SATURDAY, MAY 3

PLENARY SESSION
Neural Development and Neurodevelopmental Disorders
Saturday, May 3, 2008 8:30 AM - 10:30 AM
Location: Regency Ballroom
Chair: Raquel Gur

697. Experience and Brain Development

Holly Cline

Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Hollis Cline is the Robertson Professor of Neuroscience at Cold Spring Harbor Laboratory. She is a recent NIH Director's Pioneer Awardee, is on the Board of Scientific Counselors for the NINDS and a previous Counselor of the Society for Neuroscience. Dr. Cline's research investigates mechanisms of brain development using in vivo imaging, electrophysiological recordings and molecular manipulations. She is particularly interested in the role of experience in shaping or modifying brain circuitry.

698. Tuning up Circuits: Brain Waves and Immune Genes

Carla J. Shatz

Stanford University, Stanford, CA

Carla Shatz is Professor of Biological Sciences and Neurobiology and the Director of Stanford University's Bio-X program. She studies how our early experiences change brain circuits during critical periods of learning and development. She received her Ph.D. in Neurobiology from Harvard Medical School and has held faculty appointments at Stanford, UC Berkeley and Harvard Medical School, where she was Chairwoman of the Department of Neurobiology until 2007. Her neuroscience research has advanced understanding of how connections between eye and brain are tuned up by use. She was the first to observe how, during fetal development, the eye tests its connections to the brain's visual processing regions by sending and resending waves of electrical activity through nerve cells across the retina. She has served as the President of the 38,000 member Society for Neuroscience, and has received many honors and awards, including being elected a member of the American Academy of Arts and Sciences, the National Academy of Sciences and the Institute of Medicine.

699. Critical Period Brain Development and Disorders

Takao Hensch

Harvard University, Cambridge, MA

Takao K. Hensch is joint Professor of Neurology (Children's Hospital Boston) at Harvard Medical School and Professor of Molecular and Cellular Biology (Center for Brain Science) at Harvard University. After his undergraduate studies on sleep mechanisms with Dr. J Allan Hobson at Harvard, he was a student of Dr. Masao Ito at the Univ Tokyo (MPH) and Fulbright Fellow with Dr. Wolf Singer at the Max-Planck Institute for Brain Research, prior to receiving a PhD in Neuroscience from the University of California San Francisco in 1996 working with Dr. Michael Stryker. He then helped to launch the RIKEN Brain Science Institute as Lab Head for Neuronal Circuit Development then served as Group Director since 2000. Hensch's research focuses on critical periods in brain development. By applying cellular and molecular biology techniques to neural systems, he identified inhibitory circuits that orchestrate the structural and functional rewiring of connections in response to early sensory experience. His work impacts not only basic understanding of brain development, but also the potential treatment for devastating cognitive disorders in adulthood. Hensch has received several honors, including the Tsukahara Prize (Japan Brain Science Foundation); Japanese Minister of Education, Culture, Sports, Science and Technology (MEXT) Prize; NIH Director's Pioneer Award and the first US Society for NeuroscienceYoung Investigator Award to a foreign scientist. He serves among others on the editorial board of J Neurosci (reviewing editor), *Brain Structure & Function, NeuroSignals, Neural Development, HFSP Journal and Neuron.*

700. Translating Between Genes, Brain, and Behavior: "Top-Down" and "Bottom-Up" Searches for Mechanisms in Schizophrenia and Williams Syndrome

Karen Berman

Section on Integrative Neuroimaging, National Institute of Mental Health, Bethesda, MD

Dr. Berman is the Chief of the Section on Integrative Neuroimaging in the Clinical Brain Disorders Branch and the Genes, Cognition, and Psychosis Program at the National Institutes of Health, NIMH Intramural Research Program. After receiving her M.D. degree at St. Louis University, she undertook a medical internship at Washington University in St. Louis and had residency training in psychiatry at the University of California at San Diego. Dr. Berman also completed residency training in nuclear medicine at the NIH Warren G. Magnusen Clinical Center and is board certified in both psychiatry and nuclear medicine. Among other awards, she has received the A.E. Bennett Award for Neuropsychiatric Research of the Society of Biological Psychiatry. Dr. Berman's research group conducts translational investigations, using multimodal neuroimaging to bridge the gap between neurogenetic, molecular, cellular, and system-level mechanisms of brain dysfunction and the cognitive and behavioral manifestations of neurosychiatric disorders neurodevelopmental and genetic sources such as schizophrenia and Williams syndrome, as well of other conditions impacting cognition such as normal aging. They also study the effects of gonadal steroid hormones on brain function. This body of work has been published in *Nature Neuroscience, Neuron*, the *Journal of Clinical Investigation*, the *Proceedings of the National Academy of Sciences*, and the *Journal of Neuroscience*.

PRESIDENTIAL INVITED LECTURE
Saturday, May 3, 2008 11:00 AM - 12:00 PM
Location: Regency Ballroom
Chair: Raquel Gur

701. Mental Disorders as Developmental Brain Disorders

Thomas R. Insel

NIMH, Bethesda, MD

Thomas R. Insel, M.D., is Director of the National Institute of Mental Health (NIMH), which leads the nation's research effort to understand, treat, and prevent mental disorders. Appointed as Director in 2002, Dr. Insel's association with NIMH actually spans over two decades, as he began his research career at the Institute in 1979, leaving it in 1994 to become Professor of Psychiatry at Emory University in Atlanta, Georgia. While at Emory he founded and led the Center for Behavioral Neuroscience, and continued his groundbreaking line of research, begun

at NIMH, on the molecular basis of social behaviors. Among Dr. Insel's many scientific achievements, he is perhaps best known for his research on oxytocin and affiliative behaviors. Dr. Insel identified the important role of neuropeptides such as oxytocin or vasopressin for social attachment in comparative neurobiological studies of monogamous mammals. This discovery led to greater understanding of the molecular and cellular basis of parental behavior, pair bonding, and aggression. A prolific author, Dr. Insel has published over 200 scientific articles and four books. He is a member of the Institute of Medicine, a Fellow of the American College of Neuropsychopharmacology, and the recipient of several awards. Dr. Insel graduated from the combined B.A.-M.D. program at Boston University.

WORKSHOP

Use of Epigenetic, Genetic, and Molecular Approaches in Suicide Research

Saturday, May 3, 2008 12:30 PM - 2:00 PM
Location: Yorktown
Chair: Yogesh Dwivedi*
Moderator: Ghanshyam N. Pandey**

*Supported by RO1MH068777
**Supported by RO1MH56528

702. Use of Epigenetic, Genetic, and Molecular Approaches in Suicide Research

Gustavo Turecki[1], Karoly Mirnics[2], Dan Rujescu[3], Yogesh Dwivedi[4]

[1]McGill Universuty, Canada, Montreal, QC, Canada, [2]Vanderbilt University and VU Kennedy Center, Nashville, TN, [3]Ludwig-Maximilians-University, Munich, Germany, [4]University of Illinois at Chicago, Chicago, IL

Novel mechanistic concepts of the neurobiology of suicide are rapidly evolving based on studies conducted in postmortem brain or in peripheral tissues of patients with suicidal ideation or of suicide attempters. One such recent breakthrough in understanding the neurobiology of suicide is associated with the recently observed abnormalities in the regulation of gene expression. Studies using cDNA microarray, epigenetic, and other molecular approaches, by revealing novel genes that may be undergoing regulation in suicide, have added new dimensions to the exploration of the neurobiology of suicide. Moreover, consistent evidence suggests that the predisposition to suicidal behavior has a genetic component and that genetic transmission of suicide risk is independent of the presence of mental disorders. The proposed workshop will detail recent crucial findings of suicide research utilizing epigenetic, genetic, and molecular approaches. Gustavo Turecki, MD, Ph.D., will present recent data of the epigenetic changes associated with suicide, particularly focusing on the polyamine system. Karoly Mirnics, MD, will compare the frontal cortical gene expression profile of patients with schizophrenia who committed suicide with the expression profile of subjects with schizophrenia who died from non-suicidal events and of the matched controls. Dan Rujescu, MD, will discuss case control genetic association studies of aggression-related genes in suicidal behavior. Lastly, Yogesh Dwivedi, PhD., will discuss recent molecular studies implicating apoptotic-regulatory genes in the pathophysiology of suicide. This workshop will demonstrate a combination of novel approaches that may be useful in identifying the pathogenic mechanisms associated with suicide and development of novel site-specific therapeutic interventions.
Supported by R01 MH079299 (KM), RO1MH068777

WORKSHOP

Re-Formulation and Novel Tests of the Dopamine Hypothesis of Schizophrenia

Saturday, May 3, 2008 12:30 PM - 2:00 PM
Location: Ticonderoga
Chair: Vishwajit L. Nimgaonkar*
Moderator: Robin M. Murray**

*Supported by R01MH56232
**Supported by MRC

703. Re-Formulation and Novel Tests of the Dopamine Hypothesis of Schizophrenia

Robin M. Murray[1], Vishwajit L. Nimgaonkar[2], David A. Collier[3], Andreas Meyer-Lindenberg[4]

[1]Institute of Psychiatry, [2]University of Pittsburgh, Pittsburgh, PA, [3]Institute of Psychiatry, London, United Kingdom, [4]Central Institute of Mental Health, Mannheim, Germany

Much schizophrenia research has been driven by the heuristic 'Dopamine (DA) hypothesis', but the original simplistic formulation of DA hyperfunction has never been satisfactory. There is growing evidence for regional differences and intricate homeostatic mechanisms, prompting more sophisticated formulations in recent years. Genetic association studies offer the opportunity to validate the DA hypothesis from an etiological perspective, but early association studies tested one or only a handful of polymorphisms, in small samples at conventional DA loci. The current availability of large samples and high throughput analytic methods offer the opportunity to re-evaluate the DA hypothesis from several perspectives. Though the focus of our symposium will be on genetic epidemiologic studies, we aim to weave in perspectives from complementary arenas in order to enable a lively debate, re-synthesis and reformulation of the DA hypothesis. The panel will include evaluations of the DA hypothesis from a genome-wide vantage, including genome-wide analyses, focused candidate gene studies, studies of environmental factors in conjunction with genetic risk and quantitative trait variation in relation to the DA hypothesis (phenomenological, cognitive and imaging variables). Chair/ Co-moderator: Vishwajit Nimgaonkar Moderator: Robin M Murray Titles and presenters: 1. The Dopamine hypothesis from the perspective of environmental factors and gene-environment interactions: Robin M Murray, Institute of Psychiatry, London, UK. 2. Focus on candidate gene studies: Vishwajit L Nimgaonkar, University of Pittsburgh, Pittsburgh USA. 3. Dopamine hypothesis from a genome-wide vantage: David Collier, Institute of Psychiatry, London, UK 4. Genetic variation impacting on dopamine and neural mechanisms of schizophrenia: Andreas Meyer-Lindenberg, Central Institute of Mental Health, Mannheim, Germany
Supported by NIMH\IRP, R01MH56232, mrc

WORKSHOP

Distinguishing Bipolar and Unipolar Depression: A Lifespan Perspective

Saturday, May 3, 2008 12:30 PM - 2:00 PM
Location: Regency A
Chair: Mary L. Phillips*
Moderator: Alan C. Swann

*Supported by 1R01 MH076971-01; NARSAD Independent Investigator Award
**Supported by Pat R. Rutherford, Jr. Chair in Psychiatry

704. Distinguishing Bipolar and Unipolar Depression: A Lifespan Perspective

Nick Craddock[1], Madhukar H. Trivedi[2], Mary L. Phillips[3], Cecile D. Ladouceur[4]

[1]Cardiff University, Cardiff, United Kingdom, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]University of Pittsburgh, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA

Individuals with bipolar disorder are often misdiagnosed with unipolar depression, leading to inadequate treatment and poor outcome. Identifying specific characteristics that distinguish bipolar and unipolar depression is critical to refining assessment and treatment strategies. As such, the goal of this workshop is to assemble a group of researchers that will contrast the genetic, clinical, and neurobiological aspects of bipolar and unipolar depression in patients and individuals at risk for these disorders. Dr. Craddock will present genotyping data on 2700 patients with bipolar spectrum illness and 3000 population controls, which he will discuss in view of elucidating the biological mechanisms underlying mood disorders and their psychiatric nosology. Dr.Trivedi will contrast data on the phenomenology, clinical course, and treatment outcomes for adult patients with bipolar and unipolar depression. Dr. Phillips will present fMRI and neurocognitive data in adult patients with bipolar and unipolar depression compared to healthy controls and discuss how distinguishable patterns of abnormal neural and behavioral responses to emotional stimuli may reflect specific endophenotypes of bipolar and unipolar depression. Finally, Dr. Ladouceur will compare neural responses to emotional stimuli in offspring at risk for bipolar disorder, offspring at risk for depression, and healthy controls. Results will be discussed focusing on the specificity of neurodevelopmental risk markers of bipolar and unipolar depression and how such findings can inform early intervention strategies. Dr. Swann will lead the discussion centered on the importance of combining genetic, clinical, and neuroimaging measures in ways that will improve diagnostic accuracy and treatment of bipolar and unipolar depression.

Supported by Wellcome Trust, NIMH, 1R01 MH076971-01; NARSAD Independent investigator Award, NARSAD

MINI SYMPOSIA

Regulation of Adult Neurogenesis in the Monkey

Saturday, May 3, 2008 12:30 PM - 2:00 PM
Location: Capitol A
Chair: Cynthia Shannon Weickert*
Co-Chair: Andrew J. Dwork

*Supported by Schizophrenia Research Institute, Sydney, Australia
**Supported by K08 MH070954 (Perera), NARSAD

705. Stress and Aging Decrease Adult Neurogenesis in the Marmoset

Elizabeth Gould

Princeton, New Jersey, NJ

Background: Adult neurogenesis in the hippocampus has been extensively studied in the rodent. Whether the findings from rodent studies are relevant to the primate brain is a matter of debate. The possibility that structural change is reduced in more complex animals, as opposed to rodents, has been raised. We examined whether the same conditions which regulate adult neurogenesis in the rodent do so in the nonhuman primate by investigating known modulators of this process, stress and age.
Methods: Adult marmoset monkeys were used for these studies. The effects of subordination stress were examined in animals subsequently injected with BrdU and perfused after a short time interval. Additional marmosets were examined for the rate of adult neurogenesis at different ages.
Results: Subordination stress decreased the number of BrdU labeled cells in the dentate gyrus of marmosets. This effect was similar in magnitude and timing to that observed for effects of stress on adult neurogenesis in rats. The rate of adult neurogenesis was also negatively correlated with age in adult marmosets. Older marmosets generated significantly fewer neurons than did young adults - the decline in adult neurogenesis occurred long before the animals reached senescence. This decline was similar in timing and magnitude to what has been observed for rats.
Conclusions: These findings indicate that adult neurogenesis in the hippocampus is a robust phenomenon in nonhuman primates. Stress and aging downregulate new neuron production in primates. Taken together, the results suggest conservation of plasticity mechanisms across mammalian species.
Supported by NARSAD and NIH

706. The Number, Type and Function of New Neurons in the Primate Frontal Cortex

Richard Saunders

NIMH

Background: Questions have been raised regarding the biological and functional relevance of newly generated cortical neurons in postnatal primate brain. While large numbers of new cells are dividing during postnatal life, only a small proportion of adult-born macaque pre-frontal cortex cells express NeuN, a marker of mature neurons. Some newly generated cortical cells are also co-labeled with GAD67 and calretinin, demonstrating that new neurons can differentiate into cortical interneurons. Newly generated cells in neurogenic zones become progressively restricted throughout life with aging brains showing only 10% of the dividing cells found in infant brains.
Methods: Determine if restricted amount of adult postnatal cortical neurogenesis could be enhanced by molecular or environmental factors and whether newly generated neurons increase in monkeys engaging prefrontal cortex during working memory relative to control and baseline.

Results: Proliferating cells doubled in the subventricular zone after peripheral injection of basic Fibroblast Growth Factor. These did not translate into a change in the number of new prefrontal cortex neurons at longer survival times (4 weeks), suggesting other factors may recruit or retain new cortical cells. There were no differences in total number of BrdU/NeuN+ cells in frontal cortex during working memory. There was a significant increase in newly generated neurons co-labeled for immediate early genes in monkeys engaging working memory.
Conclusions: These findings suggest that newly generated neurons are more likely to be activated in adult primate prefrontal cortex during working memory and that neurogenesis is a developmentally dynamic, modifiable phenomenon having functional significance in adult primates.

707. Characterizing Immature Neurons in the Primate Amygdala: A Developmental Approach

Julie Fudge

University of Rochester, Rochester, NY

Background: The amygdala, a brain structure involved emotional processing, is dysregulated in mood and anxiety disorders based on human studies. These disorders often appear in late childhood and adolescence. However, animal models of depression have focused primarily on hippocampal changes. Rodent models show that chronic stress results in deleterious effects on hippocampal size, and cell morphology and proliferation, and antidepressants prevent these changes.
Methods: To bridge the 'disconnect' between human (amygdala) and rodent (hippocampus) models, we used immunocytochemical studies to show that the primate amygdala is enriched with immature neurons, which persist through adulthood. Moreover, immature neurons are expressed in amygdala subregions associated with hippocampal inputs, based on additional tract tracing studies. We are now using markers of neuronal immaturity (polysialated neural cell adhesion and doublecortin immunoreactivity) to quantify the relative numbers of immature neurons in the primate amygdala at discrete developmental timepoints.
Results: High levels of immature neurons are regionally distributed in the adult primate amygdala. The distribution of these cells indicates that they are positioned for modulation by the hippocampus. The relative numbers of immature neurons in infant, juvenile, adult, and senescent brain will be presented.
Conclusions: In higher primates, immature neurons in the amygdala suggest a substrate for emotional processing; this system is influenced by hippocampal memory circuits. Stress may negatively impact the growth and function of these cells, based on studies in rodent hippocampus. Identification of the density curve for immature neurons across the lifespan will help pinpoint critical periods of growth and vulnerability.

708. Role of Adult Neurogenesis in Antidepressant Action Modeled in Non-human Primates

Tarique Dhyan Perera

Psychiatry, Columbia University and New York State Psychiatric Institute, New York, NY

Background: Antidepressants stimulate neurogenesis in the rodent hippocampus and blocking neurogenesis abolishes therapeutic effects of antidepressants in certain mouse strains. These results generated the hypothesis that stimulation of neurogenesis is necessary for antidepressant action. This study is the first test of this hypothesis in monkeys.
Methods: Socially housed, female, adult, bonnet macaque monkeys were randomized to CONTROLS conditions (n=6); repeated separation and reunion STRESS (n=6); temporal lobe irradiation-XRT (n=6) prior to stress. The antidepressant fluoxetine was administered to half the animals in the CONTROL and STRESS groups, and all animals XRT group. The remaining 3 subjects in the CONTROL and STRESS groups received saline-placebo. Stress and drug were administered for 15-weeks followed by sacrifice.
Results: Weekly home-cage behavior ratings showed a progressive increase in scores for 'Anhedonia' (lack of activity and social withdrawal) in placebo-treated animals compared to fluoxetine-treated animals in the STRESS group and all subjects in the CONTROL group. Postmortem hippocampal cell proliferation rates were decreased in the placebo-treated animals of the STRESS group while neurogenesis rates were increased in fluoxetine-treated animals. The XRT group showed increases in stress-induced 'Anhedonia' and decreases in neurogenesis rates despite fluoxetine treatment.
Conclusions: The results suggest that irradiation abolished antidepressant-mediated therapeutic effects by blocking the induction of neurogenesis. This is the first demonstration of the necessity of neurogenesis for antidepressant action in monkeys. Given the bio-behavioral similarities between across primate species, we predict a similar role for neurogenesis during treatment of depressed patients.
Supported by NIMH

MINI SYMPOSIA
Substance P (Neurokinin-1) Receptor: Neurobiology, Imaging, and Potential Therapeutic Target
Saturday, May 3, 2008 12:30 PM - 2:00 PM
Location: Capitol B
Chair: Robert Innis

Supported by NIMH

709. Substance P: A Pioneer amongst Neuropeptides

Tomas Hokfelt

Karolinska Institutet, Stockholm, Sweden

Background: Substance P was discovered 1931 by von Euler and Gaddum. In 1971 Susan Leeman and collaborators showed that substance P is an undecapeptide. Other members of the tachykinin family are neurokinin B and neurokinin A, the latter with some N-terminally extended forms. Recently hemokinin-1 and endokinins have been identified. The tachykinins act via three G-protein coupled receptors, NK1-3.
Methods: Radioimmunoassay, immunohistochemistry and electrophysiology have been used to explore the distribution, levels and role of substance P.
Results: In the rat brain substance P has a wide distribution with high levels in the brain stem, including substantia nigra, striatum, hypothalamus, nucleus accumbens, basal forebrain, amygdala, the periaqueductal grey and the superficial spinal trigeminal nucleus. However, cortex and hippocampus only contain comparatively low numbers of cell bodies. Neurokinin B has a partly overlapping, partly complementary distribution. Also the NK1 and -3 receptors are widely distributed. The distribution of substance P in the human lower brainstem is similar to that in rodents. In the monkey cortex substance P and substance K are present in two populations of cell bodies one being GABAergic cells. In the human cortex bipolar and some multipolar cells have been described. The hippocampus in man harbours three major classes of substance P interneurons. The NK1 receptor seems to be the predominant neurokinin receptor in the primate brain.
Conclusions: These findings suggest that tachykinin systems may be more widely expressed and possibly involved to a larger extent in higher brain functions in the primate as compared to rodent brain.

