeks vs. the following 8 weeks. The exponential survival model best fit the response pattern for all patients, the schizophrenia and psychosis NOS subsamples, and for simple and sustained response (R = 0.92–0.97). In the RCT, 293 adolescents (15.5 years) were randomized to aripiprazole 10 mg ($N = 99$) or 30 mg ($N = 97$), or placebo ($N = 98$). By week 1, 2 and 3, 23–45%, 45–57% and 78–80% of the total PANSS score reduction were achieved in the aripiprazole arms. A >20% PANSS score reduction at 2 weeks predicted a >20% PANSS score reduction at study endpoint with 97.8% specificity (NPV: 59.0%) and 47.5% sensitivity (PPV: 90.3%). In ROC analyses, the optimum cut-off was a 10% PANSS total score reduction at week 2 (sensitivity: 80.3%, specificity: 82.6%) for response, and a 13% reduction at week 2 (sensitivity: 64.7%, specificity: 64.1%) for cross-sectional "remission". Conclusions: Data in adolescents with schizophrenia-spectrum disorders confirm that most of the treatment response occurs early. Early non-response was a better predictor of later non-response in the RCT than in the naturalistic study that used more global outcome measures. Further studies in adolescents and real-world settings are needed.
ID: 551195

PREDICTORS OF PERSISTENCE ON TREATMENT WITH OLANZAPINE AND OTHER ATYPICAL ANTIPSYCHOTIC MEDICATIONS IN PATIENTS WITH SCHIZOPHRENIA

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Objectives: Poor treatment response is an important factor that contributes to a lack of persistence on treatment. The goals of this research were to determine whether improvements in PANSS symptom domains predict the likelihood of staying on treatment and whether differential responses to treatment with various atypical antipsychotics in specific symptom domains account for differences in discontinuation rates or persistence on treatment. Methods: A post hoc analysis of pooled data from 5 randomized, double-blind, 24- to 28-week clinical trials in adult patients with schizophrenia was conducted that included 1103 olanzapine-treated and 1090 risperidone-, quetiapine-, ziprasidone, or aripiprazole-treated patients. The 5 factors of the Positive and Negative Syndrome Scale (PANSS) were tested as potential predictors of persistence on treatment for all treatment groups combined. Treatment differences in the 5 PANSS factors and individual items were assessed between olanzapine and the other 4 atypical antipsychotics combined. Results: Improvement in the PANSS positive factor was the strongest predictor of persistence on treatment irrespective of the specific medication (based on standardized scores, hazard ratio [HR] = 1.58; 95% confidence interval [CI] = 1.40 1.79; $P < .0001$). Improvement in the PANSS hostility (HR = 1.23; 95% CI = 1.11, 1.37; $P = .0001$) and depressive (HR = 1.15; 95% CI = 1.05, 1.2;

$P = .0021$) factors were also significant predictors, to a lesser degree, while the negative and disorganized thoughts factors were not. Olanzapine-treated patients showed significantly greater improvements at week 24 on the PANSS positive, hostility and depressive factors compared to patients treated with other antipsychotics ($P < .001$ for all 3 factors). In particular, a significant difference on the hallucination item was observed at week 2 and was sustained throughout the treatment period. Conclusion: The results suggest that significant improvement in positive symptoms may be the best predictor of persistence on treatment, followed by significant improvement in hostility and depressive symptoms. Patients treated with olanzapine experienced greater improvements in these specific symptom domains compared to other atypical antipsychotics. These findings may add to our understanding of why olanzapine-treated patients are more likely to continue on treatment.
ID: 551182

DOES ZIPRASIDONE WORK BETTER IN LESS SEVERELY ILL PATIENTS OR IN OLDER PATIENTS?

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This trial aimed to study State Hospital patients switched to ziprasidone to see why it was not more widely used. Subjects from three State Hospitals who needed a change of antipsychotic participated. For reasons unrelated to this study one site (C) only recruited four subjects; a second (B) only recruited outpatients; the third (A) only recruited inpatients. All subjects were evaluated before the start and at weeks 1, 2, 4, 6 and 8. If on two antipsychotics one was stopped before starting ziprasidone the second halved three days after starting and stopped four days later. Ziprasidone (bid) was 80mg on day 1, 160mg day 2 and could be increased to 240mg after three weeks. 39 subjects were recruited. The 17 outpatients from site B were very different from the 18 inpatients at site A: aged 53 (32 at A), all but two white (all but two African-American and Hispanic at A) and with a baseline PANSS of 69 (92 at A). Fifteen relapsed early. The inpatients that completed at site A barely improved (PANSS 90). At site B the completers improved significantly ending with PANSS of 56. Reduction in PANSS score was significantly related to age but not to initial PANSS score or to previous medication dosage. Subjects as a group reduced their prolactin level (45 to 22), improved metabolic measures but prolonged their QTc (404 to 418). At site B outpatients did well on ziprasidone. At all sites metabolic indicators improved. Continuing the original antipsychotic longer could perhaps have prevented relapses. This study suggests that less severe subjects do not respond better but that older subjects may do so. However this could be confounded by other differences between these outpatients and inpatients especially taking the medicine with food. Such studies in the future should have blood levels to assure equal absorption. Supported by a grant from Pfizer Inc.
ID: 551168

DISCONTINUATION CHALLENGE IN REMITTED FIRST EPISODE PSYCHOSIS: RELAPSE RATES AND FUNCTIONAL OUTCOME COMPARED WITH MAINTENANCE TREATMENT

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Objective: To compare the consequences of guided discontinuation strategy and maintenance treatment in remitted first episode psychosis in terms of relapse rates and functional outcome. Method: The study was conducted in seven mental health services, covering a catchment area of 3.1 million inhabitants. A sample of 131 remitted first episode patients, aged 18–45 years, diagnosed with schizophrenia or related psychotic disorder was included. After six months of positive symptom remission they were randomly and openly assigned to discontinuation strategy or maintenance treatment. Maintenance treatment was carried out according to APA-guidelines, preferably using low dose atypical antipsychotics. Discontinuation strategy was carried out by gradual symptom-guided tapering of dosage and discontinuation if feasible. Follow-up was eighteen months. Main outcome measures were relapse rates, and social and vocational functioning. Results: Twice as many relapses occurred in discontinuation strategy (43% vs. 21%, P = .007). Of patients who received the strategy 20% were successfully discontinued. Recurrent symptoms caused another 30% to restart antipsychotics, while in the remaining patients discontinuation was not feasible. The difference regarding functional outcome was a trend favoring discontinuation strategy in holding a job 16 hours a week (OR = 2.4, P = .06). Conclusions: Only a limited number of patients can be successfully discontinued. High relapse rates do not allow discontinuation strategy to be universal practice. However, if relapse risk can be carefully managed by close monitoring, in some remitted first episode patients guided discontinuation strategy may offer a feasible alternative to maintenance treatment. Further research is needed to find predictors of successful discontinuation.
ID: 551165

THE OPUS -TRIAL; A RANDOMISED MULTI-CENTRE TRIAL OF INTEGRATED VERSUS STANDARD TREATMENT FOR PATIENTS WITH A FIRST EPISODE OF PSYCHOTIC ILLNESS—FIVE-YEARS FOLLOW-UP

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Context: Intensive early treatment for first episode psychosis have shown to be effective. It is unknown if the positive effects are sustainable at five-year follow-up. Objective: To determine long term effects of intensive early intervention programme (OPUS) for first episode psychotic patients. Design: Single-blinded randomised controlled clinical trial of two years of intensive early intervention programme versus standard treatment. Follow-up was two and five years. Setting: Copenhagen Hospital Corporation and Psychiatric Hospital Aarhus, Denmark Patients: 547 patients with a first episode of psychosis. Participation was 369 patients at two-year follow-up and 301 at five-year follow-up. All 547 patients were followed for five years in the registers. Interventions: Two years of intensive early intervention programme (OPUS) versus standard treatment. OPUS treatment consisted of ACT with manuals for family involvement and social skills training. Standard treatment offered contact with a community mental health centre. Main Outcome Measures: Psychotic and negative symptoms, secondary outcome measures were service use and social functioning. Results: Analysis was based on the principles of intention to treat. Assessment was blinded for previous treatment allocation. At five-year follow-up we found that the effect of the treatment seen after two years (psychotic dimension; −0.32 95% CI = −0.58 to −0.06, P = .02, negative dimension; −0.45 95% CI = −0.67 to −0.22, P = .001) had equalized between the treatment groups. A significant smaller percentage of patients from the experimental group were living in supported housing (4 % vs. 10%, OR 2.3, 95% CI = 1.1 to 4.8, P = .02) and were hospitalized fewer days (mean days 149 vs. 193, mean difference 44, 95% CI = 0.15 to 88,12 P = .05) in the entire five-year period. All other social outcome measures showed no significant differences between the groups. Conclusions: The intensive early intervention programme improved clinical outcome after two years of treatment, but the effects were not sustainable up to five years after. We found a difference on supported housing and use of bed days at the five-year follow-up in favour of intensive early intervention programme.
Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial.

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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY TO ASSESS EFFICACY AND SAFETY OF PALIPERIDONE PALMITATE IN ADULT SUBJECTS WITH SCHIZOPHRENIA

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Efficacy and safety of 3 fixed doses of the investigational, injectable atypical antipsychotic paliperidone palmitate (PALM) vs placebo (PBO) were assessed in a 13-week, double-blind, multicenter study in subjects with DSM IV schizophrenia. Adult subjects with acute exacerbation of schizophrenia were randomly assigned in a 1:1:1:1 ratio to fixed dose PALM 25, 100, 150mg eq. or PBO. PALM groups received an initiation dose of PALM 150mg eq. in the deltoid muscle on Day 1, followed by the assigned fixed dose (deltoid or gluteal muscle) on Day 8, and every 4 wks thereafter. ITT analysis set (n = 636) included 67% men and 54% white (30% black); mean (±SD) baseline PANSS total score = 87.1(±11.21). Mean (±SD) changes in PANSS total score from baseline to end point (primary outcome) showed significant reductions ($P \leq .034$) in a dose-related manner for all 3 PALM groups vs PBO: 25mg eq. = −8.0 ± 19.90; 100mg eq. = −11.6 ± 17.63; 150mg eq. = −13.2 ± 18.48 vs PBO (−2.9 ± 19.26). Significant improvement in PANSS total score was observed at Day 8 for PALM 25mg eq. and 150mg eq., and at Day 22 for all PALM groups vs PBO and maintained thereafter. Dose-related improvement in mean Personal and Social Performance (PSP) scale scores was observed among PALM groups (25mg eq. = 2.9 [P = .509]; 100mg eq. = 6.1 [P = .007]; 150mg eq. = 8.3 [P < .001]) vs PBO (1.7). Treatment-emergent AEs (TEAEs) occurred at similar rates among PALM groups (60.0–63.2%) and PBO (65.2%). Among the most common TEAEs, events that occurred ≥2% more frequently with PBO than PALM (total group), were: insomnia (16.5 vs 11.5%) and schizophrenia (11.6 vs 8%). The incidence of serious TEAEs was higher with PBO (14.0%) than any PALM group (25mg eq. = 9.4%, 100mg eq. = 13.3%, 150mg eq. = 8.0%). The incidence of EPS-related TEAEs was low; akathisia was the most frequently reported EPS-related AE across all groups (PBO = 4.9%, 25mg eq. = 1.3%, 100mg eq. = 4.8%, 150mg eq. = 5.5%). Incidence of ≥7% weight increase was dose-related with PALM (25mg eq. = 6%, 100mg eq. = 8%, 150mg eq. = 13%) vs PBO (5%). Local injection site tolerability was good. PALM treatment was safe and effective in subjects with acute exacerbation of schizophrenia when initiated with a 150mg eq. dose in the deltoid muscle (Day 1) followed by 25–150mg eq. doses monthly, beginning on Day 8 in deltoid or gluteal muscle. There was a dose-response in primary and secondary efficacy endpoints (PANSS and PSP), and there were no unexpected AEs. The benefit/risk profile of PALM was favorable.
ID: 551118