710. Patients with Panic Disorder Show Widespread Loss of NK1 Receptor Binding in Brain Measured with Positron Emission Tomography

Robert Innis

NIMH, Bethesda, MD

Background: Studies in animals have shown that pain and stress cause the release of substance P, which binds to and leads to the internalization of NK1 receptors. For example, NK1 receptor internalization occurs in rat dorsal horn of the spinal cord after exposure to pain and in several forebrain regions after forced swim test. We sought to determine if similar internalization occurs in patients with panic disorder after induction of a panic attack.
Methods: One or two PET scans with [18F]SPA-RQ were performed in a total of 14 patients with panic disorder and 14 healthy subjects. Of these two groups, 7 patients and 10 healthy subjects were scanned twice, at baseline and after injection of doxapram (to induce a panic attack).
Results: Doxapram effectively produced panic attacks in 6 of 7 patients with panic disorder but only 2 of 10 healthy subjects. Doxapram caused no significant change of [18F]SPA-RQ binding in either patients or healthy subjects. However, the binding at baseline in patients (n=14) compared to healthy subjects (n=14) showed widespread and statistically significant decreases. For example, most neocortical regions had 15~20% decrease (P<0.007).
Conclusions: Induction of a panic attack had no significant effect on NK1 receptor binding in brain, suggesting that any released substance P neither displaced the radioligand nor that caused internalization of the receptor. Although the acute stress of a panic attack had no effect, the chronic presence in panic disorder caused the patients to have widespread decrease of NK1 receptor binding in brain.
Supported by NIMH

711. PET Neuroimaging Studies of Substance P NK1 Receptors in Major Depression

Jarmo Hietala

University of Turku, Finland, Turku, Finland

Background: Experimental studies have implicated substance P NK1 receptors in the regulation of mood and anxiety but clinical trials do not support a role of NK1 receptor antagonism as an antidepressant mechanism (aprepitant studies, Keller et al Biol Psychiatry 2006). However, direct measurements of NK_1 receptors in vivo in patients with major depression have not been reported.
Methods: This is a cross-sectional case-control study in an outpatient setting in Finland. Nine antidepressant-naïve patients with major depression and nine age- and gender-matched screened healthy controls were included. Brain NK_1 receptor availability (BP_{ND}) was measured in vivo using positron emission tomography and fluorine-18 labeled substance P NK1 receptor antagonist SPA-RQ. Symptom severity was measured with the 17-item Hamilton depression rating scale (HAM-D).
Results: Patients with major depression had increased hippocampal NK_1 receptor BP_{ND}. In addition, total HAM-D total scores correlated positively with NK_1 BP_{ND} in widespread cortical and subcortical brain areas.
Conclusions: These preliminary PET neuroimaging studies suggest that hippocampal substance P NK_1 receptors are altered in medication-naïve patients with major depression. The link between NK_1 receptor availability and depresive symptoms as measured with the HAM-D supports a modulatory action of substance P NK_1 receptors in the biology of major depression.
Supported by Merck Research Laboratories, USA,

712. Therapeutic Trials of NK1 Antagonists in Neuropsychiatric Disorders

Mary F. Morrison

Psychiatry, University of Pennsylvania, Philadelphia, PA

Background: Substance P is located in brain regions that coordinate stress responses and receive monoaminergic innervation. This observation suggested that substance P antagonists might have psychotherapeutic properties, particularly in depression and anxiety.
Methods: Review of scientific literature through PubMed, OVID and other search services for published data relating to use of NK-1 antagonists in neuropsychiatric disorders, particularly depression and anxiety. Contacted pharmaceutical companies who have or had NK-1 antagonists in development, for clinical data in neuropsychiatry not yet in the public domain that the companies were agreeable to release.
Results: When small efficacy trials of two NK-1 antagonists suggested antidepressant effects, there was significant excitement by psychiatrists eager for a novel antidepressant with a different side effect profile. Larger studies of MK-869 (aprepitant) did not confirm antidepressant efficacy, while active comparator paroxetine confirmed successful trials (p <or= .05). Imaging studies in patients with anxiety disorders (simple phobia, PTSD) suggest involvement of the substance P-NK-1 system in anxiety disorders. The only therapeutic trial performed with NK-1 antagonists and anxiety was a Phase II study in social anxiety disorder, but no results have been released yet. NK-1 antagonists for pain disorders, specifically studies in dental pain and painful diabetic neuropathy, were negative. An exploratory study of MK-869 in acute psychosis did not suggest efficacy of NK-1 antagonists in schizophrenia
Conclusions: Currently, there is no clear role for NK-1 antagonists in the treatment of neuropsychiatric disorders. Future directions for NK-1 antagonists in neuropsychiatry will be discussed.

SLIDE

Schizophrenia III: Endophenotypes

Saturday, May 3, 2008 12:30 PM - 2:00 PM
Location: Congressional A
Chair: Judith M. Ford

713. Tones and "Voices" Compete for Auditory Cortical Resources: Multi-Site Fmri Study of Schizophrenia

Judith M. Ford[1], Brian J. Roach[1], Jessica Turner[2], Gregory Brown[3], Gregory McCarthy[4], Cynthia Wible[5], Keator David[2], Steven Potkin[2], Douglas Greve[5], Aysenil Belger[6], Daniel O'Leary[7], John Lauriello[8], Bryon Mueller[9], Kelvin O. Lim[9], Gary Glover[10], Vince Calhoun[11], Daniel H. Mathalon[1]

[1]Psychiatry, UCSF, San Francisco, CA,[2]Psychiatry, UCI, Irvine, CA,[3]Psychiatry, UCSD, San Diego, CA,[4]Psychology, Yale, New Haven, CT,[5]Psychiatry, Harvard, Cambridge, MA,[6]Psychiatry, University of North Carolina, Chapel Hill, NC,[7]Psychiatry, University of Iowa, Iowa City, IA,[8]Psychiatry, University of New Mexico, Albuquerque, NM,[9]Psychiatry, University of Minnesota, Minneapolis, MN,[10]Psychiatry, Stanford University, Stanford, CA,[11]Engineering, University of New Mexico, Albuquerque, NM

Background: Auditory hallucinations are experienced as one or more voices speaking in sentences or fragments, sometimes to the patient, sometimes to each other, in the absence external stimulation. Activation of primary auditory

cortex may account for why these voices are "heard" as coming from outside the head, rather than as inner speech or thoughts. Hubl et al (2007) showed the N1 component of the event-related brain potential to auditory probes was reduced during periods of hallucinations, suggesting competition for primary auditory cortex resources during hallucinations. Although N1 generation involves primary auditory cortex, it also involves other nearby structures. The current study uses the superior spatial resolution of functional magnetic resonance imaging (fMRI) to examine primary auditory cortex activation to frequently occurring tones as a function of hallucination presence, severity, and specific type (i.e., Schneiderian First Rank Symptoms of Voices Commenting or Voices Conversing).

Methods: fMRI data were collected from 65 frequently hallucinating patients with schizophrenia (DSM-IV), at 9 different national MR sites, as they performed an auditory oddball task. The strength of the neural response to 2320 frequently occurring 1000 Hz tones was regressed against ratings of auditory hallucinations from the SAPS.

Results: Recent presence of auditory hallucinations, as well severity of hallucinations, were associated with less auditory cortex activation to tones ($p<.01$, uncorrected). This effect was most pronounced in patients who experienced voices conversing ($p<.05$, corrected).

Conclusions: This may reflect direct competition between voices and tones for auditory processing resources, particularly when the hallucinations involved interacting voices.

Supported by Biomedical Informatics Research Network U24RR021992.

714. In Vivo Assessment of Thalamocortical Connectivity in Schizophrenia Using DTI and Integrative Evidence from fMRI

Antonina A. Savostyanova[1], Jason L. Stein[1], Hao Y. Tan[1], Aaron L. Goldman[1], Joseph H. Callicott[1], Jose A. Apud[1], Andreas Meyer-Lindenberg[2], Daniel R. Weinberger[1], Stefano Marenco[1]

[1]Clinical Brain Disorders Branch, National Institute of Mental Health, Bethesda, MD,[2]Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany

Background: Despite evidence of altered dorsolateral prefrontal cortex (dlPFC) function in schizophrenia, the literature has been mixed regarding structural deficits in the thalamic medio-dorsal nucleus, which projects to the prefrontal cortex. We investigated in vivo whether the region of the thalamus preferentially projecting to the dlPFC is reduced in size in patients with schizophrenia and explored its functional significance.

Methods: We acquired diffusion-weighted images on 15 patients with schizophrenia and age- and gender- matched healthy volunteers. The thalamus was parcellated using probabilistic tractography (Behrens et al., 2003), allowing for overlapping connectivity defined regions (CDRs) by using a threshold of 25% of connections reaching a particular cortical region of interest (ROI). A subset of our sample also underwent functional magnetic resonance imaging (fMRI) while engaging in the n-back working memory task.

Results: A significant interaction of cortical target ROI by diagnosis was found for the size of thalamic CDRs (Repeated-measures ANOVA: $p=0.03$). Post-hoc analyses revealed that only the size of the thalamic CDR connecting to the dlPFC differed between groups, with patients < controls ($p=0.02$). The size of this CDR correlated with blood-oxygenation-level-dependent (BOLD) activation in the dlPFC during n-back performance in healthy controls (BA9/46: $r=-.843$, $p<.001$) but not patients, who had less efficient activation despite matched performance.

Conclusions: These results suggest that connectivity between the thalamus and the dlPFC may be altered in patients with schizophrenia. The association of greater probabilistic thalamus-dlPFC connectivity with BOLD activation efficiency during a working memory task corroborates the biological significance of our tractography-derived measure.

Supported by NIMH-IRP

715. An fMRI Investigation of D-Cycloserine and Symptom Provocation in Spider Phobia

Robin L. Aupperle[1], Lisa R. Hale[2], Rebecca J. Chambers[1], Sharon E. Cain[3], Frank X. Barth[3], Susan C. Sharp[3], Douglas R. Denney[4], Cary R. Savage[3]

[1]Hoglund Brain Imaging Center, University of Kansas Medical Center, Kansas City, KS,[2]Department of Neurology, University of Kansas Medical Center, Kansas City, KS,[3]Department of Psychiatry and Behavioral Sciences, University of Kansas Medical Center, Kansas City, KS,[4]Department of Psychology, University of Kansas, Lawrence, KS

Background: Research has shown acute D-cycloserine administration to enhance effects of exposure-based therapy. This fMRI study aims to elucidate mechanisms of DCS by examining brain activity associated with symptom provocation in spider phobia.

Methods: This study is in progress and results are preliminary. Data have been collected for 22 phobic and 20 non-phobic participants; 2 remain to be tested. We randomized all participants to receive 100mg DCS or placebo. At two hours (Session 1) and one week (Session 2) post-medication, two BOLD scans were acquired and included blocks of spider, butterfly, and Gaussian-blurred pictures. We broke the blind and analyzed data for 8 phobic (3-DCS, 5-Placebo) and 11 non-phobic (6-DCS, 5-Placebo) participants. Multiple regression analyses were conducted comparing Session 1 and 2 activations. Regions considered significant met $p\leq.01$ (corrected) and cluster size>10.

Results: The DCS-phobic group showed greater activation to phobic stimuli during Session 1 v. 2 in bilateral amygdala (x,y,z=15,-4,-14), bilateral hippocampus (x,y,z=-30,-10,-17), left cingulate (x,y,z=-3,8,46), right fusiform gyrus (x,y,a=27,-1,-35), left orbitofrontal cortex (x,y,z=-30,32,1), left premotor cortex (x,y,z=-57,-3,40), and left prefrontal cortex (PFC;BA9,x,y,z=-30,44,38; BA10,x,y,z=-16,65,19; BA46,x,y,z=-54,35,11). The same contrast in the placebo group revealed activations in only the left primary motor cortex (x,y,z=-51,2,31) and left PFC (BA44;x,y,z=-51,-1,22). The control groups showed no differential activations between sessions.

Conclusions: Results indicate that, compared to placebo, DCS produces greater differential activations between sessions involving symptom provocation. This suggests that DCS modulates activity in regions important for emotional learning - primarily amygdala, hippocampus, and PFC. This study will be completed and results updated for presentation.

Supported by KUMC Research Institute; HBIC Pilot Funds; APA Dissertation Research Award; APF Research Scholarship

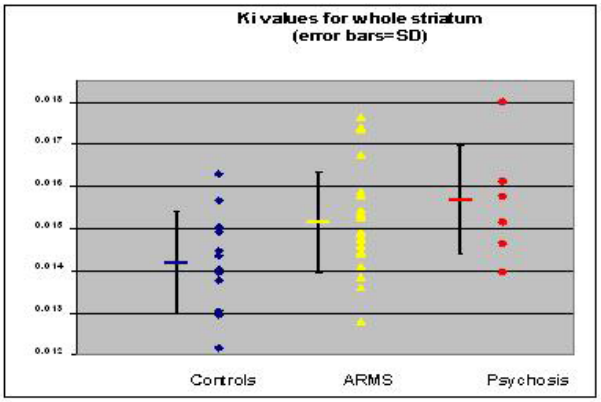
716. Striatal Dopaminergic Dysfunction Underlies 'Prodromal' Psychotic Symptoms and Predates the Onset of Schizophrenia: Results from an [18F]-DOPA PET Study

Oliver D. Howes[1], Andrew Montgomery[2], Isabel Valli[1], Marie-Claude Asselin[3], Robin M. Murray[1], Philip K. McGuire[1], Paul M. Grasby[4]

[1]Psychological Medicine, Institute of Psychiatry, London, United Kingdom,[2]Hammersmith Hospital, PET centre, Clinical Sciences Centre, LONDON, United Kingdom,[3]Wolfson Molecular Imaging Centre, University of Manchester, Manchester, United Kingdom,[4]Hammersmith Hospital, PET Centre, Clinical Sciences Centre, London, United Kingdom

Background: It is not known when dopaminergic overactivity first occurs in schizophrenia. We investigated this in people with 'prodromal' schizophrenic symptoms, who have an 'at risk mental state' (ARMS) and are at ultra high risk of developing schizophrenia in the next year.

Methods: The following age-matched groups have received an [18F]-DOPA PET scan: A) individuals with ARMS (n= 24); B) patients in the first episode of schizophrenia (n=7); C) healthy controls (n=12). To date six ARMS and five control subjects have been re-scanned after over one year. Subjects were antipsychotic naïve/ free. [18F]-DOPA influx constants (Ki values) were calculated from region-of-interest (ROI) derived time-activity curves (Patlak et al, 1985).
Results: Figure 1 shows the results of the ROI analysis for the whole striatum. Dopamine synthesis capacity was significantly greater in the ARMS group (t=2.2, df=34 , p=0.038), and psychosis group (t=2.5,df=17, p=0.02) than the healthy controls. Within the ARMS group, there was a positive correlation between the whole striatal Ki values and the total prodromal symptoms (r=0.48, p=0.019) and PANSS score (r=0.49, p=0.014), but not other symptoms.
Conclusions: Striatal dopaminergic overactivity predates the onset of psychosis in people at risk of schizophrenia, and is related to psychotic psychopathology. Further follow-up scans are required to determine if ARMS convertors and non - convertors (to psychosis) show differential striatal FDOPA uptake over time.



Supported by Medical Research Council UK

717. [11C]PHNO and [11C]racloride PET Imaging of Dopamine Receptors in Drug-Naive Parkinson's Disease

Isabelle Boileau[1], Mark Guttman[1], Sylvain Houle[2], Pablo Rusjan[2], Alan A. Wilson[2], Shitij Kapur[2], Stephen J. Kish[1]

[1]Human Neurochemical Pathology Laboratory, Centre for Addiction and Mental Health, Toronto, ON, Canada,[2]Vivian M. Rakoff PET Imaging Centre, Centre for Addiction and Mental Health, Toronto, ON, Canada

Background: Long-term treatment of Parkinson's disease (PD) with dopaminergic drugs often leads to abnormal movements as well as disabling psychological disturbances. Animal models suggest that changes in the expression of dopamine receptors (DA_r) might contribute to these complications. It has been proposed that a disproportionate stimulation of D_3DA_r could be responsible for complications secondary to levodopa. To date, there are no data on the status of the D_3DA_r system in PD. Recently it has been shown that the new DA_r ligand [11C]PHNO is a D_3-preferring agonist and therefore allows better measurement of the D_3DA_r system in humans. The objective of this study was to investigate the expression of D_2DA_r ([11C] raclopride binding) and D_3DA_r ([11C]PHNO binding) in PD.
Methods: 8 never-treated PD patients and 9 healthy-controls participated in (2) scans: following [11C]PHNO and [11C] raclopride.
Results: Preliminary results indicate that relative to controls, PD patients have decreased [11C]PHNO binding in D_3-rich regions including the ventral striatum (-13%; p=0.03) and globus pallidus (-35%; p=0.02). In contrast, [11C] PHNO as well as [11C]raclopride binding in the predominantly D_2-dense putamen is increased (26%; p=0.002; 26%; p=0.001).
Conclusions: These preliminary findings suggesting a downregulation of D_3DA_r and upregulation of D_2DA_r in never-treated PD patients are in line with previous PET [11C]raclopride studies and with animal models of dopaminergic denervation. A better understanding of the role of the D_3DA_r in the mechanism of sensitization to DA replacement therapy could provide insight into identifying new drug targets for PD.

718. Comorbid Major Depression Accounts for Lower Early Morning Plasma Cortisol Levels and Alterations in Plasma Dehydroeandosterone Sulphate (DHEA- S) in Posttraumatic Stress Disorder

Jessica M. Gill[1], Dave Luckenbaugh[2], Carlos Collin[3], Katherine Plumb[2], Kathleen West[2], Omer Bonne[4], Dennis Charney[5], Meena Vythilingam[2]

[1]National Institute of Nursing Research, National Institutes of Health, Bethesda, MD,[2]National Institute of Mental Health, National Institutes of Health, Bethesda, MD,[3]Behavioral Health, Community Behavioral Health, Rockville, MD,[4]Department of Psychiatry, Hadassah Medical Center, Jerusalem, Israel,[5]Psychiatry, Neuroscience, Mount Sinai School of Medicine, New York, NY

Background: Alterations in function of the hypothalamic-pituitary-adrenal (HPA) axis have been reported in posttraumatic stress disorder (PTSD) patients; however the influence of co-morbid major depressive disorder (MDD) has not been well studied.
Methods: Overnight (7pm- 7am) plasma cortisol, adrenocorticotropic hormone (ACTH), dehydroeandosterone sulphate (DHEA- S) levels were measured in 15 patients with PTSD without MDD, 6 with PTSD and MDD and 16 non-traumatized healthy controls. Linear mixed models with BMI and age as covariates and Bonferroni corrected post hoc tests were used to examine group differences.
Results: When plasma cortisol levels in patients with PTSD with and without MDD were compared to healthy controls, there was a significant group by time interaction (F=1.50, df=48,500, p=.02). Patients with PTSD and MDD had significantly lower plasma cortisol levels at 1:30 am and between 2:30 and 4:30 am compared to healthy controls (p's<.02), whereas those with PTSD without MDD did not differ from the control group at any time point (p's>.07). Plasma DHEA-S levels were also significantly different between the three groups. While plasma DHEA-S levels in healthy controls returned to baseline (7 pm) levels by 6:00 am, the PTSD patient groups returned to baseline slower. ACTH levels did not differ by group.
Conclusions: Co-morbid MDD may contribute to lower plasma cortisol levels and abnormalities in plasma DHEA-S levels seen in PTSD patients.
Supported by NIMH-03-M-0292

SLIDE
Schizophrenia IV: Neural Mechanisms
Saturday, May 3, 2008 12:30 PM - 2:00 PM
Location: Congressional B
Chair: See Program Addendum

719. One Year Stability of Cognitive and Neurophysiological Endophenotypes of Schizophrenia

Gregory A. Light[1], Neal R. Swerdlow[1], Kristin S. Cadenhead[1], Joyce Sprock[1], Allen Radant[2], David L. Braff[1]

[1]Psychiatry, University of California, San Diego, La Jolla, CA,[2]Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA

Background: Endophenotypes are quantitative, laboratory-based measures that are thought to represent intermediate links in the pathways between genetic variation and the clinical expression of the disorder. The aim of the present study was to examine the one-year stability of several neurocognitive and neurophysiological endophenotypes in schizophrenia patients and nonpsychiatric community comparison subjects (NCS).
Methods: Schizophrenia patients (N=120) and NCS (N=40) were assessed on a battery of neurocognitive and neurophysiological measures at intake (N=200) and after 12 months.
Results: Neurocognitive endophenotypes, mismatch negativity, P3a, prepulse inhibition, and oculomotor antisaccade measures were highly stable (ICCs=0.80 to 0.95) in both schizophrenia patients and NCS. Startle habituation was reliable in NCS (ICC=0.86) but not in the schizophrenia patients (ICC=0.42). While P50 suppression ratios were not stable in either NCS or patients (ICCs=0.10, 0.22 respectively), the stability of individual S1 (ICCs>0.80) and S2 amplitudes (ICCs>0.65) and S1-S2 difference scores were significant (ICCs>0.50) for both groups. No significant differences in the baseline characteristics were observed across several clinical, cognitive, functional, or endophenotype variables for the patients who returned vs. failed to return for follow-up testing.
Conclusions: The results of the present study indicate that the majority of putative endophenotypes in schizophrenia research are highly reliable over a 1 year interval. These measures did not demonstrate practice or maturation effects, suggesting that they are suitable as repeated measures for clinical outcome studies (e.g., drug effects). Attrition in the schizophrenia sample was not associated with baseline clinical, cognitive, or functional variables.
Supported by NARSAD, VISN-22 MIRECC, MH042228, MH079777, and MH065571

720. Epigenetic Regulation of the Reelin and GAD1 Promoters in Schizophrenia

Dennis R. Grayson

Psychiatry, University of Illinois at Chicago, Chicago, IL

Background: Evidence is accumulating that in schizophrenia, cognitive deficits appear to relate to a GABAergic neuronal pathology. The reelin and GAD1 down-regulation in post mortem schizophrenia brains is well established and likely part of a larger GABAergic core deficit associated with the disease. Dnmt1 is highly expressed in post-mitotic neurons and is increased in those same neurons in which the reelin and GAD1 mRNAs are decreased. This suggests that Dnmt1, possibly acting together with other Dnmts and methyl binding proteins, functions in establishing DNA methylation patterns in post-mitotic neurons.
Methods: We have used a combination of methylation and HDAC inhibitors to activate reelin and GAD1 expression in human neural progenitor cells. Using Western blots, competitive PCR and ChIP assays, we are able to examine changes in local chromatin remodeling.
Results: Inhibitors of Dnmt and HDAC activity induce reelin and GAD1 mRNAs with identical EC50 values and a comparable time frame. These treatments are accompanied by reduced amounts of Dnmt activity, Dnmt1 mRNA and protein. ChIP assays show that expression of the human reelin gene correlates with the dissociation of Dnmt1, Dnmt3a, Dnmt3b and MeCP2 from the promoter.
Conclusions: Our data are consistent with the concept that reelin and GAD 1 are epigenetically regulated through changes in methylation. Moreover, the data suggest that both Dnmt and HDAC inhibitors act through a common mechanism by disrupting a large repressor complex that blocks expression. It seems likely that Dnmts and HDACS may represent new targets for developing drugs that may be useful in treating patients with schizophrenia.
Supported by R01MH062682

721. Neurophysiological Distinction between Schizophrenia and Schizoaffective Disorder

Daniel H. Mathalon, Ralph Hoffman, Brian Roach, Todd D. Watson, Judith M. Ford

Psychiatry, Yale University School of Medicine, West Haven, CT

Background: Schizoaffective disorder (SAD) is distinguished from schizophrenia (SZ) based on the presence of prominent mood symptoms over the illness course. Despite this clinical distinction, SAD and SZ patients are often combined in research studies, in part because data supporting a distinct pathophysiological boundary between the disorders are lacking. Indeed, few studies have addressed whether neurobiological abnormalities associated with SZ, such as the widely replicated reduction and delay of the P300 event-related potential (ERP), are also present in SAD.
Methods: Scalp EEG was acquired from patients with DSM-IV SAD (n=15) or SZ (n=22), as well as healthy controls (HC; n=22), to assess the P300 elicited by infrequent target (10%) and novel (10%) stimuli in separate auditory and visual "oddball" tasks.
Results: P300 amplitude was reduced and delayed in SZ, relative to HC, consistent with prior studies. These SZ abnormalities did not significantly interact with stimulus type (target vs. novel) or modality (auditory vs. visual). Across sensory modality and stimulus type, SAD patients exhibited normal P300 amplitudes (significantly larger than SZ patients and indistinguishable from HC). However, P300 latency and reaction time were both equivalently delayed in SZ and SAD patients, relative to HC. P300 differences between SAD and SZ patients could not be accounted for by variation in symptom severity, socio-economic status, education, age, or antipsychotic medication.
Conclusions: Although both groups show similar deficits in processing speed, SAD patients do not exhibit the P300 amplitude deficits evident in SZ, providing validating evidence for an underlying pathophysiological boundary between these disorders.