FAMILY MOTIVATION INTERVENTION IN EARLY ONSET PSYCHOSIS AND CANNABIS ABUSE: A RANDOMIZED CLINICAL TRAIL

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There is a high prevalence of cannabis abuse in individuals with schizophrenia and related disorders. This is unfortunate as it has been found that cannabis abuse is an independent risk factor for aggravation of psychotic symptoms, longer treatment duration, more re-admissions and poorer treatment compliance. For relatives of patients with schizophrenia it is often frustrating that the patient seems unwilling to change the cannabis use, even when the negative consequences are so obvious. As a result most relatives develop a highly critical attitude towards the cannabis use, which in turn evokes more resistance to change in the patient. In the Amsterdam Adolescent Clinic we designed an innovative family group intervention called Family Motivational Intervention (FMI). FMI combines evidenced based insights from motivational interviewing, psychoeducation and family interventions into one integrated approach. We hypothesize that training parents in a motivational approach will ameliorate their interaction with the patient and facilitate positive behavioural changes in patients with early onset psychosis. A total of 85 relatives of 53 patients with early psychosis were randomly assigned to psychoeducation only (PE) or to FMI. Outcome measures were changes in cannabis use and in compliance, consequences for caring and needs, and consequences for the interaction between patient and carers. Preliminary results of the first two FMI groups show that 44% patients in the FMI group ($n = 15$) reached abstinence in cannabis use at the end of treatment compared to 18% in the PE group ($n = 17$). Other benefits of FMI included an increase in percentage of days the patient were abstinent from cannabis. No significant differences were found between the groups in changes in use of other substances and in compliance to medication. With regard to the relatives, there were no significant difference between PE ($n = 22$) and the FMI ($n = 24$) groups concerning consequences for caring and needs. These preliminary findings suggest that teaching relatives motivational techniques is beneficial over psychoeducation only in reducing cannabis use in patients with recent onset psychosis. Although, our family intervention did not show advantages over psychoeducation in reducing carers concern and needs. At this moment we are completing the data set to establish the overall effectiveness of FMI.
ID: 551039

QUETIAPINE FOR THE TREATMENT OF PATIENTS WITH SCHIZOPHRENIA AND ALCOHOL USE DISORDERS

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Preliminary studies suggest that quetiapine, a mixed dopaminergic and serotonergic agent used for the treatment of psychosis, may decrease substance use or craving for substances in patients with schizophrenia. We report here on an open label, 3-month study of 23 patients with schizophrenia or schizoaffective and co-occurring alcohol use disorder conducted at two sites. Results for the 17 study subjects who completed at least one month of quetiapine treatment (mean dose 472 ± 255 mg) revealed that psychiatric symptoms improved (mean total PANSS changed from 73.41 ± 16.9 to 62.94 ± 17.72; $t = -2.72$, $df = 16$, $P = .015$). Due to substantial site differences, drinking outcomes are reported separately for the two study sites. At Site 1 ($N = 11$), mean days of drinking each week did not change significantly (3.18 ± 1.63 to 2.71 ± 2.32, $t = 1.2$, $df = 10$, $P = .26$). At site 2 ($N = 6$) mean days of drinking dropped from 3.42 ± 1.32 to 0.37 ± 0.35, $t = 6.1$, $df = 5$, $P = .002$. In that site, the majority of patients (83.3%) were in a psychiatric unit prior to medication initiation. Additionally, other site differences were present. Conclusion: Quetiapine may have a positive impact on psychiatric symptoms and on alcohol use in patients with co-occurring schizophrenia and alcohol use disorder but significant site differences impact our ability to interpret the findings of this pilot study. Randomized, controlled trials are needed to clarify, confirm and extend these findings.
ID: 550966

PRIOR PARTICIPATION IN CLINICAL TRIALS IN SCHIZOPHRENIA: HOW COMMON IS IT?

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Background: As documented in a recent article , there has been a historical reduction in the drug-placebo difference in multicenter trials of antipsychotic medications in schizophrenia. Many possible explanations for this finding have been raised, including the fact that clinical trial subjects may have different characteristics. One possible difference between subjects entering clinical trials now and those who entered earlier clinical trials may be prior participation in a clinical trial. We examined data obtained during screening of patients for a global clinical trial to determine the extent to which subjects had been involved in a previous clinical trial for schizophrenia. Additionally, we describe how subject trial experience varied across geographical regions. Methodology: The clinical trial examined was of 6-weeks duration and enrolled patients with an acute exacerbation of schizophrenia. One of the protocol criteria excluded subjects who had participated in a trial within 6 months of screening. Screening data included whether the subject had participated in a prior clinical trial for the treatment of scizophrenia. These forms were examined on all subjects screened. Results:Number of Subjects (Percentage) with Prior Trial Experience In Region: US 45/86 (52%) Russia 16/75 (21%) Ukraine 2/49 (4%) India 1/60 (2%) All Subjects 64/270 (24%). Conclusions: This data demonstrates that prior trial experience of subjects varies significantly based on geographical region with over half of the US subjects screened having reported prior participation in a clinical trial for the treatment of schizophrenia. These data underscore the importance of further careful study of the characteristics of clinical subject entering clinical trials.