722. 18F-Fluorodeoxyglucose PET-Gided Versus Left Standard 10 Hz Repetitive Transcranial Magnetic Stimulation in Patients with Medication-Resistant Depression: A Randomized Sham-Controlled Add-On Study

Marie-Laure Paillère Martinot[1], André Galinowski[2], Damien Ringuenet[3], Frank Bellivier[4], Jean-Pascal Lefaucheur[5], Christine Picq[6], Thierry Gallarda[2], Pascale Bruguière[6], Jean-François Mangin[7], Denis Rivière[8], Bruno Falissard[9], Jean-Claude Willer[10], Marion Leboyer[11], Jean-Pierre Olié[12], Eric Artiges[13], Jean-Luc Martinot[13]

[1]Adolescent Medicine, APHP, Hôpital Cochin, Paris, France,[2]Service Hospitalo-Universitaire, Hôpital Sainte-Anne, Paris, France,[3]Psychiatry, APHP, Hôpital Paul Brousse, Villejuif, France,[4]Psychiatry, APHP, Hopital Henri Mondor-Albert Chenevier, Créteil, France,[5]Physiology, APHP, Hôpital Henri Mondor-Albert Chenevier, Créteil, France,[6]Physical Medicine and Rehabilitation, APHP, Hôpital Pitié-Salpêtrière, Paris, France,[7]NMR Lab, Inserm-CEA-U797, I2BM, CEA Neurospin, IFR49, Gif-sur-Yvette, France,[8]NMR Lab, Inserm-CEA U797, I2BM, CEA Neurospin, IFR49, Gif-sur-Yvette, France,[9]Biostatistics, APHP, Hôpital Paul Brousse, Villejuif, France,[10]Physiology, APHP, Hôpital Pitié-Salpêtrière, Paris, France,[11]Psychiatry, APHP, Hôpital Henri Mondor-Albert Chenevier, Créteil, France,[12]Service hospitalo-universitaire, Hôpital Sainte-Anne, Paris, France,[13]Service Hospitalier Frédéric Joliot, Inserm-CEA U797, I2BM, IFR49, Orsay, France

Background: Whether the antidepressant effects of repetitive Transcranial Magnetic Stimulation (rTMS) relate to targeting metabolic prefrontal changes or specific anatomical areas remains unclear. We investigated the effects of high-frequency rTMS over the most hypometabolic prefrontal area in patients with medication-resistant depression, in a multisite, double-blind, randomized placebo-controlled add-on study.
Methods: 48 patients with major depression underwent Magnetic Resonance imaging (MRI) and 18-Fluorodeoxyglucose Positron Emission tomography (PET) to determine a target for rTMS. They were randomized to PET-guided (N=16), standard (N=18) or sham rTMS (N=14) conditions to receive 10 sessions of 10-Hz rTMS, 1600 pulses/session, at 90% motor threshold. Primary outcome was the Montgomery and Asberg Depression Rating Scale (MADRS) symptom score change from baseline. Anatomical stimulated Brodmann areas (BA) were a posteriori determined from MRIs. Right and left PET-guided rTMS effects and effects of stimulation over dorsolateral prefrontal cortex (BA9-46) were assessed in exploratory analyses.
Results: Neither PET-guided nor standard rTMS was superior to sham rTMS on the MADRS at 2-week end-point. However, left PET-guided patients (N=9) showed a significant improvement over sham-treated, and a larger improvement over standard-treated patients. Right PET-guided was similar to sham stimulation. Eight patients in the PET-guided and 7 patients in the standard group were stimulated over BA9-46. BA9-46 stimulation was more effective than stimulation over other areas.
Conclusions: High-frequency rTMS is more effective over left hypometabolic prefrontal areas and over the left dorsolateral prefrontal cortex (BA9-46). Left prefrontal metabolic status and anatomical area underneath the coil might both interact to account for the antidepressant effects of rTMS.
Supported by PHRC/AOM-98099, Inserm-Progres A99013LS, & APHP/Inserm interface grant

723. A Novel Electrophysiological Model of Chemotherapy-Induced Cognitive Impairment in Mice

Michael J. Gandal[1], Rich S. Ehrlichman[2], Noam D. Rudnick[2], Steven J. Siegel[2]

[1]Medical Scientist Training Program, University of Pennsylvania, Philadelphia, PA,[2]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA

Background: Chemotherapeutic agents have been shown to produce moderate, persistent cognitive deficits in cancer patients. However, little progress has been made in developing an animal model to explore underlying mechanisms and potential therapeutic interventions. Here, we have created an electrophysiological model of chemotherapy-induced cognitive deficits using a sensory gating paradigm, to correspond with performance in two behavioral tasks.
Methods: Adult mice (n=24) were divided into three groups and received four weekly injections of Methotrexate and 5-Fluorouracil at high dose (37.5mg/kg MTX + 75mg/kg 5-FU), low dose (1:2 dilution), or control. Whole-brain ERPs were recorded at weeks 1,3, and 5 with unipolar electrodes using a paired-click paradigm. Mice underwent contextual fear conditioning and novel-object recognition testing. Data was analyzed using repeated-measures ANOVA.
Results: A significant interaction (p=0.00306) was found between gating ratios and week, with higher ratios (suppressed auditory gating) in low (p=0.022) and high-dose (p=0.036) groups compared to control at week 5. There was no effect of drug on the amplitude of P20-N40 or latency of P20. The drug treated animals showed significantly increased freezing during fear conditioning (p=0.044) but no impairment during novel object recognition.
Conclusions: Treatment with chronic chemotherapy causes decreased ability to gate incoming auditory stimuli, which may underlie its associated cognitive deficits. These gating deficits were associated with a hyperactive response to fear, suggesting an additional component of emotional dysregulation. However, amplitudes and latencies of ERP components were unaffected, as was NOR performance, indicative of the subtle nature of these deficits.
Supported by Abramson Cancer Center, University of Pennsylvania

724. Abbreviated Cognitive Assessment in Schizophrenia: Prediction of Functional and Cognitive Outcomes

Philip D. Harvey[1], Christopher R. Bowie[2], Robert K. Heaton[3], Thomas L. Patterson[4]

[1]Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA,[2]Psychiatry, Mt. Sinai School of Medicine, New York, NY,[3]Psychiatry, UCSD School of medicine, LaJolla, CA,[4]Psychiatry, UCSD School of Medicine, LaJolla, CA

Background: The aim of this study was to identify the best subset of neuropsychological tests for prediction of different aspects of functioning in a large (n=236) sample of older people with schizophrenia. Efficient neuropsychological assessment may increase availability of neuropsychological assessment and improvements in research methods.
Methods: Scores on ten different NP tests were used to predict global NP performance (indexed with averaged or general deficit scores), performance-based indices of everyday living skills and social competence, and ratings of real-world functioning. Stepwise regression analyses were used to identify the best predictors for each of the outcomes measures. Then, a set of three NP tests previously shown to predict overall NP performance was applied to each of the outcomes measures.

Results: Substantial amounts (over 70%) of the variance in NP performance were accounted for by a limited number of NP tests. Considerable variance in measures of functional capacity were accounted for by a limited number of tests. Processing speed was the best predictor of all outcomes, although the other predictors included working and episodic memory. When the a priori set of three tests was applied to each outcome variable, the level of predictability was minimally affected.
Conclusions: A substantial proportion of the variance in several different NP and functional outcomes can be accounted for by a small number of NP tests that can be completed in a few minutes. Future studies should determine if responses to treatments can be captured with brief assessments as well.
Supported by NIMH R01MH63116

SLIDE
Mechanisms of Neural Plasticity
Saturday, May 3, 2008 12:30 PM - 2:00 PM
Location: Concord/Lexington
Chair: See Program Addendum

725. Predictors of Neonatal Hypothalamic-Pituitary-Adrenal Axis Activity at Delivery in Women with Psychiatric Illness

Alicia K. Smith[1], Elyse R. Katz[2], D. Jeffrey Newport[3], Patricia A. Brennan[4], James C. Ritchie[5], Morgan P. Ashe[3], Charles B. Nemeroff[3], Joseph F. Cubells[1], Zachary N. Stowe[3]

[1]Human Genetics, Emory University, Atlanta, GA,[2]Neuroscience, Emory University, Atlanta, GA,[3]Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA,[4]Pyschology, Emory University, Atlanta, GA,[5]Pathology & Laboratory Medicine, Emory University, Atlanta, GA

Background: Evidence suggests that maternal psychiatric illness during pregnancy influences both the maternal and neonatal hypothalamic-pituitary-adrenal (HPA) axis, potentially predisposing the neonate to significant, long-term consequences.
Methods: Measures of HPA axis components [adrenocorticotrophic hormone (ACTH), total cortisol, free cortisol, and cortisol-binding globulin (CBG)] were analyzed in 216 paired maternal and umbilical cord blood samples collected at delivery from women with a history of psychiatric illness. ANOVA was used to test the association of maternal race, age, body-mass index (BMI) at delivery, current psychiatric diagnosis, method of delivery and neonatal estimated gestational age at delivery with neonatal HPA axis measures, followed by logistic regression to determine if indices of the maternal HPA axis predicted corresponding neonatal measures.
Results: Method of delivery was associated with neonatal ACTH concentrations ($p = 0.025$) as well as total and free cortisol concentrations ($p<0.0001$-0.027). Estimated gestational age (weeks) was associated with neonatal free cortisol ($p=0.031$). After controlling for method of delivery and estimated gestational age where appropriate, we found that maternal ACTH predicted 25.0% of the variance in neonatal ACTH ($p<0.0001$), and maternal free and total cortisol predicted of 42.3% and 23.5% of the variance in neonatal free and total cortisol, respectively ($p<0.0001$).
Conclusions: Indices of maternal and neonatal HPA axis activity at parturition are remarkably similar. We hypothesize that the neonate is not insulated from neuroendocrine sequelae of maternal stress. Future investigations are required to determine if there is a persistent effect on later child development.
Supported by K02 DA15766; P50 MH-58922 (Conte Center); P50 MH-77928 (TRCBS)

726. High Dose Magnetic Seizure Therapy (HD-MST) Increases Mossy Fiber Sprouting but not Cellular Proliferation in the Primate Dentate Gyrus

Sarah H. Lisanby[1], Jason Scalia[1], Elisabeth Bernhardt[1], Timothy Spellman[1], Mark D. Underwood[2], Andrew J. Dwork[2], Victoria Arango[2]

[1]Brain Stimulation and Therapeutic Modulation Division, Columbia University, New York, NY,[2]Molecular Imaging and Neuropathology Division, Columbia University, New York, NY

Background: Dentate gyrus mossy fiber sprouting (MFS) and cellular proliferation are elicited by electroconvulsive therapy (ECT), however their role in clinical efficacy and cognitive side effects is not understood. Magnetic seizure therapy (MST) is under development to improve the safety of ECT through enhanced control over stimulation and seizure initiation. We previously reported that MST does not induce cellular proliferation or MFS in monkey dentate gyrus, while electroconvulsive shock (ECS) induced both. Possible explanations include inadequate MST dosing and the use of ketamine as a pre-anesthetic. We sought to determine whether high dose MST (HD-MST) shares the neuroplastic effects of ECS, using a ketamine-free protocol.
Methods: 18 rhesus monkeys were randomly assigned to receive 5 weeks of daily HD- MST (6x seizure threshold), ECS (2.5x seizure threshold), or anesthesia-alone SHAM. Bromodeoxyuridine (100 mg/kg qD x 6 days) was injected 5 weeks prior to sacrifice. Masked raters counted BrdU positive nuclei and scored the degree of MFS (Timm stain).
Results: HD-MST and ECS increased MFS relative to sham ($p's<0.01$). ECS and HD-MST did not differ in the degree of MFS. ECS increased BrdU labeled cells relative to MST ($p<0.05$), while MST did not differ from SHAM.
Conclusions: Both ECS and HD-MST increase MFS, while only ECS increases cellular proliferation. This suggests that inducing a seizure is insufficient to enhance hippocampal proliferation and that the distribution of the induced electrical field and/or the seizure propagation may be critical. Differences in the neuroanatomical effects of HD-MST and ECS may be informative about their differential cognitive effects.
Supported by R01 MH60884

727. 5-HTTLPR Polymorphisms (SLC6A4 & rs25531) do not Affect 5-HT Transporter Expression in the Living Human Brain

Naga Venkatesha Murthy[1], Philip J. Cowen[2], Sudhakar Selvaraj[2], Wim J. Riedel[3], Polly Peers[4], James Kennedy[5], Marc Laruelle[6], Eugenii Rabiner[6], Paul M. Grasby[7]

[1]Psychiatry CPDM, GSK Clinical Imaging Centre, Imperial College London, London, United Kingdom,[2]Department of Psychiatry, University of Oxford, Oxford, United Kingdom,[3]Department of Neruo & Psychopharmacology, Maastricht University, Maastricht, The Netherlands,[4]MRC-CBU, University of Cambridge, Cambridge, United Kingdom,[5]CAMH, University of Toronto, Toronto, ON, Canada,[6]Molecular Imaging, GSK Clinical Imaging Centre, Imperial College London, London, United Kingdom,[7]PET Psychiatry, MRC CSC, Imperial College London, London, United Kingdom

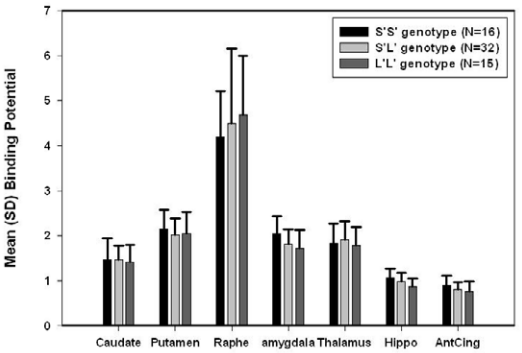
Background: Studies in vitro suggest the expression of the serotonin transporter (5-HTT) is regulated by polymorphic variation in the promoter region of the 5-HTT gene (5-HTTLPR; Lesch, 1996, Science, 274:1527-1531; Hu, 2006, Am J Hum Genet, 78(5):815-826). However, evidence for this effect in vivo is inconsistent in human studies e.g. Praschak-Rieder, 2007, Biol Psychiatry, 62:327-331; Parsey, 2006, Am J Psychiatry, 163:48-51. The reasons for this inconsistency may be smaller subject numbers or use of sub-optimal radiotracer.
Methods: We used positron emission tomography in conjunction with

the selective 5-HTT ligand [^{11}C] DASB to examine the availability of the 5-HTT in seven brain regions in 63 healthy volunteers who were genotyped for short (S) and long (L) variants (SLC6A4 & rs25531) of the 5-HTTLPR.

Results: [^{11}C] DASB binding potential was not influenced by allelic status of participants whether classified on a biallelic or triallelic basis in any of the seven regions tested (see figure).

Conclusions: Our PET findings, in a large cohort with a near optimal radiotracer, suggest 5-HTTLPR polymorphic variations do not affect the expression of the 5-HTT in adult human brain. The reported impact of 5-HTTLPR polymorphic variations on emotional processing and vulnerability to depression are more likely therefore to be expressed through effects during neurodevelopment.

[11C]DASB Binding Potential in different brain regions in healthy volunteers by 5-HTTLPR gain-of-function triallelic genotype



Supported by Funded in part by GlaxoSmithKline & Medical Research Council

728. Cognitive Effects of DBS in the Ventral Striatum in Patients with Severe Major Depression and Obsessive Compulsive Disorder

Cynthia S. Kubu[1], Benjamin Greenberg[2], Don Malone[1], Steve Rasumssen[2], Gerhard Friehs[3], Andre Machado[1], Ali Rezai[1]

[1]Center for Neurological Restoration, Cleveland Clinic, Cleveland, OH,[2]Department of Psychiatry, Butler Hospital and Brown University, Providence, RI,[3]Neurosurgery, Brown University, Providence, RI

Background: Deep brain stimulation (DBS) for the treatment of severe Major Depression (MDD) and Obsessive Compulsive (OCD) appears to be a promising treatment. Thus far, little is known regarding neuropsychological outcome following DBS for the treatment of severe psychiatric disorders. We present neuropsychological data from our series of OCD (n=10) and MDD (n=10) patients who underwent DBS in the anterior limb of the internal capsule/ventral striatum (AC/VS).

Methods: The data reported in this study were obtained with approval by the relevant IRBs and the FDA. All patients completed a neuropsychological battery prior to and following surgery. Patients who had been undergoing maintenance ECT prior to surgery were not included in the study. Standardized change scores taking into account test-retest reliability and practice effects were computed. The OCD and MDD groups were compared to each other on the neuropsychological variables and the relationships between changes in neuropsychological status were analyzed with respect to improvements in psychiatric status.

Results: There were no significant group differences in neuropsychological outcome. DBS in the ventral striatum resulted in significant improvements in immediate (t(19)=2.7,p=0.014) and delayed (t(19)=2.8,p=0.012) recall of short stories. The cognitive improvements were not significantly related to improvements in psychiatric status (all r values <0.126, p>0.5).

Conclusions: These initial data suggest that DBS in the AC/VS for the treatment of severe OCD and MDD is safe from a cognitive perspective. These data also suggest that DBS in this region may result in improvements in memory independent of the concomitant improvements in psychiatric disability.

Supported by Medtronic; NARSAD

729. New Onset Depression in Parkinson Disease is Associated with Increased Memory Decline Following Deep Brain Stimulation in the Subthalamic Nucleus

Cynthia S. Kubu, Hooman Azmi, Darlene Floden, Andre Machado, Ali Rezai

Center for Neurological Restoration, Cleveland Clinic, Cleveland, OH

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) for the treatment of Parkinson disease (PD) is well accepted. Unfortunately, few studies have identified clear risk factors for cognitive decline following STN DBS. We examined the role of depression and neuroimaging variables in neuropsychological outcome following STN DBS in patients with PD.

Methods: 38 patients with PD who underwent placement of bilateral DBS electrodes in the STN completed pre- and post-operative neuropsychological assessments as part of routine clinical care. Patients were divided into two groups (Depressed, n=11; Nondepressed, n=27) based on pre-operative Beck Depression Inventory score. Repeated measures ANOVAs were completed to evaluate differences in neuropsychological outcome between the two depressed groups. The two groups were compared on several different neuroimaging variables (e.g., corrected hippocampal volumes, total brain volumes, ventricular ratio, white matter disease).

Results: The groups did not differ with respect to demographic, pre-operative neuropsychological, or any of the neuroimaging variables. Several significant interactions were evident indicating that the Depressed group sustained greater declines on measures of verbal learning following surgery despite improvements in self-reported symptoms of depression after surgery.

Conclusions: Depressed PD patients who undergo bilateral placement of DBS electrodes in the STN are at greater risk for memory decline compared to non-depressed patients. This relationship does not appear to reflect differences in neuroimaging variables. We argue that new onset depression in PD may be a marker of increased disease burden and, hence, reflect increased vulnerability for cognitive decline following STN DBS in patients with PD.