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ID: 550959

GROUP COGNITIVE BEHAVIORAL SOCIAL SKILLS TRAINING FOR SCHIZOPHRENIA

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The majority of clinical trials of cognitive behavioral therapy (CBT) for schizophrenia used an individual therapy, but some promising results have been reported using group therapy. Group CBT tends to be more common in the U.S. than in the U.K. One important difference between group and individual CBT is that groups tend to emphasize skills training over detailed case formulation. There is less time in groups to fully explore the

unique content and history of each person's belief system. Group therapy is also a useful format for behavioral skills training, like social skills training. Social functioning is also a more common treatment target in the U.S. than in the U.K., where positive symptom reduction is the predominant primary treatment target. An example of a more behavioral group CBT approach that targets psychosocial functioning in the U.S. is cognitive behavioral social skills training (CBSST). CBSST is a 24 to 36 session weekly group therapy intervention that combines cognitive therapy with social skills training and problem solving training to improve functioning in people with schizophrenia. Behavioral practice of communication skills and goal-focused problem-solving skills are combined with practice of thought challenging skills. A focus of CBSST is on challenging thoughts that interfere with use of skills in the community (eg, "I will be harmed if I go out;" "It won't be fun;" "I won't be able to do it"). By challenging these dysfunctional performance beliefs and illness-related thoughts (eg, paranoia) that interfere with the execution of everyday activities, participants are more likely to engage in community functioning activities. In a randomized controlled trial that compared treatment as usual (TAU) with TAU plus group CBSST in 76 outpatients with chronic schizophrenia, participants in CBSST groups showed significantly greater self-reported independent community functioning, but not symptoms, than participants in standard care, and improvements in functioning were maintained at 1-year follow-up. Similar greater benefit for functioning than for symptom outcomes was found at end of treatment in a second trial of 90 people with schizophrenia randomized to CBSST or a supportive goal-focused contact control condition. In contrast to U.K. CBT interventions for psychosis, which typically show greater benefit for symptoms than for functioning, group CBSST developed in the U.S. showed greater benefit for functioning than for symptoms.
ID: 550952

A COMPREHENSIVE RETROSPECTIVE AUDIT OF THE USE OF RISPERDAL CONSTA IN AN AREA MENTAL HEALTH SERVICE IN MELBOURNE, AUSTRALIA

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Background: Risperdal Consta is the first depot atypical antipsychotic on the market. Early use of new medications is often a matter of trial and error, until real world usage data becomes available. Aim: To investigate how Risperdal Consta has been used during the 1st 12 months after release on the PBS in patients with schizophrenia, and to describe patient outcomes. Method: Medical records of all clients initiated on RC during the first 6 months after approval on the PBS were reviewed for 12 months pre RC, and 12 months post RC. Data captured pre and post RC included; pharmacotherapy, hospitalisations, adherence, substance use, reason for switch to RC, start dose of RC, location of initiation, and length of treatment on RC. Results: 141 files were reviewed. Mean age was 40.4 years. Two thirds were men. Mean duration of illness was 12 years. 85% had been hospitalised in the 2 years prior to RC, but only 45% were hospitalised post RC. Previous primary AP's were oral risperidone 28%, Zuclo deconoate 22%, and lanzapine 16%. 70% of clients were initiated on RC while inpatients, 80% of clients had 2 or less dose changes of RC in the 1st 12 months. More than 35% of clients were continuing on RC after 12 months. 81.5% of clients received some concomitant oral antipsychotics medications during the 1st 12 months, most commonly oral risperidone (76%). 10.4% of clients were reported to have good adherence pre RC compared while 70.4% had good adherence post RC. The most common reason for discontinuation of RC was inadequate response (43%), and the most common AP post RC was clozapine (33%). Conclusion: This study provides real world data about

the use of RC in an Area Mental Health Service, which will help guide clinicians in the use of this medication in treating patients with schizophrenia.
ID: 550935

TRANSLATION AND CULTURAL ADAPTATION OF THE MATRICS CONSENSUS COGNITIVE BATTERY

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The development of the MATRICS Consensus Cognitive Battery (MCCB) established a "gold standard" cognitive endpoint for clinical trials of treatments that target the core cognitive deficits of schizophrenia. Use of this standard battery allows reliable and valid measurement of seven key cognitive domains and valid comparisons across different clinical trials. The current applications of the MCCB in English in several clinical trials have made clear that availability of the MCCB in multiple languages is now a key issue, as it will be used in numerous international clinical trials. This presentation describes the steps that have been taken over the last two years to translate and culturally adapt the MCCB for five initial languages (simplified Chinese, German, Hindi, Russian, and Spanish), plus three dialects of Spanish for Central and South America. To ensure a high-quality MCCB version in each language that complies with copyrights, the process has involved multiple steps of professional forward translation, back translation, reconciliation of differences, evaluation by native language psychologists/psychiatrists, review and approval by the original test developers and intellectual property owners, pilot testing, and page composition/printing. This presentation will describe examples of issues that arise in translation and cultural adaptation of cognitive performance measures and ways to successfully resolve them. The presentation will also focus on the ongoing steps to develop norms for the MCCB in these languages. The progress of academic researchers who are translating the MCCB into a number of additional languages will be summarized. Together these steps are furthering a key NIMH goal for the MATRICS initiative—to facilitate the evaluation of promising new treatments for the core cognitive deficits of schizophrenia.
ID: 550920

FOLLOW UP OF PATIENTS WITH TREATMENT REFRACTORY SCHIZOPHRENIA AFTER A SOCIAL LEARNING PROGRAM

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Since the 1970s, research shows that social learning programs (SLPs, token economies) effectively transition chronically hospitalized patients with schizophrenia to the community. A major criticism of SLPs is the benefits do not continue in the community since the behavioral interventions are no longer present. The Second Chance Program (SCP) is an inpatient SLP located at a private academic hospital. Most patients come from NY state hospitals (80%). Admission criteria are willingness to come, primary psychotic disorder, and no recent sustained community tenure. Most patients have been institutionalized the majority of their adult lives, 2/3 are male, 2/3 have substance abuse histories, and approximately 1/2 have criminal histories. The length of stay is 6 to 12 months. The SLP focuses on skill training in areas such as ADLs and rewarding community appropriate behaviors. Pharmacology is optimized with about 2/3s of patients being on clozapine. For this study, patients received routine clinical care by community