Supported by National Parkinson's Foundation

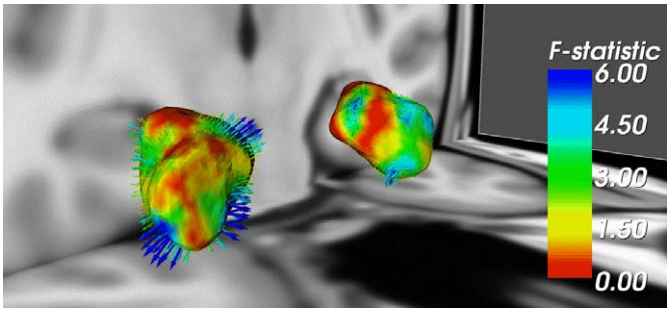
730. Amygdala Enlargement and Shape Distortion in Bipolar Disorder

David C. Glahn[1], Mark Jenkinson[2], E Serap Monkul[1], Jennifer L. Robinson[1], Carrie E. Bearden[3], Michael A. Escamilla[4], Peter T. Fox[5], Stephen Smith[2], Brian Patenaude[2]

[1]Psychiatry & Research Imaging Center, UTHSCSA, San Antonio, TX,[2]Oxford University Centre for Functional MRI of the Brain (FMRIB), Oxford University, Oxford, United Kingdom,[3]Psychiatry & Biobehavioral Sciences & Psychology, UCLA, Los Angeles, CA,[4]Psychiatry, UTHSCSA, San Antonio, TX,[5]Research Imaging Center, UTHSCSA, San Antonio, TX

Background: Although the amygdala may be central to the pathophysiology of bipolar disorder (BP), MRI-based findings of aberrant amygdala volumes in BP are inconsistent. Here, we applied a novel computational method to test for

shape and volume changes in the amygdala of BP patients.
Methods: 31 BP and 36 control subjects matched for age, gender, education and race participated. 800 µm isotropic neuroanatomic images were acquired and analyzed with a novel neural-network method that segments an individual's anatomy, parameterize regions into a surface mesh, and models each vertex in a mesh as a multivariate point distribution.
Results: Gender (p=0.01) and age (p=0.05) significantly contributed to amygdala volume. After controlling for these factors, left (1763±235 vs 1614±257, t=2.70, p=0.01) and right (1801±257 vs 1665±208, t=2.74, p=0.01) amygdala volumes were larger in BP patients compared to healthy subjects. Neither valproate (n=10; p=0.8) nor lamotrigine (n=9; p=0.3) significantly affected amygdala volumes in the BP sample. Shape analysis indicated that the amygdala enlargement was not uniform, rather significant group differences were primarily within the basolateral region (see Figure).
Conclusions: These data represent the first in vivo demonstration of basolateral amygdala disturbances in BP and help to confirm the importance of this region in the pathophysiology of the illness.



Supported by NIMH, NARSAD

SYMPOSIUM
Mechanistic Convergence of D2 and mGlu2/3 Receptors in Treating Schizophrenia
Saturday, May 3, 2008 2:30 PM - 5:00 PM
Location: Regency A
Chair: Patricio O'Donnell
Co-Chair: Bita Moghaddam

Supported by R01MH57683

731. Preliminary Clinical Evidence Supporting the Therapeutic Potential of mGluR2/3 Agonists for the Treatment of Schizophrenia

John Krystal

Yale University School of Medicine

Background: Schizophrenia is a disorder associated with reduced pyramidal neuronal neuropil in post-mortem studies and abnormal cortical connectivity in structural neuroimaging and diffusion tensor imaging studies. Thus, it might seem that the efficacy of of metabotropic glutamate receptor 2/3 (mGluR2/3) agonists, drugs that inhibit glutamate release, might seem paradoxical.
Methods: This presentation would briefly review two human studies.
Results: 1) a human laboratory study conducted in our laboratory that suggested that pretreatment with single doses of LY354740 reduced the cognitive effects of the NMDA receptor antagonist, ketamine, in healthy human subjects and 2) a recently published treatment study conducted by Eli Lilly and Company that provided initial evidence that another drug from this class, LY2140023, was efficacious in treating symptoms of schizophrenia. To our knowledge, these two studies constitute the entire published human literature linking mGluR2/3 agonism to schizophrenia.
Conclusions: These two studies support the further exploration of mGluR2/3 agonism as a treatment strategy for schizophrenia.
Supported by NARSAD, NIMH, VA

732. Antipsychotic Drugs and mGlu2/3 Agonists Normalize the Impact of NMDA Hypofunction on Cortical Neurons

Bita Moghaddam

University of Pittsburgh, Pittsburgh, PA

Background: Hypofuntion of NMDA receptors may lead to some symptoms of schizophrenia, especially cognitive deficits such as impairments in working memory and attention that are dependent on the functional integrity of the prefrontal cortex (PFC). Postmortem studies indicate that schizophrenia may be associated with reduced cortical GABA function. We hypothesized that NMDA receptor hypofunction results in functional deficits of cortical GABA interneurons and that antipsychotic drugs ameliorate this deficit.
Methods: Ensemble recording in behaving animals was used to assess the firing rate and pattern of pyramidal and putative GABA interneurons in the prefrontal cortex
Results: NMDA receptor hypofunction selectively inhibits the firing of cortical GABA interneurons thus reducing the inhibitory influence of these neurons on cortical pyramidal cells. This reduced inhibitory control leads to a tonic state of disinhibition at these neurons as demonstrated by a sustained increase in random firing of cortical pyramidal neurons. This effect may diminish the capacity of PFC neurons to fire appropriately to task relevant stimuli and provides a neuronal model for large-scale integration abnormalities in schizophrenia. We also find that in behaving animals, existing antipsychotic drugs (including clozapine and haloperidol) as well as an mGlu2/3 receptor agonist reduce the impact of NMDA hypofunction on firing of cortical pyramidal neurons.
Conclusions: These data indicate that inhibition of D2 receptors and activation of mGlu2/3 receptors normalizes the disruptive effects of NMDA receptor hypofunction on spike activity and bursting of PFC pyramidal neurons. This mechanism may provide a physiological basis for the clinical efficacy of these compounds.
Supported by R37MH48408

733. Altered Dopaminergic Modulation of GABA and Glutamate Cortical Transmission in a Developmental Animal Model of Schizophrenia

Patricio O'Donnell[1], Kuei-Yuan Tseng[2], Carlos Feleder[3]

[1]Departments of Anatomy & Neurobiology and Psychiatry, University of Maryland School of Medicine, Baltimore, MD,[2]Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science, North Chicago, IL,[3]Basic and Pharmaceutical Sciences, Albany College of Pharmacy, Albany, NY

Background: Interneurons are critical for prefrontal cortical (PFC) function and are affected in schizophrenia. As the D2 modulation of PFC interneurons changes during adolescence, we sought to determine whether this late maturation was altered in adult animals with a neonatal ventral hippocampal lesion (NVHL) or a neonatal immune challenge.
Methods: PD6-8 rat pups were injected in the ventral hippocampus with either ibotenic acid (NVHL) or a bacterial endotoxin (LPS). Once NVHL, LPS or sham animals were adults (PD>60), sensorimotor gating deficits were tested

with PPI; a week later whole-cell recordings were conducted from PFC fast-spiking interneurons.
Results: The D2 agonist quinpirole increased cell excitability of PFC interneurons in slices from sham and naïve animals, but only in slices from adult rats. In pre-adolescent rats, quinpirole did not affect interneuron excitability in any group. In NVHL and LPS treated adult rats, quinpirole decreased interneuron excitability in many cases.
Conclusions: In the developmental animal models tested, the D2 agonist decrease in interneuron excitability may render prefrontal cortical circuits in a hyperactive state in which salient stimuli cannot be highlighted by decreasing background pyramidal neuron activity yielding an inefficient PFC; a functional equivalent of hypofrontality due to reduced cortical capacity. D2 blockade by antipsychotics is likely to restore some balance in these circuits by alleviating the abnormal D2 inhibition of interneurons and restoring local inhibitory function to some extent. Any compound that can restore interneuron function could provide a similar outcome, and this could be a reasonable target for novel therapeutic approaches in schizophrenia.
Supported by R01MH57683

734. The Role of D-Serine in NMDA Receptor Hypofunction in Schizophrenia

Joseph T. Coyle

McLean Hospital, Harvard Medical School, Belmont, MA

Background: For glumamate to open the channel on the NMDA receptor(R), the glycine B receptor on the NR1 subunit must be occupied by either glycine or D-serine. D-serine appears to be the primary agonist in cortical-limbic regions. Recent genetic studies strongly implicate G72, an activator of D-amino acid oxidase (DAAO), DAAO itself and serine racemase (SR) as risk genes for schizophrenia.
Methods: To inactivate the gene encoding SR, lox-P sites were introduced flanking exon 1, which encodes the pyridoxal 5'-phosphate cofactor site. The mutant mice were crossed with mice expressing cre-recombinase, resulting the excision of exon 1.Studies were carried out on mice back-crossed for >6 generations.
Results: SR-/- mice had no detectable SR mRNA on qPCR, and D-serine levels in brain were decreased by >80% by HPLC and at background levels with immunocytochemical staining. Whole cell clamping of the hippocampal CA1 pyramidal cells revealed reduced NMDAR currents and profoundly impaired long-term potentiation that could be restored by perfusion with exogenous D-serine. Male SR-/- mice exhibited mild persistent hyperactivity and anxiety traits. In the Morris water maze, SR-/- acquired the task similar to WT but showed significant impairments in the working memory component. qPCR revealed significant reductions in the expression of glutamate decarboxylase (GAD72) and parvalbumen in the hippocampus, the signature neurocheical pathology of schizophrenia.
Conclusions: Reduced D-serine impairs NMDAR function. Cortical GABAergic neurons appear to be particularly vulnerable, resulting in the activation of a pathologic circuit responsible for cognitive dysfunction and psychosis in schizophrenia.
Supported by NIMH

SYMPOSIUM
Gray Matter Abnormalities in Schizophrenia - What Do They Mean?
Saturday, May 3, 2008 2:30 PM - 5:00 PM
Location: Ticonderoga
Chair: Nitin Gogtay*

*Supported by NIMH Intramural Program

735. Gray Matter Abnormalities in Childhood-Onset Schizophrenia and Their Full Siblings from Early Childhood to Young Adulthood

Nitin Gogtay

NIMH, Bethesda, MD

Background: Cortical gray matter(GM) abnormalities, which are most prominently seen in childhood-onset schizophrenia(COS), are now an established feature in schizophrenia
Methods: COS Patients and their full siblings are studied longitudinally and clinical, genetic, and structural brain MRI data are obtained every two years. Cortical GM and white matter(WM) development are mapped using novel algorithms.
Results: Dynamic maps revealed a pattern of 'back to front wave' of GM loss for COS during adolescence that merged into the adult pattern by age 25. This pattern was distinct from that seen in pediatric bipolar illness. Preliminary analysis (n=12, 36 scans, ages 12 to18) showed delayed WM maturation for COS compared to matched healthy controls. Healthy COS siblings (n=52, 110 scans) shared GM abnormalities in the prefrontal and temporal cortices in early ages, which were normalized by age 20. Analysis of 59 COS probands(160 scans), their 39 healthy siblings(80 scans) and 183 healthy controls (221 scans) showed that both COS probands and siblings with risk allele for glutamate decarboxylase(GAD1) risk allele had steeper slopes of prefrontal cortical GM loss. Slopes of GM thickness in healthy siblings correlated with overall functional outcome in healthy siblings and with remission status at discharge in COS probands.
Conclusions: Cortical GM loss in COS is profound, diagnostically specific, not due to WM encroachment, and neurobiologically continuous with AOS. GM development in schizophrenia could be considered an endophenotype that is influenced by individual risk gene status, overall functioning, and treatment outcome.
Supported by NIMH Intramural Program

736. Genetic Imaging in a High Risk Population for Schizophrenia

Stephen Lawrie

Edinburgh University Division of Psychiatry, Edinburgh, United Kingdom

Background: We have recently completed a ten year longitudinal study of brain structure and function in a group of individuals at high risk of schizophrenia for familial reasons, and have taken blood for genetic analyses.
Methods: 162 initially healthy people aged 15-25 at high genetic risk of schizophrenia, because they had at least one close relative with the disorder, were recruited and examined with structural MRI and functional MRI. The development of psychotic symptoms and/or schizophrenia itself was monitored at serial assessments, which most participants had at 18-24 month intervals over up to 10 years.
Results: 21 developed schizophrenia during the study and an additional 66 subjects had psychotic symptoms at one or more assessments. Single nucleotide polymorphisms in the BNDF and DAO genes were associated with abnormalities of frontal and temporal function, but not structure, in the high

risk cohort as a whole. The Val(158)Met polymorphism in the Catechol-O-MethylTransferase (COMT) gene predicted schizophrenia in this cohort in a dose-dependent manner. It was also associated with reduced gray matter density and BOLD signal in anterior cingulate cortex.
Conclusions: These patterns of altered brain structure and function have previously been associated with schizophrenia in this and other samples. DAO may have trait effects, while the NRG1 variant appears to be a risk factor for an extended or intermediate phenotype and the COMT Val allele is associated with an increased risk of schizophrenia. This genetic background provides a mechanistic framework in which to study the effects of environmental risk factors.
Supported by Medical research Council and the Sackler Foundation

737. High Resolution Neuroimaging in Schizophrenia

Hilleke E. Hulshoff Pol, Rene C. W. Mandl, Martijn P. Van den Heuvel, Rene S. Kahn

University Medical Center Utrecht, Utrecht, The Netherlands

Background: Progressive brain tissue loss in patients, particularly of gray matter (GM), suggest that a pathophysiological process is ongoing in schizophrenia. Finding the causes for this pathophysiological process is important. It could enable us to attenuate or halt the progressive brain changes. However, we do not know what process(es) underlie(s) the brain changes in schizophrenia. High field MRI may aid us in our search.
Methods: In 40 patients with schizophrenia and 40 healthy comparison subjects at 1.5 Tesla and in 18 patients with schizophrenia and 18 healthy comparisons at 3 Tesla, a T1w and T2w MRI, DTI and MTR of the whole head were acquired. In addition, a resting-state fMRI acquisition was done at 3 Tesla in 26 healthy subjects.
Results: Altered levels of myelination in the uncinate fasciculus, connecting the decreased GM density areas of medial inferior frontal and anterior temporal lobes, were found in patients as compared to controls (t=2.64, p=0.01). Seven resting state networks with underlying anatomical connections were found in healthy subjects and are currently assessed in patients.Included was the default mode network with medial frontal GM and precuneus, both decreased in GM density in schizophrenia.
Conclusions: GM areas with decreased density in schizophrenia show structural and functional connectivity in health and aberrant connectivity in schizophrenia. Methods to detect subtle variations in cortical GM tissue composition at ultra high field MRI (7 Tesla) are under way. With these new possibilities we can be carefully optimistic about future progress in finding pathophysiological processes in schizophrenia.
Supported by a grant from the Dutch Science Organization for Medical Research NWO ZON-MW VIDI Program (917.46.370) (HEH) and by a grant from the High Potential (HiPo) Program of the Utrecht University (HEH)

738. Cellular Substrates and Molecular Mechanisms Underlying Cortical Gray Matter Abnormalities in Schizophrenia

David A. Lewis, Guillermo Gonzalez-Burgos

University of Pittsburgh, Pittsburgh, PA

Background: The core features of schizophrenia include deficits in cognitive processes mediated by the circuitry of the dorsolateral prefrontal cortex (DLPFC). These deficits are associated with a range of molecular and morphological alterations in the DLFPC, including smaller somal volumes and a lower density of dendritic spines on pyramidal cells.
Methods: This presentation will review postmortem studies that address four questions: 1) Is the decrease in spine density specific to a certain subpopulation of DLPFC pyramidal neurons? 2) Is the decrease in spine density associated with a deficit in a specific source of excitatory inputs? 3) What molecular mechanisms mediate the lower spine density in schizophrenia? 4) How might developmental plasticity in excitatory synapses contribute to dendritic spine alterations in schizophrenia?
Results: Findings from recent postmortem human studies suggest that a convergence of both pre-synaptic (alterations in specific sources of inputs) and post-synaptic (expression changes in certain molecular cascades that regulate the actin cytoskeleton) are required for the reduction in spine density. Consistent with this interpretation, recent anatomical and electrophysiological findings in monkey DLPFC indicate that the pruning of axospinous synapses during adolescence is not determined by the functional maturity of the synapse but by the source of the input.
Conclusions: Together, these findings suggest possible cellular and molecular substrates for a smaller cortical gray matter volume in schizophrenia and may aid in the identification of novel targets for therapeutic or preventative interventions.
Supported by MH45156

SYMPOSIUM

Three Consortia on Genetics & Schizophrenia: New Approaches and Results

Saturday, May 3, 2008 2:30 PM - 5:00 PM
Location: Yorktown
Chair: David L. Braff*

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*Supported by NIMH

739. Update on the Project among African Americans to Explore Risks for Schizophrenia (PAARTNERS)

Rodney C. P. Go

Epidemiology and International Health, University of Alabama at Birmingham, School of Public Health, Birmingham, AL

Background: A genetic etiology is now widely accepted for schizophrenia (SZ). Recent reviews have identified several suggestive linkages, , e.g., 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 heritable cognitive domains are reported on 217 (n=1.078) linkage informative families in Table 1
Conclusions: Our preliminary results indicate that several of the cognitive domains exhibit significant heritabilities, and that several significant linkage peaks are in common among clinical and endophenotypic phenotypes, indicating there maybe genes with pleiotropic effects on several of these phenotypes.

Table 1. Heritability Estimates (AIREML) and Representative Linkages for Cognitive Traits (MERLIN)

Study	Type	ATT	VME	FME	SME	LAN
PAARTNERS	Accuracy	0.18	0.45	0.39	0.27	0.32
	Heritability					
	Chromosome	13	6	1	17	1
	LOD	2.8	3.8	4.7	3.1	2.5
	Location (cM)	110	88	82	128	230

Attention (ATT); Working Memory (WME); Verbal Memory (VME); Face Memory (FME); Spatial Memory (SME); Language (LAN);

Supported by R01MH66181,R01MH6606, R01MH66278, R01MH66049, R01MH66121, R01MH66005, R01MH66050, R01MH66263, R01MH66004

740. Update on the Multiplex Multigenerational Investigation of Schizophrenia (MGI)

Raquel E. Gur[1], Laura Almasy[2], Vishwajit Nimgaonkar[3], Karin Haack[2], Shelley A. Cole[4], Monica E. Calkins[1], Konsale Prasad[3], Michael F. Pogue-Geile[5], Ruben C. Gur[1]

[1]Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA,[2]Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX,[3]Psychiatry, University of Pittsburgh, Pittsburgh, PA,[4]Southwest Foundation for Biomedical Research, University of Pennsylvania School of Medicine, San Antonio, TX,[5]Psychology, University of Pittsburgh, Pittsburgh, PA

Background: Marked cognitive deficits are evident in schizophrenia. They may provide complementary7 measures to the diagnostic phenotype in the efforts to elucidate the neurobioloby of liability to schizophrenia.
Methods: The MGI Consortium ascertained European-Americans from multiplex multigenerational families, with two first-degree affected members, as well as community controls. Participants underwent clinical assessments, neurocognitive measurements and provided blood samples. The computerized neurocognitive battery (CNB) was administered to provide quantitiative traits that complement clinical diagnosis. The CNB measures accuracy and speed on abstraction and mental flexibility, attention, verbal, face, and spatial memory, emotion processing, and sensorimotor processing. A genome-wide linkage screen was performed using standard variance component methods.
Results: Performance on the neurocognitive phenotypes was most impaired in schizophrenia, with unaffected relatives' performance intermediate between probands and community controls. Significant heritability estimates were obtained in several neurocognitive domains. There was significant evidence of linkage for the diagnostic phenotype of schizophrenia on chromosome 19q (LOD=3.44). This finding is novel. For the neurocognitive phenotypes, significant linkage was observed for abstraction and mental flexibility on chromosome 5q (LOD=3.43). Other neurocognitive traits also showed nominal evidence of linkage in the 5q region. Chromosome 5 has been implicated in previous linkage studies of the schizophrenia phenotype.
Conclusions: Complementary phenotypes in the study of complex brain disorders may guide functional hypotheses on the cascade of neurobiological pathways linking genotypes to clinical manifestations of the disease.
Supported by MH042191, MH61622, MH063480

741. Update on the Consortium on the Genetics of Schizophrenia (COGS)

David L. Braff

Department of Psychiatry, University of California San Diego, School of Medicine, La Jolla, CA

Background: Converging model organism, candidate gene and genome-wide association (GWA) studies offer much promise in explicating the neurobiological 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.
Results: 129 (of 350) families have been examined using the COGS SNP Chip. Figure 1 illustrates the distribution of SNPs that are interrogated. Figure 2 shows the striking results. Genes such as NEURG 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. These results will be discussed.

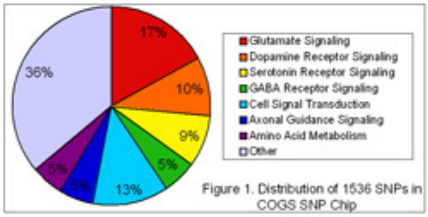

Figure 1. Distribution of 1536 SNPs in COGS SNP Chip

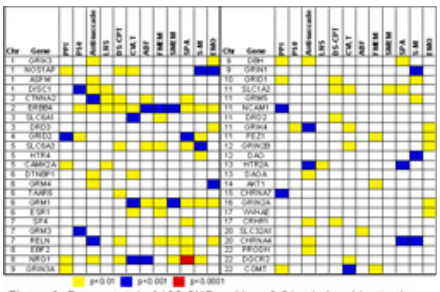
Figure 2. From a total of 192 SNPs with p<0.01 relationships to the 12 COGS endophenotypes

Supported by NIMH R01MH065571, NARSAD Distinguished Investigator Award

742. Advances in Statistical Genetics: Applications to Schizophrenia and Related Neuropsychiatric Disorders

Nicholas J. Schork

Scripps Health and The Scripps Research Institute, La Jolla, CA

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. Unfortunately, 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 genic regions -- may contribute to phenotypic expression.
Results: We describe, in a non-mathematical way, the use of novel data analysis methods for pursuing genetic background assessments on the subjects in a large-scale genetic study as well as haplotype-based studies that accommodate allelic complexities in GWAS contexts. These methods are showcased on actual data and a 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.
Supported by NIMH R01MH065571

SYMPOSIUM
Progressive Brain Changes in Schizophrenia
Saturday, May 3, 2008 2:30 PM - 5:00 PM
Location: Capitol A
Chair: Robert W. McCarley*

*Supported by P50MH080272, R01MH40799

743. Cross-Sectional and Longitudinal Ventricular Volume Changes in Chronic Schizophrenia, First-Episode Psychosis, and Ultra-High Risk Individuals

Christos Pantelis[1], Gregor E. Berger[2], Sephen J. Wood[1], Anthony Ang[1], Warrick J. Brewer[3], Lisa J. Phillips[4], Alison R. Yung[3], Tina M. Proffitt[3], Dennis Velakoulis[1], Patrick D. McGorry[3]

[1]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne & Melbourne Health, Melbourne, Australia,[2]Department of Psychiatry, University Hospital Basel, Basel, Switzerland,[3]ORYGEN Research Centre, Department of Psychiatry, University of Melbourne & Melbourne Health, Melbourne, Australia,[4]Department of Psychology, University of Melbourne, Melbourne, Australia

Background: Ventricular enlargement (VE) has been robustly replicated in schizophrenia. However, studies are limited by small samples, illness chronicity and medication effects. Studies of first-episode psychosis (FEP) suggest VE occurs early, with evidence of progression, although it is unclear if these changes occur premorbidly. We recently identified structural grey matter brain changes in individuals at ultra-high risk of psychosis (Pantelis et al, Lancet, 2003), with further progressive cortical changes following illness onset. We report cross-sectional and longitudinal ventricular changes in this ultra-high risk group compared with FEP, chronic schizophrenia and controls.
Methods: MRI scans were acquired on 473 subjects: chronic schizophrenia (CHR, 89), FEP (162), ultra-high risk for psychosis (UHR, 135, with 39 â€˜convertersâ€™ to psychosis), and controls (CTLS, 87). Follow-up scans conducted on 13 CHR, 25 FEP, 29 UHR and 24 CTLS.
Results: Significant group effect (F3,473=7.165; P<.001); compared with CTLS, VE was 43.9% greater in CHR, 11.9% larger in FEP and 3.3% larger in UHR (regardless of subsequent psychosis status). VE enlargement in CHR correlated with illness duration (r=0.388; p<0.01). Longitudinal ventricular expansion found in patients with schizophreniform FEP (18% increase, p=0.023, Cohenâ€™s d=1.47).
Conclusions: The cross-sectional findings indicate that VE is a feature of chronic schizophrenia, mildly enlarged in FEP, with no VE pre-illness onset. Longitudinal results suggest progressive changes occur soon after onset of schizophreniform psychosis. These results indicate that VE is progressive early in schizophrenia and does not represent an endophenotype of schizophrenia.
Supported by National Health & Medical Research Council (Australia)

744. Effects of Genes and Illness on Brain Changes in Schizophrenia and Bipolar Disorder

Rene S. Kahn

Dept. Psychiatry, Rudolf Magnus Institute of Neuroscience, UMC Utrecht, Utrecht, The Netherlands

Background: Brain abnormalities have been demonstrated in both schizophrenia and bipolar disorder although the data on bipolar disorder are less consistent. It is unclear whether the brain changes in bipolar disorder and schizophrenia are related to the illness or to the genetic risk of developing this disorder. Moreover it is unclear what if any genes may be related to these abnormalities.
Methods: Two separate twin MRI studies, one in schizophrenia and one in bipolar disorder, were conducted including in total over 350 subjects. A separate cohort of around 100 patients (non-twins) and a similar number of healthy subjects were scanned using MRI and genotyping was done in these subjects.
Results: In both bipolar disorder and schizophrenia, reductions in white matter volume were related to the genetic risk to develop these disorders. Grey matter reductions were related to the effects of illness in both disorders, although the effect was less pronounced in bipolar disorder. This smaller effect could almost completely be accounted for by the effect of lithium. Some of the fibroblast growth factor (FGF) genes were found to be significantly related to the white matter volumes in controls and patients.
Conclusions: White matter abnormalities may be related to a shared (genetic) vulnerability to develop schizophrenia and bipolar disorder and may be related to abnormalities in the FGF gene family. This gene is essential for normal neuronal growth, especially in the dopaminergic system. The FGF gene family may be interesting candidates for risk genes in schizophrenia as well as bipolar disorder.

745. Progression of MRI and Electrophysiological Abnormalities in First Episode Patients with Schizophrenia & Affective (Bipolar) Psychosis

Robert W. McCarley[1], Motoaki Nakamura[2], Martha E. Shenton[3], Dean F. Salisbury[4]

[1]Psychiatry, Harvard Medical School/VA Med Ctr-Brockton, Brockton, MA,[2]Psychiatry, Yokohama City University Medical School, Yokohama, Japan,[3]Psychiatry, Harvard Medical School/Brigham & Women's Hospital, Boston, MA,[4]Psychiatry, Harvard Medical School/McLean Hospital, Belmont, MA

Background: The nature of post-onset progression of structural and functional changes in schizophrenia is important for understanding its pathophysiology and rational treatment.
Methods: Using 1.5T MRI and evoked potentials, we examined schizophrenia and affective psychosis (bipolar) patients at first hospitalization (first episode, FE) and 1.5 years later, together with their healthy controls. Patients with chronic schizophrenia (mean 16yr illness) were studied longitudinally over 3 years.
Results: In FE schizophrenia, MRI showed progressive neocortical gray matter (NCGM) volume loss, whose degree varied: overall NCGM -1.7%, temporal and frontal NCGM -2.5% (parieto-occipital not significant); right superior temporal gyrus (STG), -2.9%; left STG, Heschl's Gyrus, and Planum Temporale -8 to -9%. Progression rate was maximal near initial hospitalization. Volume

increases occurred in subcortical CSF (7.2%) and lateral ventricles (10.4%). NCGM loss/CSF increases were associated with a worse longitudinal course of clinical symptoms. The Mismatch Negativity evoked potential, initially normal, became abnormal at 1.5 yr retest, with a degree of progression highly correlated with the degree of volume loss in left Heschl's gyrus. FE affective psychosis showed a longitudinal increase in overall NCGM (3.6%), associated with lithium and valproate medication, but not with clinical symptoms. In contrast, chronic patients showed no statistical evidence of progressive volume loss in STG and hippocampus/amygdala or MMN progression.
Conclusions: These data suggest most of the post-onset structural and functional brain alterations in schizophrenia occur near the onset (first hospitalization), implying that this epoch is critical for therapeutic intervention. In contrast to schizophrenia, FE affective psychosis showed a lithium/valproate medication-related NCGM volume increase.
Supported by P50MH080272, R01MH40799

746. Mapping Progressive Brain Changes in an Antipsychotic Trial

Paul M. Thompson

Laboratory of NeuroImaging and Brain Research Institute, UCLA School of Medicine, Los Angeles, CA

Background: With recent innovations in brain mapping, structural brain changes in schizophrenia patients can now be charted as they spread dynamically in the living brain. Using time-lapse maps, we visualized the dynamics of schizophrenia progression, showing that cortical changes spread in a pattern that depends on the type of antipsychotic treatment.
Methods: Dynamic, four-dimensional models of disease progression were created from 4 repeated MRI scans of 36 subjects experiencing their first episode of non-affective psychosis (30 men/6 women; mean age: 24.2+/-5.1SD years); 15 and 21 were randomized to haloperidol or olanzapine treatment, respectively. All subjects underwent high-resolution brain MRI, at baseline, 3, 6, and 12 months (144 scans). Surface-based cortical models and point-by-point measures of gray matter volume were combined to create a time-lapse map for each treatment.
Results: Disease trajectories differed for atypical versus typical neuroleptic drugs. A rapidly advancing parietal-to-frontal deficit trajectory was tracked in haloperidol-treated patients, mirroring normal cortical maturation but greatly intensified. Areas with fastest tissue loss shifted anteriorly in the first year of psychosis. This trajectory was not seen with olanzapine, which may be less neurotoxic or neuroprotective. Time-lapse maps may be viewed here:
http://www.loni.ucla.edu/~thompson/MOVIES/HGDH/sz.html
Conclusions: These maps reveal a disease trajectory that advances even after symptom normalization and engulfs the frontal cortex within 12 months with typical drug treatment. These maps revise current models schizophrenia progression, reconciling several discrepant findings from cross-sectional studies by mapping time-varying disease effects.
Supported by NIH grants EB01651, RR019771, AG016570, LM05639, HD050735 and P41 RR13642.

SYMPOSIUM

Effects of Altered 5-HTT function on Cognition and Learning – Evidence from Genetic Studies in Mice, Monkey & Man

Saturday, May 3, 2008 2:30 PM - 5:00 PM
Location: Capitol B
Chair: Ahmad R. Hariri*

*Supported by K01MH072837

747. Genetic Factors Modulating Executive Control in the Mouse

Andrew Holmes

NIAAA, Rockville, MD

Background: There is growing evidence that the 5-HT is an important modulator of executive functions including cognitive flexibility. How variation in 5-HT genes such as the 5-HTT, might impact cognitive flexibility is stll not well understood.
Methods: I will provide evidence ofaltered reversal learning in 5-HTT knockout mice.
Results: Using a touchscreen-based operant assay of cognitive flexibility I will compare the executive function of 5-HTT knockout mice with the effects of pharmacological and genetic depletion of central serotonin.
Conclusions: Our studies may provide further insight into the influence of 5-HTT gene variation on executive functions.
Supported by NIH IRP

748. Genetic Modulation of Cognitive Flexibility and Socioemotional Behavior in Rhesus Monkeys

Elisabeth (Betsy) A. Murray

Laboratory of Neuropsychology, NIMH, Bethesda, MD

Background: In human and nonhuman primates, structural variants of the gene encoding the serotonin transporter (5-HTT) affect the transcription and functional efficacy of 5-HTT. Prior work has shown that structural variants differentially affect the function of the amygdala, as well as the orbital and medial sectors of prefrontal cortex, regions important for the regulation and expression of emotion. However, relatively little is known about the impact of 5-HTT allelic variants on cognition.
Methods: Rhesus monkeys carrying orthologous structural variants of 5-HTT were tested on a battery of tasks that assess cognitive flexibility, reward processing, and emotion.
Results: Relative to monkeys carrying one or two copies of the long allele (SL and LL), monkeys carrying two copies of the short allele (SS) of the rhesus 5-HTT gene-linked polymorphic region (rh5-HTTLPR) show significantly reduced cognitive flexibility as measured by two tasks in the battery: object discrimination reversal learning and instrumental extinction. Socioemotional behavior also differed by genotype. Genotype variation was not related to visual perceptual abilities, valuation of food rewards, or the ability to express a wide range of defensive responses.
Conclusions: Although emotional alterations associated with 5-HTT variation have been described as the primary phenotype, the rh5-HTTLPR variation appears to influence cognitive functions outside the affective domain. Because behaviors modulated by the 5-HTTLPR are a subset of those dependent on the orbital and medial sectors of prefrontal cortex, analysis of structural and functional correlates of gene variation in this region may inform the nature of the genetic modulation of cognition.
Supported by NIMH Intramural Research Program

749. 5-HTTLPR Variants in Rhesus Monkeys Modulate Anterior Cingulate Dependent Cognition without Impact on Transporter Levels

Charles W. Bradberry

Psychiatry, University of Pittsburgh, Pittsburgh, PA

Background: Rhesus monkeys carry 5-HTTLPR variants orthologous to those in humans shown to alter risk for affective disorders and cognitive performance. The basis for these effects are unknown. Monkey studies permit a comparison of environmental manipulations such as peer- vs mother rearing with genotype effects on cognitive function and 5-HT transporter binding in-vivo.
Methods: Rhesus monkeys carry 5-HTTLPR variants orthologous to those in humans shown to alter risk for affective disorders and cognitive performance. The basis for these effects are unknown. Monkey studies permit a comparison of environmental manipulations such as peer- vs mother rearing with genotype effects on cognitive function and 5-HT transporter binding in-vivo.
Results: Analyzed by genotype, striking group differences in cognitive performance were seen that were consistent with altered cingulate cortex function. In addition to the genotype effects, a rearing effect was seen on the stop signal response time, a measure of instrumental impulsivity. Imaging the 5-HT transporter revealed a very close match with the regional distribution seen in humans, however no significant differences were seen either by genotype or rearing condition.
Conclusions: A clear impact of 5-HTTLPR genotype on cognitive performance was seen in the monkey. The type of functionality impacted is consistent with anterior cingulate cortex as a locus for differences. Consistent with the bulk of in-vivo and ex-vivo studies, there are not differences in 5-HT transporter by genotype, suggesting other mechanisms are mediating the effects observed.
Supported by R01AA014646

750. The Effect of Serotonin Transporter Polymorphism on Cognitive Function in Healthy Volunteers

Jonathan P. Roiser

Institute of Cognitive Neuroscience, University College London, London, United Kingdom

Background: Genetic variation at the serotonin transporter linked polymorphic region (5-HTTLPR) has been associated with psychopathology, brain structure and function. However, few studies have reported an association between 5-HTTLPR polymorphism and behavioral measures.
Methods: Data from three studies investigating the effect of 5-HTTLPR polymorphism on cognitive function in healthy volunteers will be presented. The first study was an investigation of the effect of 5-HTTLPR polymorphism on cognitive function in ecstasy users and controls. The second study examined how 5-HTTLPR genotype modulated response to acute tryptophan depletion (ATD), utilizing measures of motivation, memory and attention. The third study examined the neural correlates of economic decision-making in volunteers of different 5-HTTLPR genotypes.
Results: 5-HTTLPR genotype had significant effects on emotional processing in all three studies. In the first study, carriers of the ss genotype exhibited more irrational decision-making; in the ecstasy users, the ss group reported the highest levels of current depressive symptomatology. In the second study, the ss group outperformed the ll group on measures of verbal recall memory and attention, and were also most vulnerable to serotonin depletion, demonstrating motivational and mnemonic deficits following ATD. Data from a neuroimaging study of economic decision-making in volunteers of different 5-HTTLPR genotypes will also be presented.
Conclusions: Polymorphism at the 5-HTTLPR appears to affect cognitive performance, particularly on tests making use of emotionally-valenced material, and ss individuals appear to be more susceptible to serotonin depletion. Studying the effects of the 5-HTTLPR polymorphism using functional neuroimaging may aid our understanding of the pathophysiology of mood and anxiety disorders.
Supported by Wellcome Trust

SYMPOSIUM
Functional Studies of DAOA
Saturday, May 3, 2008 2:30 PM - 5:00 PM
Location: Congressional A
Chair: Elliot S. Gershon*
Co-Chair: Chunyu Liu**

*Supported by 5R01 MH61613
**Supported by NIH 1R01MH080425-01

751. G72/G30 Transgenic Mice: A Model for Schizophrenia?

Andras Bilkei-Gorzo

Institute of Molecular Psychiatry, University of Bonn, Bonn, Germany

Background: The G72/G30 gene locus is a strong candidate susceptibility region for schizophrenia and bipolar disorder, whose function remains to be elucidated. LG72 is an evolutionary novel, primate-specific gene encoding for a protein with no recognizable motifs and controversial functions. One hypothesis suggests that LG72 is an activator of the D-amino acid oxidase (DAO), an enzyme known to oxidize D-amino acids such as D-serine, an agonist of N-methyl-D-aspartic acid (NMDA) receptors.
Methods: To further analyze the function of G72 in vivo we generated BAC transgenic mice. The presence and intensity of gene expression was tested using in-situ hybridization method. Animals were tested in a series of models covering the most prominent symptoms of schizophrenia: cognitive deficits, emotional and information processing disturbances, positive and negative symptoms.
Results: The G72 transgenic mice expressed G72 transcripts in the brain with high levels in different brain areas and showed a complex alternative splicing pattern. Biochemical and histological analysis of the brain of the transgenic animals did not support the existence of interaction between G72 and DAO. Behavioral analysis of the transgenic strain revealed a phenotype of the transgenic strain in models relevant to schizophrenia.
Conclusions: The phenotypic analysis of this strain showed that G72 transgenic mice might represent an interesting disease model.
Supported by NGFN2 01GS0474

752. Gene Expression, Biochemistry, and Behavior Study in a G72 Transgenic Mouse Model

Lijun Cheng

University of Chicago, Chicago, IL

Background: The G72/G30 gene has multiple reports of association with both bipolar disorder and schizophrenia. A G72-D aminoacid oxidase (DAAO)-NMDA receptor hypothesis and a G72- mitochondria hypothesis have been proposed as possible G72 roles.
Methods: The human 110kb BAC clone "RP11-166E2" encompassing the G72/G30 gene complex was microinjected into C57BL/6J mouse eggs to generate a G72/G30 transgenic mouse line. RT-PCR and real-time PCR were used to examine G72 expression in human and transgenic mouse brain. The genome expression profile of transgenic mouse cortex was studied with

the Illumina Mouse-6 beadChip. DAAO enzyme activity was examined in transgenic mouse to test the G72-DAAO-NMDA hypothesis. Behavioral tests (open-field, sucrose preference, water maze et al) were performed to evaluate possible behavioral phenotypes.
Results: We have established G72 hemi- and homozygous transgenic mice lines. G72 expresses at very low level in human brain and testis. G72 expresses at a relatively high level in transgenic mouse brain cortex, followed by striatum, hippocampus and (almost undetectably) cerebellum. No significant changes in G72 expression level were observed during brain postnatal development. Thirteen novel G72 splicing forms were identified from human and transgenic mouse. Preliminary results indicated significantly different expression of several genes between transgenic and wild type mouse in beadchip study. DAO enzyme activity of transgenic mouse cerebellum is higher than that of wild type mouse. Transgenic mice did not show abnormal locomotor activity in open field test.
Conclusions: The G72 transgenic mice may serve as a useful in vivo model to study G72 function and its role in disease etiology.
Supported by RO1MH61613-05A1; RO1MH65560-02

753. Evidence Implicating the Candidate Schizophrenia/Bipolar Disorder Susceptibility Gene G72 in Mitochondrial Function

Mirna Kvajo

Psychiatric Instutute, Columbia University, New York, NY

Background: G72 is a strong candidate susceptibility gene for schizophrenia and bipolar disorder, whose function remains enigmatic. One hypothesis regarding its role is based on in vitro observations suggesting that one splice variant of G72 (LG72) binds to and activates D-amino acid oxidase (DAO), an enzyme known to oxidize D-amino acids such as D-serine, an agonist of NMDA receptors. These in vitro results suggested a role for the G72 gene in the regulation of NMDA-type glutamate receptors signaling.
Methods: We investigated the subcellular localization of exogenous LG72 in several cell lines using immunocytochemistry and Western blotting. We further established the localization of the endogenous LG72 protein, and determined its role in the modulation of mitochondrial morphology. Furthermore, primary neuronal cultures were used to assess its function in dendritic arborization. Immunocytochemistry, immunoprecipitation and activity assays were performed to analyze its interaction with DAO.
Results: We show that LG72 encodes for a mitochondrial protein and provide convergent lines of evidence showing that increase of LG72 levels promotes robust mitochondrial fission in cell lines and primary neurons, which proceeds in a manner that does not depend on induction of apoptosis or alteration in mitochondrial transmembrane potential. Finally we show that increase in LG72 levels in immature primary neurons is accompanied by a marked increase in dendritic arborization. By contrast, we fail to confirm the originally proposed functional interaction between LG72 and DAO in mammalian cell lines.
Conclusions: Our results suggest an alternative role for at least some G72 isoforms in modulating mitochondrial function and dendritic development.
Supported by NIMH; New York Academy of Science

754. DAOA and Intermediate Phenotypes

Terry E. Goldberg

Zucker Hillside Hospital/Feinstein Institute, Glen Oaks, NY

Background: DAOA (formerly called G72) has been found to be associated with schizophrenia and has impacted several important intermediate phenotypes. Meta-analyses have also been positive. The gene may have an indirect effect on NMDA neurotransmission; it may also have a role in modulating mitochondrial function.
Methods: We examined DAOA's impact on intermediate phenotypes using cognitive measures and fMRI.
Results: In an NIMH sample diagnosis x genotype interaction effects for DAOA alleles at the 3' end of the gene were significant for cognitive variables assessing working memory, attention, and episodic memory, such that in the schizophrenia group an exaggerated allele load effect in the predicted direction was observed (i.e., epistasis was perhaps present). In a ZHH sample a counter intuitive finding was observed: A previously identified risk haplotype from the 5' region of the gene was associated with better semantic fluency.
Patients with schizophrenia who were carriers of the advantageous DAOA allele demonstrated more improvement in executive function and episodic memory than those with the disadvantageous allele when administered antipsychotic medication.
In healthy controls a strong effect of DAOA genotype was observed on fMRI BOLD activation in the MTL during an episodic memory paradigm that involved encoding visual scenes.
Conclusions: We have provided evidence that variations in the DAOA gene region may modulate some aspects of cognition in schizophrenia and influence BOLD signal in regions critical for memory processing. More broadly, the studies raise important questions about what constitutes a replication, multiple comparisons, and the possibility of balanced selection.