providers and were tracked in the community. METHODS: Consenting patients are administered a baseline assessment (T0) upon discharge from the SCP. This battery assesses symptoms (BPRS and SANS), subjective well being, independent living skills (ILSS), and quality of life. Patients are followed at 6 and 12 months post-discharge. Only 6 months data (T1) are currently available. Results: In the last 5 years, 156 patients have been discharged from SCP; 86% were discharged to the community; of these, 22% relapsed and returned to SCP. Most of these patients were subsequently discharged back to the community. 34 patients consented for the study. At 6 months, 20 were still in their placements while the others had been rehospitalized or had left the residential program. Of these, 12 were available and completed their 6-month follow-up. There was no significant difference from baseline to 6 months in symptoms, as measured by the BPRS ($T0 = 52.6$, $T1 = 46.1$, $P = .119$) and SANS ($T0 = 28.1$, $T1 = 29.7$, $P = .744$). Quality of life remained the same ($T0 = 5$, $T1 = 5.9$, $P = .121$). The ILSS showed no significant changes in hygiene ($T0 = 93.2$, $T1 = 92.5$, $P = .795$) or personal appearance ($T0 = 96.1$, $T1 = 97.5$, $P = .576$). Conclusion: These results show the benefits of a SLP continue in the community even with no additional reinforcement of the skills learned. Symptoms as well as important skills such as ADLs are maintained during this time for those patients, who were available at follow-up.
ID: 550885

LURASIDONE FOR SCHIZOPHRENIA: SYMPTOMATIC REMISSION DURING SHORT-TERM TREATMENT

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Background: Lurasidone is a novel psychotropic agent with high affinity for D_2 and $5\text{-}HT_{2A}$ receptors, as well as for receptors implicated in enhancement of cognitive function (partial agonist at $5\text{-}HT_{1A}$; antagonist at $5\text{-}HT_7$). In this analysis, we investigated rates of symptom resolution for lurasidone treatment, using data from a double-blind, placebo-controlled, 6-week trial in hospitalized patients with schizophrenia. Methods: Adult outpatients were recruited who were hospitalized for an acute exacerbation of schizophrenia meeting DSM-IV criteria. After completing a single-blind, 3–7 day placebo washout period, eligible patients were randomized to 6 weeks of fixed-dose treatment with lurasidone 40 mg ($N = 50$; baseline PANSS total, 92.8), lurasidone 120 mg ($N = 49$; PANSS total, 89.6), or placebo ($N = 50$; PANSS total, 93.3). Symptomatic remission was defined, using consensus criteria (Andreasen et al. Am J Psychiatry 2005;162:441–449), as an LOCF-endpoint score $\leqq 3$ (mild or less) on 8 core PANSS items (P1-3, G5, G9, N1, N4, N6). Results: Treatment with lurasidone (40 mg and 120 mg, respectively) was associated with significantly greater LOCF-endpoint improvement than placebo on the PANSS total score (-12.9 and -16.1 vs. -5.7; $P < .05$ for both comparisons to placebo). Treatment with lurasidone 120 mg or 40 mg was also associated with significantly higher remission rate at endpoint compared to placebo (31% and 34% vs. 6.1%; $P < .01$). Number needed to treat rates (NNT [95%-CI]) for achieving remission were similar for lurasidone 40 mg (NNT = 4.0 [3, 10]), and lurasidone 120 mg (NNT = 3.6 [2, 8]). A significantly higher proportion of patients treated with lurasidone 120 mg completed the 6-week study and met criteria for remission compared to placebo ($P = .02$), a numeric trend favoring LUR 40 vs. placebo was found ($P = .08$). Conclusion: In this short-term, placebo-controlled, phase 2 trial, the novel psychotropic lurasidone was associated with higher remission rates than placebo. Further studies are underway to fully characterize lurasidone's clinical profile and dose-response characteristics.
ID: 550841

EFFECT OF ARIPIPRAZOLE VS HALOPERIDOL ON PANSS PROSOCIAL ITEMS IN EARLY EPISODE PATIENTS WITH SCHIZOPHRENIA

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Previous work has demonstrated that a certain negative symptoms show little change with antipsychotic drug treatment. Other work has shown that relatively small improvement in these symptoms appear to be correlated with larger change in function. Thus these residual symptoms may pose an important barrier to functional recovery. Clinical reports have suggested a specific benefit from aripirazole in some patients on these "barrier symptoms." To assess this observation, we compared the effect of aripirazole vs haloperidol in early episode patients with schizophrenia on relevant PANSS items using two PANSS scales, the Prosocial scale and a modified Proscial scale. Early episode was defined as less than or equal to 40 years of age, and less than or equal to five years since first diagnosis. The PANSS Prosocial subscale consists of six PANSS items broadly related to social engagement (1), the modified prosocial subscale consists of four PANSS items, including difficulty with abstract thinking, anitem not contained within the prosocial subscale but an empirically demonstrated prominent residual symptom. Measurements were taken at approximately monthly intervals for up to one year. Least square mean changes from baseline in both groups were compared for each subscale using an ANOVA model with last observation carried forward. Aripiprazole demonstrated significant improvements vs haloperidol as early as week 18 on both the prosocial subscale (-4.75 for aripiprazole ($n = 237$) vs -3.78 for haloperidol ($n = 123$, $P < .05$)) and on the modified prosocial subscale (-3.16 for aripiprazole vs -2.27 for haloperidol $P < .05$). Patients showed similar significant improvements over time at all remaining testing intervals through week 52 using the modified subscale, but less consistent improvement over time with the prosocial subscale. Similar significant improvements at weeks 46 and 52 (endpoint) were observed with both subscales. In patients with early episode schizophrenia, aripiprazole demonstrates greater improvements in prosocial PANSS items than haloperidol. The cognitive and functional implications of these findings remain to be clarified in future prospective studies.

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MODAFINIL IMPROVES WORKING MEMORY AND EMOTIONAL FACE RECOGNITION IN FIRST EPISODE PSYCHOSIS

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Cognitive and emotional impairments are important determinants of functional outcome in schizophrenia. People suffering from first-episode

psychosis (FEP) also show these dysfunctions and current antipsychotic drugs do not help. Modafinil is a wake-promoting drug commonly used for sleep disorders. Modafinil can enhance mood, attention, memory and executive functions in healthy volunteers, schizophrenia and bipolar depression. Following the research into the effects of modafinil in chronic schizophrenia, we aimed to establish the role of modafinil in the adjuvant treatment of schizophrenia in the FEP, a time when strict diagnosis is often difficult to establish but when therapeutic endeavor is arguably most vital. A within-subject, randomized, double-blind, placebo-controlled crossover study was carried out. To date, 27 patients attended on two occasions separated by at least one week. On each occasion, patients received either a single dose of 200 mg modafinil or a placebo prior to cognitive assessment. Our preliminary results show that a single dose of modafinil significantly improved digit backward ($P = .016$). Modafinil showed significant improvement in face recognition for baseline low performers ($P = .028$), but not for high performers. There was a trend for an improvement in emotional face recognition with modafinil ($P = .053$) and a significant improvement in recognition of sad faces ($P = .008$). Modafinil showed a significant improvement in emotional face recognition ($P = .042$) for high performers when groups were segregated. Modafinil improves working memory in the FEP, confirming the results found in chronic schizophrenia. But, more interestingly, modafinil also improves face recognition for low performers, who probably have more difficulties in this type of processing. Modafinil improves emotional face recognition, and this is particularly true for high performers. Low performers are impaired in face recognition, which is improved by modafinil but does not seem enough to improve their ability in recognizing emotional faces. Conversely, high performers do not seem to need help for recognizing faces, but modafinil does help them in the discrimination of emotional faces.
ID: 563567

TELEHEALTH MONITORING OF PATIENTS WITH SCHIZOPHRENIA AND SUICIDAL BEHAVIOR

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Suicide is the leading cause of premature death in patients with schizophrenia. This project evaluates feasibility and impact of implementing a specialized telemental health case management program using the ''Health Buddy'' (HB) to reduce suicidality among patients with schizophrenia. We hypothesized that use of this device would result in a greater decrease in psychiatric symptoms for patients with schizophrenia recently hospitalized for escalating suicidality. Subjects with ages > 17 years with schizophrenia were admitted for worsening suicidal ideation or recent suicide attempt. In addition, patients had scores > 0 on items 4 and/or 5 from the Scale for Suicidal Ideation (SSI). Exclusion criteria: a) MMSE score < 20, b) a serious active medical or other psychiatric disorder which could impact diagnosis, safety, or anticipated adherence. Subjects were randomly assigned to receive 24-week intensive case management (ICM; weekly face-to-face assessments and twice weekly phone calls for safety monitoring by outpatient nursing staff) or 24-week ICM with the addition of the HB. Frequency of contact was decreased contingent on suicidal ideation. Subjects assigned to the HB condition provided daily reports of depressive and suicidal symptoms; this was monitored by inpatient nursing staff twice per

8 hour shift over a 24-hour period. Repeated measures ANOVA was used to measure treatment differences in symptom change for HB versus control (CON) cases from baseline to Month 1 and Month 2 on the SSI, the Calgary Depression Rating Scale , Clinical Global Impressions, and the Scale for Positive Symptoms. Out of 186 patients screened, 32 had recent escalation of suicidal ideation or suicide attempt. Seventeen patients signed informed consent and 13 were randomized to treatments: 7 to the Health Buddy (HB) group and 6 to the control (CON) group. Preliminary findings reveal relatively good adherence to use of the Health Buddy (rates ranged from 87–100% over month 1 and 78% to 100% over month 2). After 2 months there were greater improvements in suicidal ideation ($P = .04$) and positive symptom ($P = .02$) scores for HB subjects relative to CON patients. These preliminary findings suggest that patients show relatively high levels of adherence to HB monitoring and that HB monitoring over 2 months is associated with more rapid remission of suicidal ideation among patients with schizophrenia recently discharged from the hospital for treatment of suicide.
ID: 554174

MULTI-REGIONAL BRIDGING STUDIES: COMPARING EFFICACY AND TOLERABILITY OF INTRAMUSCULAR/ORAL ZIPRASIDONE AND HALOPERIDOL IN ASIA TO EUROPE/SOUTH AMERICA

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Background and Aims: Availability of second-generation antipsychotics (SGAs) in Asian countries has lagged behind in the United States, Europe and South America because there have been limited numbers of adequate, well-controlled studies of efficacy and tolerability in these patient populations. ICH E5 has provided some guidance for use of multi-regional bridging studies to support global drug development that could remedy this problem. There are methodological questions about how to design such studies and combine evidence from studies in different ethnic groups and regions. Two identically designed randomized clinical trials of IM/oral ziprasidone and haloperidol conducted in Asia and Europe/South America provide the opportunity to synthesize results of an initial and replication bridging study. Methods: IM/oral ziprasidone ($N = 130$) was compared to IM/oral haloperidol ($N = 122$) in a 6-week,randomized trial in acute schizophrenia conducted in Hong Kong, Malaysia, Philippines, Singapore, Taiwan and Thailand. The study replicated an identically designed randomized trial conducted in Europe and South America (79% Caucasian, $N = 600$) (Brook et al. 2005). The weighted Z-test method (Lan et al. 2005) was applied to synthesize the ANCOVA results from Asian bridging and initial European/South American studies. Results: At the end of IM treatment ($<= 3$ days), mean change in BPRS total score was -7.7 in the ziprasidone group compared with -5.8 in the haloperidol group ($P = .066$), and the magnitude of treatment difference (LS mean -1.9; 95% CI [$-3.9, 0.1$]; $Z_{Asian} = -1.832$) was similar to that observed in (Brook et al. 2005) (LS mean -2; 95% CI [$-3.3, -0.8$]; $Z_{Foreign} = -3.149$). The combined weighted Z-statistics for the two studies combined was $Z_{Weighted} = -3.17$ ($P < .001$). At endpoint, between-group differences in BPRS total score and COVI scores were not significant ($P > .74$) within studies and in combined studies. Ziprasidone was significantly superior to haloperidol in movement disorder related measures (ESRS and Barnes Akathisia Scales) and EPS adverse event rates (4.6% vs. 22% in the IM phase; 20% vs. 61% in the IM and oral phases). Conclusions: These findings demonstrate consistent efficacy and tolerability

advantages of ziprasidone over haloperidol in different ethnic groups, and support extrapolation of bridging evidence from the initial European/South American study to Asian patients with schizophrenia.
ID: 553531