SYMPOSIUM

Mapping the Development of Cortical Circuits Through Adolescence in Healthy Subjects and Neurodevelopmental Disorders

Saturday, May 3, 2008 2:30 PM - 5:00 PM
Location: Congressional B
Chair: Aysenil Belger*
Co-Chair: Larry J. Seidman**

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*Supported by NIMH 5P50 MH064065-06; NIMH 2R01 MH58251-06-A2; Foundation of Hope; NARSAD Independnet Investigator Award
**Supported by MH 43518 63951 65562 P41RR14075 NARSAD Stanley Medical Research Institute MIND Institute

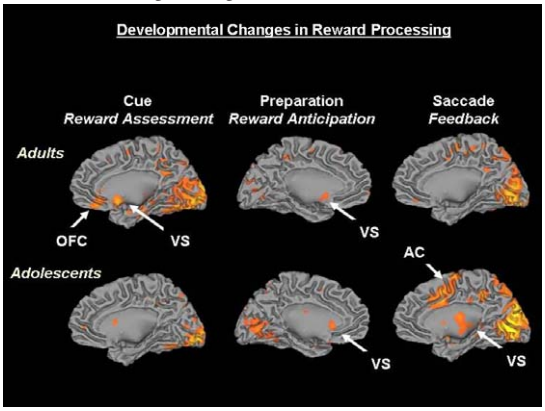
755. Immaturities of Cognitive Control and Reward Processing in Adolescence

Beatriz Luna

University of Pittsburgh School of Medicine, Pittsburgh, PA

Background: Adolescence is a time of vulnerability for mortality due to risk taking behavior and the emergence of major psychopathology. The neural basis of the development of cognitive control and reward processing through adolescence is not well-understood.
Methods: We use oculomotor tasks that assess fundamental aspects of the maturation of cognitive/executive control as well as fMRI to assess changes in brain function and DTI neuroimaging to characterize maturation of white matter integrity reflecting protracted myelination.
Results: Behavioral results indicate a continued maturation of cognitive control into adolescence and enhanced modulation of reward processing. fMRI results indicate immaturities in adolescence in the neural circuitry supporting the ability to inhibit responses and importantly to retain an inhibitory response 'state'. Reward studies indicate under-activity of reward assessment in ventral striatum and orbitofrontal cortex and over-activity of the motivational/anticipatory processing of rewards. DTI studies indicate immaturities in pathways connecting frontal regions with other cortical regions, as well as subcortical regions including

ventral striatum, regions that underlie cognitive control and reward processing.
Conclusions: Collectively, our work indicates that adolescence is a critical stage of developmental transition when collaborative function between widely-distributed brain systems reaches adult-like levels of maturities. Importantly, however, adolescence may also be a stage of development particularly vulnerable to error and disruption, as risk-taking behavior and major psychopathology have been shown to emerge during this time.



Supported by MH067924

756. Functional and Structural Indices of Adolescent Brain Development in the Risk for Schizophrenia

Larry J. Seidman

Department of Psychiatry, Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Boston, MA

Background: In the Harvard Adolescent High Risk study, we sought to demonstrate that young, non-psychotic relatives of persons with schizophrenia (i.e., who are at genetic risk (GR) for the illness) have altered brain structure and function during adolescence prior to onset of psychosis, in order to define brain vulnerability indicators for schizophrenia.
Methods: We focused on working and declarative memory probes of medial temporal lobe (MTL) and prefrontal (PFC) activation, measures of the default network, volumetric measures of the hippocampus, and measures of cortical thickness. Participants were 35 non-psychotic, unmedicated first-degree relatives of persons with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type and 55 unmedicated controls (ages 13-28). Twenty-seven persons at GR for schizophrenia and 48 controls received structural MRI. Twenty-one persons at GR for schizophrenia and 26 controls were studied with functional MRI (fMRI).
Results: The GR subjects showed significant impairments on working and declarative memory tasks outside the scanner and significantly greater task-elicited activation in the right prefrontal cortex (PFC) on the working memory task, and greater activation in the parahippocampal gyrus bilaterally on the verbal encoding task. Compared to controls they exhibited significantly reduced task-related suppression of activation in the default network including medial prefrontal cortex, lateral parietal cortex, and hippocampus. GR subjects had smaller hippocampi, significantly smaller in the left hemisphere, and reduced cortical thickness.
Conclusions: Data support physiological and structural brain differences in adolescents at genetic risk for schizophrenia, independent of psychosis. Further work is necessary to identify predictors of psychosis.
Supported by MH 43518 63951 65562 P41RR14075 NARSAD Stanley Medical Research Institute MIND Institute

757. Functional Cortical Alterations in Children and Adolescents at Genetic Risk for Schizophrenia

Aysenil Belger

Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC

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: We studied neural maturation of circuits supporting exective attention and affective processing in 22 healthy control (HC) subjects and 23 individuals at genetic risk for schizophrenia (GHR) between the ages of 9 and 18 using functional magnetic resonance imaging (MRI) on a 3T GE scanner. Subjects performed an emotional oddball task, where they identified rare visual targets while ignoring emotional and neutral distractor pictures.
Results: There were no significant group differences in age, gender, ethnicity, education ($p<.08$) and parental education ($p<.06$). GHR children had greater early prodromal symptoms of schizophrenia as assessed using the Scale of Prodromal Symptoms ($p<.001$). FMRI Random effects analyses revealed that prefrontal regions, in particular the insular and dorsal prefrontal regions and the anterior cingulate gyrus showed significantly greater activation amplitude and extent in GHR subjects during executive attention ($p<.01$). Similarly, limbic regions including the amygdala and the ventral prefrontal regions also showed significantly greater activation in GHR subjects.
Conclusions: Cortical information processing inefficiency in fronto-limbic and fronto-striate regions during puberty may be an early neurodevelopmental alteration in children at risk for schizophrenia, and may represent vulnerability markers for illness onset. Longitudinal assessments will further inform about their predictive value for illness onset in high-risk populations.
Supported by NIMH 5P50 MH064065-06; NIMH 2R01 MH58251-06-A2; Foundation of Hope; NARSAD Independnet Investigator Award

758. Neuroimaging and Treatment of Pediatric Bipolar Disorder

Jean A. Frazier

Child Psychiatry, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA

Background: Neurodevelopmental models of bipolar disorder (BPD) posit subtle disease processes that affect brain circuits early in development that then manifest in illness around puberty. Puberty is pivotal in these models, yet to date no neuroimaging studies in early-onset BPD have assessed associations between pubertal development, brain abnormalities, and disease expression. This presentation will include cross-sectional neuroimaging data that evaluate developmental processes and expression of BPD.
Methods: Subjects received neurological and psychiatric assessment, semi-structured interviews, and structural MRIs on a 1.5 Tesla scanner. After image segmentation, subcortical gray matter volumes were analyzed using three-way (diagnosis, sex, Tanner) univariate analysis of variance, controlling for cerebral volume and age.
Results: Fifty-four BPD I youths (19 with psychosis) and 29 healthy controls, similar in age, participated in this study. There were more males in both groups. Just over half of both diagnostic groups were prepubertal; however, most boys with BPD were prepubertal (80%), while most girls (67%) were pubertal. Youths with BPD had larger right nucleus accumbens (NA) volumes. Relative to controls, the hippocampus was smaller in the BPD pubertal female group. Amygdala volumes were similar between groups, though only BPD youth showed increasing amygdala volume with age.
Conclusions: Our data suggest that limbic structures in children with BPD are vulnerable to sexual dimorphism and peripubertal change. Future longitudinal

studies with larger samples may enhance our knowledge about critical developmental periods during which interventions might be most helpful to prevent illness onset and progression for these youths, perhaps in a sex-specific way.
Supported by K08MH01573

SYMPOSIUM
New Human Genetic and Neurobiological Data Implicate Bcl-2 in the Pathophysiology and Treatment of Severe Mood Disorders

Saturday, May 3, 2008 2:30 PM - 5:00 PM
Location: Concord/Lexington
Chair: Husseini K. Manji*
Co-Chair: Jing Du**

*Supported by NIMH Intramural Research Program
**Supported by NIMH intramural

759. Efficacy and Neurochemical Effects of Adjunctive Cytidine Supplementation in Treating Bipolar Depression: 12-week Results from a Randomized, Double-Blind, Placebo-Controlled Trial

Sujung J. Yoon[1], In Kyoon Lyoo[2,3], Bruce M. Cohen[3], **Perry F. Renshaw**[3]

[1]Department of Psychiatry, Catholic University Medical College, Seoul, Republic of Korea,[2]Department of Psychiatry, Seoul National University Hospital, Seoul, Republic of Korea,[3]Department of Psychiatry, Harvard Medical School, Belmont, MA

Background: Recent magnetic resonance spectroscopy (MRS) studies suggest that mitochondrial dysfunction is a central component of bipolar pathophysiology. For instance, increases in lactate, glutamate and glutamine (Glx) levels, measured in bipolar patients with proton MRS, indicate disturbances in energy metabolism. Impaired oxidative phosphorylation leads to glycolytic energy production and a decrease in phospholipid metabolism. Hypometabolism decreases de novo synthesis of pyrimidine in mitochondria, which requires high-energy phosphates. Consequently, exogenous pyrimidine administration should reduce the energy requirements of the mitochondria and ameliorate the energy imbalance in bipolar patients.
Recent animal studies found that pyrimidine nucleosides, cytidine and uridine, have antidepressant-like effects. Exogenous pyrimidine administration has been shown to have beneficial effects on 1) catecholamine levels, including norepinephrine and dopamine, 2) phospholipid metabolism, and 3) mitochondrial function.
In the current study we investigated whether cytidine, given in conjunction with valproate, improved depressive symptoms in bipolar patients.
Methods: Sixty-five adult, bipolar depressed subjects were randomly assigned to receive valproate with either placebo or oral cytidine. Clinical assessments were conducted at baseline and weekly intervals during the 12-week trial. 35 patients underwent MRI scans at baseline, week 2, week 4, and week 12 to investigate the association between cytidine administration and the brain levels of Glx, as measured by 1H-MRS.
Results: As compared with placebo, cytidine supplementation significantly improved the depressive symptoms of bipolar patients in early treatment and reduced Glx levels.
Conclusions: Due to its efficacy and its rapid onset, cytidine supplementation should be considered as a viable treatment for depressive bipolar disorder.
Supported by the Stanley Medical Research Institute

760. Dynamic Regulation of Mitochondrial Functions by Glucocorticoids and Stress

Jing Du[1], Yun Wang[1], Richard Hunter[2], Rodrigo Machado-Vieira[1], Yanling Wei[1], Cynthia Falke[1], Bruce MvEwen[2], Husseini Manji[1]

[1]NIMH/NIH, Bethesda, MD,[2]The Rockefeller University, Laboratory of Neuroendocrinology, New York, NY

Background: Corticosterone plays an important role in modulating neuroplasticity and in morphological reorganization, especially during chronic stress. The mechanisms underlying corticosterone's ability to modulate neuronal functions, especially mitochondrial functions, remain unclear.
Methods: Mitochondrial GR and Bcl-2 levels, mitochondrial calcium holding capacity, mitochondrial oxidation, and membrane potential were determined after corticosterone treatment in cultured cortical neurons. Formation of Bcl-2 and GR complex also were tested by immunoprecipitation. In addition, the mitochondrial GR and Bcl-2 levels in prefrontal cortex of chronically stressed or corticosterone-treated animals were analyzed by Western blot analysis.
Results: We found that glucocorticoid receptors (GRs) formed a complex with Bcl-2 in response to corticosterone treatment, and translocated with Bcl-2 into mitochondria after acute treatment with low and high doses of corticosterone in primary cortical neurons. However, after three days of treatment, high corticosterone resulted in a decrease in GR and Bcl-2 levels in the mitochondria. In addition, three independent mitochondrial functional measurements, mitochondrial calcium holding capacity, mitochondrial oxidation, and membrane potential were also regulated by low and high doses of corticosterone after long-term treatment in a bell-shaped manner. Similarly, after chronic stress and long-term treatment with corticosterone, GR and Bcl-2 levels in the mitochondria were significantly decreased in prefrontal cortex.
Conclusions: These findings suggest that, in response to corticosterone, GR recruits Bcl-2 into mitochondria and regulate mitochondrial functions. These findings have the potential to contribute to a more complete understanding of the mechanisms by which chronic stress and hormones regulate cellular plasticity and resilience, and to inform the future development of improved therapeutics.
Supported by NIMH intramural

761. Mitochondria in Synapse Development and Plasticity

Zheng Li

NIMH/NIH, Bethesda, MD

Background: Synapses are contact sites between neurons that transmit neuronal activity and undergo structural and functional modifications (synaptic plasticity) in development, cognition and diseases. NMDA receptor-dependent long-term modifications of synapses (such as long-term potentiation (LTP) and long-term depression (LTD)) are important cellular mechanisms of synaptic plasticity. Mitochondria are vital organelles in all eukaryotic cells that function in aerobic respiration, buffering of intracellular Ca^{2+} and in the mechanisms of apoptosis. The association of mitochondrial dysfunctions with many neurological diseases suggest that mitochondria are important for neural functions.

Methods: We took time-lapse confocal images of mitochondria in primary culture of hippocampal neurons to monitor the motility and subcellular distribution of mitochondria and their response to neuronal activity. We induced LTP and LTD in hippocampal slices and tested the effect of caspase inhibitors on LTP/LTD. Using an antibody feeding assay, we examined the endocytosis of AMPA receptors following a chemical LTD stimulation.
Results: Our studies reveal that mitochondria dynamically redistribute into dendritic protrusions in response to synaptic excitation and correlated with synaptogenesis and spine formation. The dendritic distribution of mitochondria is essential for synapse development. Mitochondria play an important role in synaptic plasticity as well. After LTD stimulation, caspases are activated by the mitochondria pathway. Inhibition of caspases block LTD and AMPA receptor endocytosis.
Conclusions: Our results suggest that mitochondria are critical for synapse development and plasticity. Mitochondria support synapse formation during development. In synapstic plasticity, the mitochondrial pathway is activated by LTD stimulation, which leads to activation of caspases and subsequent endocytosis of AMPA receptors.
Supported by F2NS046126

762. Bcl-2: A Key Regulator of Affective Resilience in the Pathophysiology and Treatment of Severe Mood Disorders

Husseini K. Manji

Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Bethesda, MD

Background: Recent studies have suggested that the neurotrophic protein Bcl-2 not only regulates cell survival and death, but also plays a critical role in 'here and now' synaptic plasticity. As such, it represents a potentially critical molecule in the pathophysiology and treatment of severe mood disorders.
Methods: An integrated series of human genetic, molecular neurobiologic, and rodent behavioral studies were undertaken to determine the precise role of Bcl-2 in mood disorders.
Results: Human genetic studies demonstrated that a SNP in the Bcl-2 gene was significantly associated with bipolar disorder in two large, independent samples. Furthermore, a Bcl-2 SNP was also associated with the likelihood of going into full remission with chronic citalopram treatment in the STAR*D study. The Bcl-2 SNP associated with bipolar disorder resulted in significantly lower Bcl-2 mRNA, ~ 50% lower Bcl-2 protein levels, and greater cellular sensitivity to stress-induced apoptosis. Bcl-2 +/- mice displayed higher rates of helplessness, and lower rates of recovery from helplessness in the learned helplessness paradigm. The Bcl-2 +/- mice also displayed blunted responsiveness to citalopram treatment in the forced swim test, tail suspension test, and helplessness paradigm. Infusion of a Bcl-2 inhibitor into the third ventricle of the brain resulted in a similar behavioral profile in wild-type mice.
Conclusions: The human genetic and neurobiologic data suggest that Bcl-2 regulates affective-like behavioral resilience in animals and that targeting Bcl-2- mediated plasticity cascades may result in improved therapeutics for mood disorders.
Supported by NIMH Intramural Program-NIH

POSTER SESSION
Mixed Topics
Saturday, May 3, 2008 5:00 PM - 6:30 PM
Location: Columbia

763. Cortical Thinning in Comorbid ADHD and Bipolar Disorder

Joseph Biederman[1], Nikos Makris[2], Eve M. Valera[1,3], Michael Monuteaux[1], Steven Hodge[4], Jonathan Kaiser[4], Ariel B. Brown[1,5], Megan Aleardi[1], Verne Caviness[6], Stephen Faraone[7], Larry Seidman[1,8]

[1]Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Boston, MA,[2]Departments of Neurology and Radiology, Massachusetts General Hospital, Boston, MA,[3]Department of Psychiatry, Harvard Medical School, Boston, MA,[4]Center for Morphometric Analysis, Martinos Center For Biomedical Imaging, Charlestown, MA,[5]Ph.D. Program in Behavioral Neuroscience, Boston University School of Medicine, Boston, MA,[6]Department of Neurology, Massachusetts General Hospital, Boston, MA,[7]Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY,[8]Massachusetts Mental Health Center Public Psychiatry Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Although attention deficit-hyperactivity disorder (ADHD) and bipolar disorder (BPD) frequently co-occur and represent a particularly morbid clinical form of both disorders, neuroimaging research addressing this comorbidity is scarce. In a previous study, we found significant cortical thinning in ADHD in a distinct cortical network supporting attention especially in the right hemisphere involving the inferior parietal lobule, the dorsolateral prefrontal, and the anterior cingulate cortices. Our current study investigates cortical thinning in a sample of adults with comorbid ADHD+BPD, and we hypothesize that additional cortical areas, specifically involved in emotional circuitry, will be affected in this sample.
Methods: We carried out a structural magnetic resonance imaging study of cortical thickness in a sample of adults with ADHD+BPD (N=31) and controls (N=23), hypothesizing that emotional as well as attentional and executive circuitry would be affected. Participants were group matched on age, sex, handedness and whole brain volume.
Results: Compared to controls, individuals with ADHD+BPD showed cortical thinning in lateral prefrontal and paracingulate cortex as well as anterior insula, medial frontal cortex, orbitofrontal cortex and the frontal pole.
Conclusions: As compared to a previous study that showed cortical thinning in attentional and executive circuitry in individuals with ADHD alone, this sample with comorbid bipolar disorder showed additional areas of significant thinning, particularly in areas associated with emotional processing and self-monitoring such as insula, orbitofrontal cortex, and frontal pole. Dysfunction in these regions, critically important for emotional regulation, may predispose individuals with comorbid ADHD +BPD to particularly significant behavioral and mood problems.
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764. Effect of Dopamine Transporter Gene (DAT1) on Dorsal Anterior Cingulate Activation in ADHD

Ariel B. Brown[1,2], Joseph Biederman[2], Eve M. Valera[3], George Bush[3], Thomas Spencer[2], Nikos Makris[4], Stephen Faraone[5], Alysa Doyle[2], Eric Mick[2], Michael Monuteaux[2], Larry Seidman[2,6]

[1]Ph.D. Program in Behavioral Neurosciences, Boston University School of Medicine, Boston, MA,[2]Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Boston, MA,[3]Department of Psychiatry, Massachusetts General Hospital, Charlestown, MA,[4]Departments of Neurology and Radiology, Massachusetts General Hospital, Charlestown, MA,[5]Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY,[6]Massachusetts Mental Health Center Public Psychiatry Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Although ADHD is associated both with brain alterations in attentional and executive circuitry as well as with genetic variations within the dopamine system, (including the dopamine transporter gene [DAT1] 10R allele), few studies have directly investigated how genetic variations are linked to brain alterations. We sought to investigate how a polymorphism in the 3' untranslated region (UTR) of DAT1 is associated with functional activation in the Dorsal Anterior Cingulate (dACC), an area involved in complex cognitive tasks, rich in dopamine, and altered in ADHD.
Methods: We collected fMRI scans on 43 individuals with ADHD, all of European descent and over the age of 17, while they performed the Multi-Source Interference Task (MSIT), shown to robustly activate dACC. DAT1 genes for these individuals were sequenced, and brain activations were compared for groups based on genotype.
Results: ADHD individuals homozygous for the 10R allele showed significant hypoactivation in the dACC compared to others. Further breakdown of genotype groups showed similar dACC activation in individuals with zero 10R alleles and with one 10R allele. Exploratory analysis showed hypoactivation in the 10R homozygotes in left cerebellar vermis and right prefrontal cortex; however, statistical significance did not withstand correction for multiple comparisons.
Conclusions: Activations in ADHD may be influenced by DAT1 genotype. Activation in other areas of attentional and executive networks found previously to be affected in ADHD, including cerebellar vermis and prefrontal cortex, are also likely influenced by DAT genotype. This genotype may add variation to brain alterations found within ADHD samples.
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765. A 12-month Outcome Study of Insight and Symptom Change in First-Episode Psychosis

Lisa Buchy[1,2], Michael Bodnar[1,2,3], Ashok Malla[3,4], Ridha Joober[3,4], Martin Lepage[1,2,3,4]

[1]Neurology & Neurosurgery, McGill University, Montreal, QC, Canada,[2]Brain Imaging Group, Douglas Mental Health University Institute, Verdun, QC, Canada,[3]Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute, Verdun, QC, Canada,[4]Psychiatry, Allan Memorial Institute, McGill University, Montreal, QC, Canada

Background: Previous work has revealed that course of insight in psychosis is variable and associated with several psychopathological features. Changes in insight may be specifically and temporally associated with changes in psychopathology, and severity of psychopathology over time may distinguish between subgroups of patients with different course of insight.
Methods: One-hundred and fourty-six patients were administered an extensive clinical evaluation and insight was rated on the Positive and Negative Syndrome Scale item G12 at admission and after 1, 2, 3, 6, 9, and 12 months.
Results: Repeated measures ANOVAs revealed that patients showed improvement in insight, positive, negative, depression and anxiety between admission and 1 month, with an additional improvement in insight and positive symptoms at 2 months. Repeated measures ANOVAs revealed that patients with persistently poor insight, patients whose insight worsened over time, and patients who showed fluctuating insight levels displayed greater negative symptoms over the 12 months, relative to patients with persistently good insight or patients whose insight improved. In contrast, those with persistently poor insight or those whose insight diminished showed greatest positive symptoms between 6-12 months, relative to the other groups. Delusions and suspiciousness/persecution contributed the greatest variance. No group differences emerged for depression and anxiety.
Conclusions: Changes in insight were detectable immediately following initiation of treatment, and psychopathology appears to mediate the course of insight.
Supported by CIHR; FRSQ; Sackler Foundation; Canada Research Chairs program