PSYCHOSOCIAL INTERVENTIONS: IGNORE THEM AT YOUR PERIL

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The effectiveness of specific psychological interventions, such as cognitive therapy, for full psychosis is established, although systematic review shows the effect size to be moderate at best and is smallest in the most rigorously designed trials. One problem with interpreting the data is that psychological treatments are always delivered in the presence of antipsychotic drug treatments and the role of non-specific effects and whether the effect might be explained by improved drug adherence. The use of cognitive therapy in at risk mental states allows an estimate of the effectiveness of such treatments for psychotic symptoms in patients who are free of drug treatments, and also allows for clearer testing of hypotheses about mechanisms of action. Data from the UK EDIE trial of cognitive therapy in ARMS ($n = 58$) and 3 year follow-up will be discussed, and the design of the multisite EDIE 2 randomised controlled trial currently in progress will be presented. No accepted clinical guidelines for the treatment of people with ARMS yet exist. Several factors suggest psychological interventions, should their effectiveness be confirmed, be the first line approach in a stepped care model. Trial data suggest them to be more acceptable than drug treatments and the number needed to harm (NNH) is likely to be lower. Clarification of the clinical target is important and reduction of current symptoms is likely to be of more relevance than prevention of full psychosis. Reliable population attributable risk estimates are still needed to allow the impact of successful treatment on the wider incidence of psychosis to be assessed.
ID: 552588

RISK VS BENEFIT: CLINICAL STAGING AS A GUIDE TO THE USE OF ANTIPSYCHOTICS AND OTHER STRATEGIES IN PREPSYCHOTIC ILLNESS

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Diagnosis in psychiatry increasingly struggles to fulfill its key purposes, namely to guide treatment and to predict outcome. The clinical staging model, widely used in clinical medicine yet virtually ignored in psychiatry, is proposed as a more refined form of diagnosis which promotes early intervention and also make more sense of the confusing array of biological research findings in psychiatry by organising data into a coherent clinico-pathological framework. Clinical staging has immediate potential to improve the logic and timing of interventions in psychiatry just as it does in many complex and potentially serious medical disorders. In particular it could prove a crucial guide for determining the sequence and timing of interventions in subthreshold psychotic and mood disorders disorder. Interventions can be evaluated in terms of their ability to prevent or delay progression from earlier to later stages of disorder, and selected on clearcut risk/benefit criteria. This framework can be used to study the timing of the use of antipsychotic and other drug and psychosocial therapies in people at incipient risk of transition to first episode psychosis. This presentation will review the available studies in UHR/CHR stages of illness and propose clinical guidelines for intervention.
ID: 552572

RELATIONSHIP BETWEEN ERYTHROCYTE MEMBRANE FATTY ACIDS AND TRANSITION TO PSYCHOSIS IN ULTRA-HIGH RISK INDIVIDUALS: BASIC RESEARCH FINDINGS FROM A RCT

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Introduction: Reduced erythrocyte membrane fatty acids, particularly arachidonic acid (AA) and docosahexaenoic acid (DHA), and an elevated omega-6:omega-3 ratio have been described in different stages of schizophrenia including drug-naive first episode samples. No study has yet examined (1) the erythrocyte fatty acid composition in the prodromal phase of psychosis, or (2) the relationship between fatty acids and transition to psychosis in ultra-high risk individuals. Methods: The study sample comprised 81 UHR individuals (according to criteria of Yung et al. 1998) (mean age = 16.4, SD = 2.1 years) who participated in a RCT of 1.2 g/day omega-3 fatty acids vs. placebo (ClinicalTrials.gov number, NCT00396643). Baseline measures included the PANSS, the MADRS, and the GAF. Erythrocyte membrane fatty acids were determined at baseline using gas chromatography. The primary outcome of interest, conversion to psychosis was operationally defined using cut-off points on the PANSS (4 or more on hallucinations, 4 or more on delusions and 5 or more on conceptual disorganisation), the frequency of symptoms (at least several times a week), and their duration (more than 1 week). Correlational analysis was used to detect associations between fatty acid levels and psychiatric measures at baseline. Cox regression analysis was used to investigate the predictive validity of baseline fatty acid levels for psychosis status at 12 month follow-up. Results: Low DHA ($P < .05$) and high n-6:n-3 ration ($P < .01$) correlated with more severe negative symptoms at baseline. Low trans-vaccenic acid ($P < .01$) correlated with more severe PANSS global symptoms at baseline. 93.8% participants (76/81) completed the intervention. By study end (12 months), 4.9% (2/41) individuals in the omega-3 group and 27.5% (11/40) in the placebo group made a transition to psychosis ($P = .004$). Cox regression analysis controlling for effects of treatment revealed low baseline trans-vaccenic acid as a significant predictor of transition to psychosis among investigated fatty acids in UHR individuals ($P < .05$), while both DHA and AA did not predict transition. Conclusions: The most important finding of the RCT is that a 12-week intervention with omega-3 fatty acids prevented the onset of psychotic disorder. However, the findings also suggest that abnormal membrane phospholipid metabolism may contribute to the onset of psychosis in UHR individuals. Supported by Stanley Medical Research Institute Grant 03-T315.
ID: 552510

PSYCHOLOGICAL AND PHARMACOLOGICAL INTERVENTIONS IN THE AT-RISK POPULATION. RESULTS OF COMPLETED AND THE RATIONALE OF ONGOING TRIALS AT THE FETZ

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The early detection and intervention center at the University of Cologne (FETZ) was founded in 1997. The UHR criteria as well as the predictive validity of the basic symptoms has been intensively researched. Moreover, one of the focuses has been the evaluation of psychological and pharmacological interventions in the at -risk population. CBT as well as antipsychotics (AP) have been found to at least delay the onset of first episode psychosis in people at risk. Recently the multicenter PREVENT-study commenced, which explores the differential treatment effects of CBT and AP in this population. This question has far reaching ethical, acceptance and compliance implications of the indicated prevention approach in general. The results of the intervention studies led by the FETZ will be presented as well as the rationale and the design of the recent PREVENT study.
ID: 552497

THE KEY TO EFFECTIVE PREVENTION OF PSYCHOSIS IS UNDERSTANDING AND TARGETING THE MECHANISMS UNDERLYING CLINICAL AND FUNCTIONAL DETERIORATION

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The psychosis prodrome is a clinical risk construct with modest ability to predict onset of psychosis. Its long-term promise is to facilitate recruitment of those at greatest risk into prevention trials. With no demonstrable prophylactic effects, and with little or no effect on motivational symptoms or functional disability, antipsychotic drug treatment is clearly not the 'silver bullet' of psychosis prevention. Specification of rational preventive interventions requires knowledge of the mechanisms underlying progression from prodromal to fully psychotic symptoms. In several recent studies, prodromal patients who progressed to psychosis showed differential profiles of neurobiological change compared with those who did not. In one study, converters showed a significantly greater rate of surface contraction in right prefrontal regions when compared directly with non-converters. The brain surface contractions in the converters resembled the patterns found in healthy controls and in first-episode schizophrenia patients. First-episode patients showed a significantly steeper rate of gray matter reduction than the healthy subjects, but in the same regions that healthy subjects evidenced maturation-related decline. In a study of white matter integrity, prodromal patients failed to show the normal increase in fractional anisotropy (FA) with age that was observed in the healthy adolescent control group, and lower FA in the patient group was predictive of poorer functional outcome at follow-up. Together, these findings suggest that regressive developmental processes active during late adolescence and early adulthood that are likely to result in reduced cellular connectivity (synaptic pruning and disrupted white matter development) may underlie the emergence and early course of psychotic symptoms. While the results of these studies are provocative in this regard, they are limited primarily by the small numbers of cases included, the uncontrolled nature of treatments received by the patients, and heterogeneity of outcomes among converters. To deliver on the promise of a prevention strategy for psychosis, the next wave of prodromal research must use very large samples and incorporate biological measures to identify the neurobiological mechanisms underlying the clinical and functional deterioration associated with psychosis onset and to develop modes of intervention that are theoretically predicted to prevent progression from a prodromal to fully psychotic state.
ID: 552379

THE PRODROMAL SYMPTOMS OF PSYCHOSIS: EXPERIENCES FROM THE TOPP CLINIC

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Background: This project is related to an ongoing international multi-site study testing the efficacy of Early Treatment and Intervention in schizophrenia (TIPS). Method: The project tests whether ''prodromal'' people (symptomatic, pre-psychotic) can be identified who are at very high risk for developing psychosis. The sample consists of treatment seeking patients aged 15–65 who are at very high risk for imminent conversion to psychosis. They are informed of their state of being at risk and recruited for a five year follow-along study with supportive psychotherapy, and assessment after 3 months, 1, 2 and 5 years. A Norwegian version of the SIPS (Structured Interview for Prodromal Symptoms) is used to assess conversion to psychosis. Results: 40 patients are included, during the first year of follow-up 8 cases have developed psychosis which equals 20%. We see a clear decrease in symptoms during the first 3 months of treatment. Approximately 50% participate in psychotherapy, antipsychotic medication is not prescribed. Conclusion: The conversion rate is lower than in similar international studies. This might be an effect of intensive psychotherapy or sample selection. Our experiences will be discussed with focus on psychotherapeutic processes. The study is supported by NARSAD (the National Alliance for Research in Schizophrenia and Depression).
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THE IMPACT OF GEOGRAPHY AND SOCIAL CONTEXT ON ULTRA HIGH RISK FOR SCHIZOPHRENIA RESEARCH IN RURAL AUSTRALIA

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Introduction: The Detection, Evaluation and Psychological Therapy (DEPTh) project, an Australian randomised controlled trial of cognitive behavioural therapy for ultra high risk (UHR) youths, began in 2006 across rural and urban sites. There are known difficulties in recruitment to UHR studies1 and a lack of research directed towards early intervention service delivery for rural youth. Factors that impact on UHR research in rural areas include limited specialist mental health services2, vast distances coupled with sparse population distribution, and the social context for rural youth3. Aim: This paper will present findings regarding recruitment and retention in treatment for DEPTh, focusing on the unique characteristics of the rural site, where no early intervention service or UHR research program existed prior to the study. Method: Recruitment at the rural site involved many non health youth services. Rural recruitment strategies involved: referrer education about UHR mental states; repeated promotion of the DEPTh project; extensive travel for staff; provision of comprehensive

assessment reports to referring agencies; case management; and enhanced interaction between research staff and referring agencies. Results: Stronger rural referral rates compared to urban were indicative of a lack of early intervention services. Rural participants were generally marginalised youth, often disengaged from "main stream" services, families and education. Clinical profiles showed some differences compared to the urban sample. Discussion: Geography, social context and presence of clinical services impact on the rate of recruitment as well as pathways and clinical profiles of youth for UHR research in rural areas. The use of videoconferencing and close linkage to existing mental health and youth related services facilitated recruitment and retention for DEPTh.

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