766. Frequency of Schizoaffective Disorder Diagnosis in Patients with Psychotic Disorders using the Mini-International Neuropsychiatric Interview

Carla M. Canuso[1], Colette Kosik-Gonzalez[1], Bryan L. Dirks[1], Amir H. Kalali[2], Robert Lasser[3], Georges M. Gharabawi[4]

[1]Scientific Affairs, Ortho-McNeil Janssen, Titusville, NJ,[2]Medical and Scientific Services, Quintiles, Inc., San Diego, CA,[3]Statistical Analyses, Neuliance Consulting, Newtown, PA,[4]Medical Affairs, Hoffman-LaRoche, Nutley, NJ

Background: Reports suggest schizoaffective disorder incidence rates ranging from 10%-30% among patients seeking psychiatric care. This international study determined the frequency of schizoaffective disorder among subjects with psychotic symptoms using the clinician-administered MINI-structured diagnostic interview and, in those with a MINI diagnosis of schizoaffective disorder, evaluated their existing chart diagnosis.
Methods: Subjects 18-65 years-of-age with symptoms consistent with acute or chronic psychosis presenting at a clinical pyschiatry setting were evaluated by MINI and charts of those with a diagnosis of schizoaffective disorder were reviewed.
Results: 208 subjects from the US (n=59), India (n=40), Eastern Europe (n=60), and Asia Pacific regions (n=49) were evaluated by MINI. 31% (65/208) were diagnosed with schizoaffective disorder. Across the 4 regions, the incidence of schizoaffective disorder by MINI ranged from 23.3% (14/60, Eastern Europe) to 40.8% (20/49, Asia Pacific). Among the 65 subjects with MINI diagnosis of schizoaffective disorder, 43.1% (28/65) also had a current psychosis chart diagnosis of schizoaffective disorder. Schizophrenia was the second most frequent chart diagnosis (38.5% [25/65]). Polypharmacy (i.e., 1 antipsychotic agent or antipsychotic agent(s) with antidepressant and/or mood stabilizer therapy) was common in all regions.
Conclusions: In this global sampling of adults presenting with symptoms consistent with acute or chronic psychosis, schizoaffective disorder incidence diagnosed by MINI varied from 23% to 41% and was also often accompanied by a schizoaffective disorder chart diagnosis. Across the regions, polypharmacy regimens involving one or more classes of agents were common.
Supported by Janssen Scientific Affairs, LLC

767. Adults with Autism integrate Auditory and Visual Information over a Wider Temporal Window than Controls

Carissa Cascio[1], Rachel E. Sassoon[2], Abigail Carroll-Sharpe[3], Gregory K. Essick[2], Grace T. Baranek[4]

[1]Department of Psychiatry, Vanderbilt University, Nashville, TN,[2]Center for Neurosensory Disorders, University of North Carolina School of Dentistry, Chapel Hill, NC,[3]Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC,[4]Department of Allied Health Sciences, University of North Carolina, Chapel Hill, NC

Background: Although anecdotal reports suggest aberrant cross-modal sensory integration in autism, few studies have tested this empirically. Audiovisual integration is of particular importance in human social and communicative abilities, and thus may be affected in autism.
Methods: Low-level audiovisual integration was tested in a group of eight high-functioning adults with autism and eight controls (groups matched overall for age and IQ) using an illusory paradigm (Shams et al., 2002) in which multiple beeps presented concurrently with a single flash evoke the illusory percept of multiple flashes. The temporal window of this integration was explored by incrementally increasing the temporal separation of the stimuli.
Results: The autism group reported perceiving the illusory flashes similarly to controls at short (< 80 msec) temporal windows. At longer temporal windows (> 80 msec), the control group did not show the illusory effect but the effect persisted in the autism group, resulting in significant group differences that extended to 153 msec (t= 2.68; p=0.03).
Conclusions: Simple audiovisual integration appears to be intact in autism, but audiovisual information is integrated over a wider temporal window than normal. This extended window may interfere with the integration of more complex audiovisual stimuli.
Supported by Autism Speaks

768. The Incidence of Personality Disorder in Adults with ADHD, and the Effects on Response to Treatment with OROS Methylphenidate (OROS MPH)

Phillip Gale, Frederick W. Reimherr, Barrie K. Marchant, Reid Robison, Erika D. Williams, Robert E. Strong, Corinne Halls, Poonam Soni

Psychiatry, University of Utah, Salt Lake City, UT

Background: This study explored the association between personality disorder and treatment response in a clinical trial of OROS MPH in adults with ADHD.
Methods: 47 patients entered a clinical trial of OROS MPH using the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) and the ADHD Rating Scale as outcome measures. Personality was assessed at baseline using the Wisconsin Personality Inventory (WISPI-IV) and the SCID-II. Following the study, a staff consensus produced a final personality diagnosis using all available information. Patients were separated into three post hoc categories: PDnegative (no personality disorder), PDpositive (subjects meeting criteria for one personality disorder or personality disorder NOS), and PDplus (subjects meeting criteria for ≥2 disorders). Improvement in ADHD symptoms was assessed using a mixed models design with treatment and personality categories as fixed variables.
Results: At baseline, 62% (SCID-II) and 33% (WISPI-IV) of subjects were PDpositive or PDplus, compared with 45% at the psychiatrist's final assessment; 30% had a Cluster C diagnosis, 17% Cluster B, and 11% Cluster A. A significant treatment response on the WRAADDS was experienced by PDnegative (40% on OROS MPH and 7% on placebo), and PDpositive (66% on OROS MPH and 9% on placebo) but not by PDplus (26% on OROS MPH and 23% on placebo) subjects.
Conclusions: These ADHD adults displayed great variability in the type and extent of personality disorder present. Subjects with ≥ 2 personality disorders exhibited poor treatment response in ADHD symptoms, while those with one or no personality disorders responded positively to OROS MPH.
Supported by Ortho-McNeil Janssen Scientific Affairs, LLC

769. The Physiological Response to Categorical Processing of Fear in Alexithymia

Alison M. Gilbert[1], J. Richard Jennings[2], Ellen Frank[1,2], Mary L. Phillips[2], Spencer Sugarman[1], Julie A. Fiez[1]

[1]Psychology, University of Pittsburgh, Pittsburgh, PA,[2]Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Alexithymia is a form of disordered emotional processing often associated with psychiatric illness and poor treatment outcomes in depression. Its clinical hallmarks are difficulty identifying, representing and evaluating emotional material. We determined the physiological response in alexithymia using explicit categorical processing tasks that manipulate emotion and cognition.
Methods: Sixty undergraduates completed the Toronto Alexithymia Scale (alexithymia ≥ 61, n=30; control ≤ 52, n=30). Participants labeled the emotion of a face that morphed from neutral to fear (emotion task) and the identity of a face that morphed from one person to another (identity task). We conducted ANOVA with morph (mostly faceA [0%-20%], ambiguous face [40%-60%], mostly faceB [80%-100%]) and group (alexithymia, control) as factors. Accuracy and heart rate were outcome measures. Planned t-tests assessed reactivity by comparing group HR responses to morphs at end-points of the emotion and identity continuums.
Results: ANOVA revealed main effects of morph, with subjects' HR and accuracy decreasing when categorizing ambiguous versus unambiguous faces ($F(2,59) \geq 12.236$, $p=.000$). No significant group effects or interaction emerged. Planned t-tests found no group differences in HR for the identity task ($t(58)=.723$, $p=.472$). In the emotion task, controls exhibited greater HR reactivity compared to alexithymic subjects ($t(58)=-1.753$, $p=.083$).
Conclusions: The effects of ambiguity across both tasks suggest that HR decreases as attention increases. This physiological pattern seems intact in alexithymia. In contrast, only controls demonstrated predicted HR reactivity to affectively arousing faces. Findings suggest potentially distinguishable physiological correlates of cognitive and emotional processing in alexithymia and may have implications for the treatment of depression.

770. Gender Differences in the Developmental Trajectories of Borderline Personality

Marianne Goodman[1,2], Uday Patil[2], Joseph Triebwasser[1,2], Elizabeth Diamond[2], Antonia New[1,2], Larry Siever[1,2]

[1]Psychiatry, James J Peters VA Medical Center, Bronx, NY,[2]Psychiatry, Mount Sinai School of Medicine, New York, NY

Background: In order to identify precursors and trajectories of the development of borderline personality disorder (BPD), we solicited information from parents of adult and adolescent children diagnosed with BPD.
Methods: We developed a survey containing approximately 100 questions for parents to complete on their offspring with and without BPD. Questions cover the child's life from pregnancy through young adulthood; family history; treatment history, and respondent demographics. BPD offspring will have met diagnostic criteria embedded within the survey and been given a diagnosis of BPD by a clinician.
Results: To date over 700 surveys have been completed, with 400 having usable

data. We report on 170 offspring that met strict criteria for BPD and 120 non-BPD siblings. Significant predictors of BPD, derived from separate multinomial logistic regressions by gender, included: 1) unusual difficulty with friends in elementary school aged girls (p< .004), 2) unusual temperament in elementary school boys (p<.008), 3) adolescent factors of moodiness (p<.004), problems with fighting (p<.004), and impulsivity (p<.000) for girls, and 4) adolescent substance abuse (p<.003) and suicidal thoughts (p<.002) in both genders.
Conclusions: BPD prodromal features can be identified as early as in elementary aged children. BPD may be viewed as a temperamental disturbance in affect that disturbs interpersonal relationships, coupled with adolescent impulsivity. These preliminary results will updated with a larger data set.

771. Cognitive and Sedative Effects of Guanfacine Extended Release in Children and Adolescents Aged 6 to 17 Years with Attention-Deficit/ Hyperactivity Disorder: Safety and Sleep Effects

Scott H. Kollins[1], Timothy Wigal[2], Bradley Vince[3], Andrew Lyne[4], Kimberly Farrand[5]

[1]Department of Psychiatry, Duke University Medical Center, Durham, NC,[2]Child Development Center, University of California, Irvine, Irvine, CA,[3]N/A, Vince and Associates Clinical Research, Overland Park, KS,[4]N/A, Shire Pharmaceutical Development LTD, Basingstoke, United Kingdom,[5]N/A, Shire Development Inc, Wayne, PA

Background: Guanfacine extended release (GXR), a selective α_{2A}-adrenoceptor agonist, has demonstrated efficacy in attention-deficit/hyperactivity disorder (ADHD) in previous studies. This study assessed the effects of GXR on cognitive tasks in subjects aged 6 to 17 years with ADHD. A secondary objective was to evaluate potential sedative effects of GXR.
Methods: In this double-blind, dose-optimization noninferiority study, 121 subjects were randomized to GXR and 57 subjects to placebo for 6.5 weeks. Cognitive assessments included the Choice Reaction Time (CRT) and Spatial Working Memory (SWM) tests (both from the Cambridge Neuropsychological Test Automated Battery), and Permanent Product Measure of Performance. The Pictorial Sleepiness Scale (PSS) measured daytime and evening sleepiness and the Pediatric Daytime Sleepiness Scale (PDSS) measured daytime sleepiness only.
Results: GXR did not impair reaction time as measured by the CRT: mean change from baseline to endpoint was 20.7±63.1 msec for GXR vs 21.9±64.0 msec for placebo, P=.84. Changes in other CRT parameters also showed no significant differences between GXR and placebo at endpoint (P=.30 for movement time, P=.72 for total time, and P=.98 for accuracy). GXR did not impair any aspect of SWM (P>.05 for all). PDSS showed that GXR slightly decreased daytime sleepiness (P=.02), while PSS subject and observer assessments showed no change in daytime sleepiness with GXR. Evaluations at 10 and 12 hours postdose showed greater evening sleepiness with GXR vs placebo.
Conclusions: GXR did not impair cognitive function or affect daytime sleepiness but did increase evening sleepiness in children and adolescents with ADHD.
Supported by funding from Shire Development Inc

772. Assessment of Personality Disorder in Adult ADHD Using Data from a Clinical Trial of OROS Methylphenidate (OROS MPH)

Barrie K. Marchant, Frederick W. Reimherr, Erika D. Williams, Robert E. Strong, Corinne Halls, Poonam Soni

Psychiatry, University of Utah, Salt Lake City, UT

Background: Studies have reported high comorbidity of personality disorder and adult ADHD. However, assessment of personality disorder is problematic and none have rigorously confirmed this observation with measures of concurrent validity.
Methods: 47 patients entered a double-blind trial of OROS MPH after administration of the Wisconsin Personality Inventory (WISPI-IV) and the SCID-II. At discharge, all information was reviewed to produce a final consensus personality diagnosis. Patients were separated into three post hoc categories: PDnegative (no personality disorder), PDpositive (subjects meeting diagnostic criteria for one disorder), and PDplus (subjects meeting diagnostic criteria for ≥2 disorders).
Results: 45% of subjects had a personality disorder on the final assessment versus 62% (SCID-II) and 33% (WISPI-IV): 11% cluster A, 17% cluster B and 30% cluster C. Compared to the final assessment, the WISPI-IV identified PDnegative subjects with sensitivity = .92 and specificity = .67 and PDplus subjects with sensitivity = .40 and specificity = 1.00. The SCID-II identified PDnegative subjects with sensitivity = .64 and specificity = .90 and PDplus subjects with sensitivity = .90 and specificity = .84. There was a significant correlation between the number of SCID-II items endorsed by each subject and their WISPI-IV average z-score (r=.67, df=46, p<.001).
Conclusions: All three systems detected personality disorder in a large proportion of patients. The WISPI tended to under-estimate personality disorders while the SCID-II over-estimated them. The self-administered WISPI-IV would be more practical in a multicenter clinical trial to provide an estimate of personality disorder.
Supported by Ortho-McNeil Janssen Scientific Affairs, LLC

773. Does DRD4 Genotype Predict Brain Volumes in Adults with ADHD?

Michael C. Monuteaux

Psychiatry, Massachusetts General Hospital, Boston, MA

Background: An emerging literature has begun to demonstrate an association between the dopamine D4 receptor (DRD4) gene and MRI findings in key brain regions in samples of children with ADHD. The present study sought to extend these findings to adults.
Methods: We examined two groups of adults: 24 with ADHD, and 20 healthy controls. Within each group, we compared subjects with and without the DRD4 7-repeat allele on brain volumes (cm^3) of a priori selected brain regions (superior frontal cortex, middle frontal cortex, anterior cingulate cortex and cerebellum cortex) using linear regression models.
Results: The omnibus interaction between diagnostic status and genotype across the four ROIs was significant in both left hemisphere structures and right hemisphere structures, providing statistically significant evidence that the association between DRD4 genotype and the brain volumes differ by diagnostic status. Among adults with ADHD, subjects with the 7-repeat allele had a significantly smaller mean volume in the left superior frontal cortex and left and right cerebellum cortex. Among the Controls, no statistically significant volumetric differences were detected between subjects with and without the 7-repeat allele.
Conclusions: Our findings suggest that volumetric abnormalities in the dorsolateral prefrontal cortex and cerebellum may be an intermediate phenotype between DRD4 risk genes and the clinical expression of ADHD in adults. These results contribute to our understanding of the pathophysiology of ADHD.
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774. Reduced Medial Prefrontal Cortex Response during an Inhibition Task in Recovered Anorexic Women: A Pilot Study

Tyson A. Oberndorfer, Walter H. Kaye, Alan Simmons, Martin P. Paulus, Scott C. Matthews

Psychiatry, UCSD, La Jolla, CA

Background: Anorexia Nervosa (AN) is characterized by restrictive eating and emaciation, obssionality, and perfectionism. Behavioral inhibition, overcontrol, and decreased impulsivity on reaction time (RT) tasks are commonly observed. Neuroimaging studies in healthy volunteers have defined a neural network that includes prefrontal cortex and anterior cingulate, where these control mechanisms are instantiated. However, little is known about the neural substrates of inhibitory processing in AN.
Methods: To date, we have studied 5 recovered restricting-type AN subjects (RAN) and 6 age-matched control women (CW). Functional magnetic resonance imaging measured neural activity while subjects performed a validated motor inhibition "Stop" task. Subjects were asked to respond as quickly as possible by pressing left and right buttons when they saw "X" and "O" stimuli, but to not press either button when they heard a tone. Mean RT measured prior to the scan was used to construct individualized "hard," "medium," and "easy" trials based on tone delivery relative to RT.
Results: Replicating prior studies of healthy controls, we observed increased inferior frontal gyrus activation in both CW and RAN for all Stop trials minus Non-Stop trials ($p<0.05$). A group-by-task interaction was observed in the medial prefrontal cortex (mPFC) where, for hard-minus-easy trial comparisons, CW showed greater but RAN lesser mPFC activity ($p<0.05$) reflecting demand-specific mPFC dysfunction in AN.
Conclusions: Preliminary data suggest that RAN show a relative inability to appropriately increase mPFC activity as inhibitory load is increased and thus may provide a neural basis for aberrant impulse control symptoms.
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775. Evidence of Endogenous Opioid System Dysregulation in Borderline Personality Disorder

Alan R. Prossin, Kenneth R. Silk, Tiffany Love, Jon-Kar Zubieta

Psychiatry/MBNI, University of Michigan, Ann Arbor, MI

Background: Affective dysregulation is central to the morbidity and mortality of borderline personality disorder (BPD). The role of the endogenous opioid system in affective control regulation in BPD's was proposed based on the known functions of this neurotransmitter system in Major Depressives and controls(Kennedy et al, 2006) and various challenge studies in BPD's(Silk et al, 2000). No neuroimaging studies have examined directly the role of this neurotransmitter system in the pathophysiology of BPD(Lis et al, 2007). We hypothesize the presence of differences in baseline μ-opioid receptor concentrations in BPD's compared to healthy controls in emotion processing regions.
Methods: 18 female BPD's and 14 controls matched by age, gender, and educational level. Utilizing PET with the μ-opioid receptor selective radiotracer [11C]carfentanil, measures of μ-opioid receptor availability (binding potential, BP≈ Bmax/Kd) were obtained during a sustained neutral state, as previously described in healthy subjects and Major Depressive Disorder(Kennedy et al, 2006). Subtraction analyses of voxel-by-voxel BP maps were then performed between groups, using SPM99 and correction for multiple comparisons at $p<0.05$.
Results: At baseline, the BPD group showed greater μ-opioid receptor BP than controls in the orbito-frontal cortex, amygdala, nucleus accumbens, and infero temporal cortex but lower μ-opioid receptor BP in the posterior thalamus.
Conclusions: These data demonstrate differences in μ-opioid receptor availability at baseline in brain regions involved in emotional regulation (posterior thalamus) and in decision making and motivated behavior (orbitofrontal cortex) between BPD and healthy subjects, implicating an important role of the endogenous opioid system in the pathophysiology of BPD.
Supported by Borderline Personality Disorders Research Foundation

776. Long-Term Safety and Efficacy of Guanfacine Extended Release in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

Floyd Sallee[1], James J. McGough[2], Timothy Wigal[3], Kimberly Farrand[4], Andrew Lyne[5], Joseph Biederman[6]

[1]Department of Psychiatry, University of Cincinnati, Cincinatti, OH,[2]N/A, UCLA Psychiatric and Biobehavioral Sciences, Los Angeles, CA,[3]Child Development Center, University of California, Irvine, Irvine, CA,[4]N/A, Shire Development Inc, Wayne, PA,[5]N/A, Shire Pharmaceutical Development LTD, Basingstoke, United Kingdom,[6]Clinical and Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Guanfacine extended release (GXR), a selective α_{2A}-adrenoceptor agonist, has demonstrated efficacy as monotherapy for attention-deficit/hyperactivity disorder (ADHD) in previous studies. The objectives of this study were to assess long-term safety and efficacy of GXR in patients aged 6 to 17 years with ADHD.
Methods: This study was an open-label extension of a placebo-controlled phase III trial and an open-label phase II safety study of GXR and psychostimulant coadministration. Patients from the phase II trial receiving coadministered psychostimulants had the option to continue their psychostimulant treatment. Of 259 patients who received GXR, 53 were coadministered psychostimulants. Optimal dose was achieved by upward titration to a maximum of 4 mg/d and maintained up to 24 months. Safety assessments included adverse events (AEs), laboratory tests, and electrocardiograms. The main efficacy measure was ADHD Rating Scale-IV (ADHD-RS-IV) total score change from baseline to endpoint.
Results: AEs were generally mild to moderate. The most common treatment-emergent AEs (TEAEs) included somnolence (30.5%), headache (24.3%), and upper respiratory tract infection (17.8%). The incidence of TEAEs was 87.3% overall. Thirty-one patients (12%) discontinued due to TEAEs (13.6% in the monotherapy group and 5.7% in the coadministration group). Small changes in blood pressure and pulse were noted. No electrocardiogram abnormality was reported as a serious AE. At endpoint, mean changes in ADHD-RS-IV total score were significant overall and for all weight-adjusted dose groups ($P<.001$ for all).
Conclusions: In this long-term GXR treatment study, (up to 4 mg/d) was generally safe and effective in children and adolescents with ADHD.
Supported by funding from Shire Development Inc

777. Higher Cortisol and Cardiovascular Stress Responses Following Psychological Challenge in Women with Borderline-Personality-Disorder with High Dissociation Compared to a low Dissociation Group

Nicole C. Schommer, Nadine Meissner, Stefan Röpke, Isabella Heuser, Claas-Hinrich Lammers

Psychiatry and Psychotherapy, Charite- Campus Benjamin Franklin, Berlin, Germany

Background: Borderline-Personality-Disorder (BPD) is a severe psychiatric disorder, characterized by a pervasive pattern of instability in affect regulation, impulse control, behaviour of self-injury, and multiple suicide attempts. About 70% of BPD patients show comorbidity with post-traumatic stress disorder (PTSD). In contrast to PTSD, there is a paucity of data on HPA and cardiovascular stress reactivity in BPD patients.

Methods: We investigated cortisol, heart rate, and blood pressure reactivity following a psychological challenge in 20 young women with BPD. We compared patients with high dissociation during the challenge with a group showing low dissociation during the stress exposure. The psychological challenge was a 15-minutes lasting interview concerning the last suicide attempt or self injury focusing on cognitive and emotional aspects. As control situations we conducted a first session without any challenge as well as a non-challenging interview.
Results: In the total group the control session and the psychological challenge resulted in slight cortisol increases (Fs>10.3;p<0.001). However, separate ANOVAs revealed only in the high-dissociation group significant increases in cortisol stress reactivity (F= 4.9; p3.9; p 4.1; p < 0.05).
Conclusions: In all sessions very low endocrine and cardiovascular stress responses compared to usual observed levels in healthy controls after psychosocial stress tests are observed, however dissociation during stress exposure results in higher endocrine and cardiovascular responses.

778. Relationships between Early Visual Processing, White Matter Integrity, and Emotion Processing Deficits in Schizophrenia

Ilana Y. Abeles[1], Matthew Hoptman[2], Maria Jalbrzikowski[1], Dean Catalano[2], Ruben C. Gur[3], Daniel C. Javitt[4], Pamela D. Butler[1]

[1]Laboratory of Clinical Neuroscience, Nathan Kline Institute, Orangeburg, NY,[2]Department of Psychiatry, Nathan Kline Institute, Orangeburg, NY,[3]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA,[4]Program in Cognitive Neuroscience and Schizophrenia, Nathan Kline Institute, Orangeburg, NY

Background: Schizophrenia patients (SCZ) have deficits in face emotion perception and show early visual processing deficits, evidenced by preferential magnocellular system dysfunction. SCZ also show decreased white matter integrity in emotion processing regions including optic radiations (OR), limbic areas, and inferior frontal cortex. We hypothesized that magnocellular deficits and decreased white matter integrity may be related to emotion perception deficits.
Methods: SCZ and controls participated. Emotion processing was examined using the PENN Emotion Recognition Task. Early-stage visual processing was assessed using contrast sensitivity (CS) measures. White matter integrity was assessed using diffusion tensor imaging. Two tracts were made using DTIStudio: the OR, which connects thalamus with primary visual cortex and the inferior fronto-occipital fasciculus (IFOF), which is thought to connect occipital and frontal regions.
Results: Emotion identification (p<0.001) and CS (p<0.001) performance were significantly impaired in SCZ vs controls. SCZ showed correlations between decreased CS in the magnocellular-biased (0.5 cycle/degree) condition and impaired emotion recognition (p=0.009). SCZ also showed reduced FA within left IFOF and OR (p<0.05). Correlations in SCZ were found between left IFOF FA and emotion identification (p=0.02).
Conclusions: We established for the first time direct associations of emotion identification, early visual processing and integrity of neural connectivity in SCZ. IFOF FA was decreased on the left side, which is in itself a novel observation, and this decrease was related to emotion recognition deficits, suggesting that impaired input to inferior frontal cortex from visual and other areas may contribute to emotion processing deficits.
Supported by NIMH

779. Social Cognition Mediates Illness Related and Cognitive Influences on Social Functioning in Schizophrenia-Spectrum Disorders

Jean Addington[1,2,3], Todd A. Girard[4], Bruce K. Christensen[5], Donald Addington[3]

[1]Psychiatry, University of Toronto, Toronto, ON, Canada,[2]Schizophrenia Program, Centre for Addiction and Mental Health, Toronto, ON, Canada,[3]Psychiatry, University of Calgary, Calgary, AB, Canada,[4]Psychology, Ryerson University, Toronto, ON, Canada,[5]Psychiatry and Behavioral Sciences, McMaster University, Hamilton, ON, Canada

Background: The objective of the current study was to use structural equation modelling (SEM) to test the hypothesis that the relationship between cognitive performance and social functioning is mediated by patients' social cognitive abilities.
Methods: The sample included 96 subjects who met criteria for a schizophrenia spectrum disorder with equal distribution amongst first and multi-episode subjects. The sample also included 55 non-psychiatric controls. Subjects were assessed on a range of measures within each of the domains of cognition, social cognition and social functioning.
Results: Using SEM, a model was derived that explained 79.7% of the variance in social functioning and demonstrated that the link between cognition and social functioning was fully mediated by social cognition.
Conclusions: This study provides some first steps in understanding the complex relationship between cognition and social functioning. Such a relationship has potential implications for the design of remediation strategies.
Supported by Canadian Institutes of Health Research

780. Sounding it Out: Auditory Processing Deficits and Reading Impairment in Schizophrenia

John Aspromonte, Erica Saccente, Rachel Ziwich, Daniel C. Javitt, Nadine Revheim

Program in Cognitive Neuroscience and Schizophrenia, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY

Background: Impaired reading abilities, associated with visual processing deficits, have been found in schizophrenia. To date, relationships of reading deficits and auditory dysfunction have not been examined. Auditory processing deficits in schizophrenia have been demonstrated by poor performance on several behavioral measures, such as tone-matching (TMT), and voice discrimination and identification tasks (KNVD/KNVID).
Methods: This study examines the relationship between phonological processing, measured by standardized reading measures (CTOPP, GORT-4), and auditory processing (TMT, KNVD/KNVID) and their relationship to reading impairment in schizophrenia. Fifty-four individuals (33 patients, 21 controls) participated in the study; 54.5% of patients (n=18) and 4.8% of controls (n=1) were diagnosed with reading impairment (p=.0001).
Results: Across groups, significant correlations were observed between both reading measures and auditory processing ability: CTOPP and KNVID, r=.53, p<.001,n=41; CTOPP and TMT, r=.43,p=.002,n=48; GORT-4 and KNVID, r=.42,p=.006,n=41; GORT-4 and TMT, r=.52,p<.001,n=48. Within group correlations differed by measure. For patients, GORT-4 and TMT were significant (r=.45,p=.009,n=33) and for controls, CTOPP and KNVID were significant (r=.55,p=.03,n=15). Using ANOVA, significant differences were found between groups for KNVID (impaired reading patients/controls, nonimpaired patients, nonimpaired controls: F=13.85,df=2,38;p<.001); post hoc analyses indicate differences are primarily between impaired patients/controls and nonimpaired controls. Conversely, significant differences were found across all groups for TMT (F=9.74,df=2,45;p<.001), with post hoc tests demonstrating differences between impaired patients/controls vs. nonimpaired patients (p=.041) or nonimpaired controls (p<.001), respectively. Findings were

similar for repeated analyses that excluded the reading impaired control.
Conclusions: These results confirm prior reports of reading dysfunction in schizophrenia and suggest significant phonological contribution.
Supported by R37-MH49334

781. Amygdala Volume and Face Recognition Memory in Schizophrenia: A Magnetic Resonance Imaging Study

Audrey Benoit, Karine Sergerie, Yvonne Czechowska, Jorge L. Armony, Martin Lepage

Brain Imaging Group, Douglas Mental Health University Institute, Montreal, QC, Canada

Background: Several studies have shown that face recognition memory is significantly impaired in schizophrenia but little is known concerning the neural basis of such a problem. Structural and functional imaging studies suggest that deficits in emotional face processing are related to hypoactivity and smaller volume of the amygdala in schizophrenia. We investigated the association between face recognition memory and amygdala volume and how emotional expression may affect this association.
Methods: Nineteen healthy subjects and 19 people with schizophrenia underwent structural magnetic resonance imaging and a face recognition memory task using happy, neutral, and sad expressions. Amygdala volumes were obtained through manual segmentation and an estimate of memory accuracy was calculated for each expression.
Results: As expected, memory accuracy was lower in people with schizophrenia compared to the healthy controls in all emotional conditions; however, amygdala volumes were not different between the two groups. In schizophrenia, the right amygdala volume significantly related with memory performance for faces when averaged across all emotion conditions ($r=0.57$, $p<0.05$) whereas no significant association was found for controls. A subsidiary analysis in the schizophrenia group based on the emotional expressions revealed that sad, happy and neutral faces yield similar correlations (range 0.36-0.48) and their strength did not significantly differ (all $p>0.60$).
Conclusions: Despite lower memory performance, a specific association between right amygdala volume and face recognition accuracy was identified in schizophrenia. Moreover, this association seems independent of facial expressions. Hence, the right amygdala volume seems to represent one important region for face memory in this disorder.
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782. Non-Linear Response of the Anterior Cingulate and Prefrontal Cortex in Schizophrenia as a function of Variable Attentional Control

Giuseppe Blasi[1], Paolo Taurisano[1], Apostolos Papazacharias[1], Grazia Caforio[1], Raffaella Romano[1], Luciana Lobianco[1], Leonardo Fazio[1], Annabella Di Giorgio[1], Valeria Latorre[1], Fabio Sambataro[2], Marcello Nardini[1], Venkata Mattay[2], Daniel Weinberger[2], Alessandro Bertolino[1]

[1]Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy, Bari, Italy,[2]National Institute of Mental Health, National Institutes of Health, Bethesda, MD

Background: Previous studies have reported evidence of abnormal neuronal responses in prefrontal and cingulate cortex during attentional control processing in schizophrenia. However, it is not clear how variation in capacity limitations in schizophrenia may modulate activity within these brain regions during increasing levels of attentional control. Aim of this study is to investigate with fMRI in schizophrenia the impact of increasing levels of attentional control processing on prefrontal and cingulate activity.
Methods: BOLD responses of sixteen outpatients with schizophrenia on stable treatment with antipsychotic drugs were compared with those of twenty-one healthy subjects while performing a task eliciting increasing demands for attentional control processing during event-related fMRI at 3 Tesla.
Results: Patients had reduced behavioral performance at greater levels of attentional control. The fMRI results indicated that there was greater prefrontal activity at intermediate levels of attentional control in patients, while greater activity in prefrontal and cingulate in controls at high demands of attentional control processing. The BOLD activity profile of these regions in healthy subjects increased linearly with increasing cognitive loads, whereas in patients it had an inverted-U shaped profile. Correlation analysis consistently indicated differential region and load specific relationships between brain activity and behavior in these two groups of subjects.
Conclusions: These results indicate that varying attentional control load is associated in schizophrenia with non linear cortical responses, possibly suggesting earlier capacity saturation of attentional control.
Supported by NARSAD Young Investigator Award

783. Reduced Language Lateralization in Schizophrenia Patients with OCD: Are They Schizophrenia or OCD Like?

Maya Bleich-Cohen[1,2], Michael Poyurovsky[3], Ronit Weizman[2], Sarit Faragian[2], Talma Hendler[1,2]

[1]Functional Brain Imaging Unit, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel,[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel,[3]Research Unit, Tirat Carmel Mental Health Center, Tirat Carmel, Israel., Haifa, Israel

Background: A substantial proportion of schizophrenia patients also meet DSM-IV criteria for obsessive-compulsive disorder (OCD). Schizo-obsessive patients are characterized by a distinct course, poorer treatment response and prognosis.
As part of a project aiming to elucidate brain mechanisms underlying a schizo-obsessive subgroup, in the present study we evaluated patterns of lateralization in the domain of language processing in schizo-obsessive patients compared to "pure" schizophrenia and OCD patients.
Methods: We used functional magnetic resonance imaging (fMRI) to investigate language lateralization during the language task of verb generation and passive music listening as a control condition. Regions-of-interest corresponded to Broca's area in the inferior frontal gyrus (IFG), Wernicke's area in the superior temporal sulcus (STS) and the auditory cortex. Eleven schizo-obsessive patients, 14 schizophrenia patients, 13 OCD patients and 14 healthy controls were recruited.
Results: No between-group differences were found in the behavioral measurements of word generation. A reduced lateralization in the IFG and STS was noted in the two schizophrenia groups with and without OCD as compared to OCD patients and healthy controls. Reduced lateralization in the schizophrenia group was due to a significantly decreased left activation and increased right activation of the IFG and STS. No differences in lateralization were found between the OCD group and the normal controls.
Conclusions: The revealed similar pattern of reduced lateralization suggests that the OCD component does not substantially modify fMRI parameters in the language domain in the schizo-obsessive subgroup.
Supported by The Levi-Edersheim-Gitter institute for human brain mapping (MBC)

784. Eyeblink Conditioning Deficits Indicate Temporal Processing Abnormalities in Schizophrenia

Amanda R. Bolbecker[1], Crystal Mehta[1], Chad R. Edwards[1], Jennifer Boggs[2], Anantha Shekhar[3], Brian F. O'Donnell[1], William P. Hetrick[1]

[1]Psychological and Brain Sciences, Indiana University, Bloomington, IN,[2]School of Social Work, University of Denver, Denver, CO,[3]Psychiatry, Indiana University Medical School, Indianapolis, IN

Background: Recent studies have documented both structural and functional abnormalities in the cerebellum of schizophrenia patients. Increasing evidence suggests that, in addition to motor coordination, the cerebellum plays a role in psychological processes. Theoretical and empirical evidence suggests that symptoms of schizophrenia may arise, at least in part, as a consequence of disturbed neural timing processes mediated by the cerebellum.
Methods: The present study employed eyeblink conditioning, a particularly appropriate test of the functional integrity of cerebellar timing processes, in a large sample of schizophrenic participants with the aim of clarifying conflicting results generated from previous reports. A single-cue tone delay eye-blink conditioning paradigm consisting of 10 blocks with 10 trials (9 paired and 1 unpaired trials) was used to examine the functional integrity of cerebellar timing circuits in 63 medicated patients with schizophrenia and 63 age-matched non-psychiatric controls. The conditioned stimulus was a 400 ms tone, which on paired trials co-terminated with a 50 ms air puff to the left eye, which served as the unconditioned stimulus.
Results: Schizophrenia patients were impaired on both the acquisition and timing of conditioned responses compared to non-psychiatric controls. The schizophrenic group produced significantly fewer conditioned responses and, when conditioned responses were produced, they were timed unusually early compared with air puff onset.
Conclusions: These results are consistent with models of schizophrenia in which timing deficits underlie information-processing abnormalities and clinical features of schizophrenia.
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785. Neurodevelopment in Adolescence and Young Adulthood: Recruitment and Evaluation of Youths At-Risk for Psychosis

Karin E. Borgmann-Winter[1,2], Christian Kohler[1], Raquel E. Gur[1], Jan Richard[1], Monica E. Calkins[1]

[1]Psychiatry, University of Pennsylvania, Philadelphia, PA,[2]Child and Adolescent Psychiatry, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Early intervention in schizophrenia is an emerging goal of investigations in the earliest phases of the illness. To develop strategies for early intervention, those at highest risk for the development of psychosis must be accurately identified. We present an approach to the longitudinal assessment of individuals at-risk for psychosis whose goal is to combine endophenotype and prodromal risk strategies to facilitate prediction of conversion to psychosis.
Methods: Participants are recruited from the University of Pennsylvania, Children's Hospital of Philadelphia, local schools, and community mental health clinics. Participants in the following groups are enrolled and re-assessed at 6-month intervals: Genetic Risk (GR: first-degree relative with schizophrenia), Clinical Risk (CR: current prodromal symptoms, no family history of schizophrenia), Psychotic (PSYG: current psychotic disorder), Low-Risk (LR: no family history of psychosis, no prodromal symptoms). To assess familiality of measures, healthy siblings are recruited. The assessment protocol provides comprehensive psychopathology assessment using standardized instruments selected to maximize coverage of Axis I, Axis II and prodromal symptoms, and thus fully categorize baseline and outcome diagnoses. Behavioral, medical, developmental and psychosocial history is assessed using self-report scales, supplemented by collateral information obtained from parent or guardian. Participants are next invited to participate in a series of individual protocols assessing neurocognitive, emotion, olfactory, psychophysiology and neuroimaging performance.
Results: 24 subjects have been recruited and assessed to date: GR=9, CR=7, PSYG=3, LR=5.
Conclusions: The establishment the NAYA cohort lays the foundation for longitudinal characterization of the neurodevelopmental course of schizophrenia in the adolescent and young adult periods.
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786. Specific Social Deficits in Schizophrenia are Differentially Predicted by Thought Disorder Subtypes

Christopher Bowie[1], Philip D. Harvey[2]

[1]Psychiatry, Mount Sinai School of Medicine, New York, NY,[2]Psychiatry, Emory University, Atlanta, GA

Background: Thought disorder, a core symptom of schizophrenia, is often subtyped as positive thought disorder (PTD; e.g., tangential speech), or negative thought disorder (NTD; e.g., poverty of speech). Few studies have examined their functional consequences.
Methods: Over a 2.5 year follow-up, 317 patients with schizophrenia were twice assessed with standard cognitive, thought disorder, and social behavior instruments.
Pearson correlations examined associations of PTD and NTD with six types of social behaviors. Stepwise linear regressions were used to predict social behaviors and adaptive functions at follow-up with cognitive measures, PTD, and NTD entered as the independents.
Results: At baseline, PTD and NTD were moderately (r's from .20 to .40) associated with impairments in communication skills, conversational skills, and instrumental social skills. PTD (r=.33), but not NTD (r=.08) was associated with socially inappropriate behavior, while NTD, but not PTD, was associated with disengagement (r=.40) and withdrawal (r=.37). Longitudinal analyses of social deficits showed a similar pattern of differential relationships with PTD versus NTD. Thought disorder accounted for more variance (R^2 ranges .09 to .15) in follow-up social behavior than cognition, with the exception of communication skills, where cognition entered first (R^2=.13), and both PTD ($R^2\Delta$=.03) and NTD ($R^2\Delta$=.02) contributed to the prediction at a statistically significant level. In contrast to social behavior, follow-up adaptive behavior was largely accounted for by baseline cognition (R^2=.18), though NTD ($R^2\Delta$=.03) and PTD ($R^2\Delta$=.02) contributed small, but significant variance.
Conclusions: Thought disorder contributes to persistent functional impairments in schizophrenia. Subtypes have differential relationships with specific functional domains.
Supported by NARSAD; NIMH MH 36692; NIMH R01 63116

787. Neurodevelopment in Adolescence and Young Adulthood (NAYA): Neurocognitive Impairments in Youths At-Risk for Psychosis

Monica E. Calkins[1], Karin E. Borgmann-Winter[1,2], Christian Kohler[1], Jan Richard[1], Noah Sasson[1], Ruben C. Gur[1], Raquel E. Gur[1]

[1]Neuropsychiatry Program, University of Pennsylvania School of Medicine, Philadelphia, PA,[2]Child and Adolescent Psychiatry, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Accumulating evidence suggests that neurodevelopmental abnormalities preceding clinical manifestation of illness are present in children at-risk for developing psychosis. Neurocognitive abilities, especially executive, attention and memory dysfunction, are extensively implicated as candidate endophenotypes in schizophrenia. Impaired endophenotype performance in adolescents deemed at-risk for schizophrenia bears directly on the endophenotype's ability to serve as a marker for early identification and treatment. The primary purpose of the NAYA program is to combine endophenotype and prodromal risk strategies to facilitate early identification of individuals at-risk for psychosis.
Methods: Youths (ages 14-25) completed a comprehensive diagnostic assessment and the University of Pennsylvania Computerized Neurocognitive Battery (CNB) in the context of this and other ongoing studies. Groups included individuals deemed at-risk for psychosis [Genetic risk (GR; first-degree relative with schizophrenia), n=45; clinical risk (CR; prodromal symptoms but no family history), n=5; schizophrenia (SCZ), n=85; and healthy controls (CNT), n=86].
Results: Compared to CNT, youths with schizophrenia and those at-risk for psychosis showed significant (all p's<0.05) impairments in accuracy of attention, memory (verbal, face, spatial), language and spatial ability. Young relatives exhibited impairments similar to adult relatives in prior studies. Pilot analyses revealed especially pronounced impairments in CR across domains.
Conclusions: Candidate neurocognitive endophenotypes are observable in youths at-risk for psychosis and may reflect pathophysiological abnormalities involved in development of schizophrenia. Thus, they may ultimately facilitate both prediction of schizophrenia and insight into its pathophysiology. As the NAYA longitudinal program grows, we will investigate heritability in at-risk groups, developmental trajectory of endophenotypes, and prediction of conversion to psychosis.
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788. Functional Connectivity Abnormalities in Schizophrenia during Rest

Jazmin Camchong[1], Christopher Bell[1], Peter Fried[1], Bryon Mueller[1], Angus MacDonald[2]

[1]Psychiatry, University of Minnesota, Minneapolis, MN,[2]Psychology, University of Minnesota, Minneapolis, MN

Background: Baseline brain activity has been observed in the normal brain at rest. Previous studies have found that this baseline brain activity is organized in functionally connected resting state networks. Schizophrenia participants have previously shown functional connectivity abnormalities in some of these resting state networks. The present study investigated the hypothesis that schizophrenia is associated with altered functional connectivity by performing independent components analysis (ICA) on resting state functional magnetic resonance imaging (rs-fMRI) data.
Methods: Twenty nine chronic schizophrenia 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. Participants underwent a 6 min rs-fMRI scan (Siemens Trio 3T scanner) during which they were instructed to stay still with their eyes closed and remain awake. ICA (FSL - Melodic) was used to identify functionally connected networks.
Results: Functionally connected networks resulting from ICA were consistent with previous studies. Unpaired t-test results showed specific functional connectivity abnormalities associated with schizophrenia. The schizophrenia group showed lower functional connectivity in resting state networks that included prefrontal cortex, superior parietal lobule, precuneus, cuneus and cerebellum ($p<0.05$).
Conclusions: Results suggest that altered functional connectivity in schizophrenia is specific to networks associated with visual and attention (e.g. precuneus, cuneus) as well as cognitive (e.g. prefrontal cortex and superior parietal lobule) processing. The present study provides supporting evidence for the hypothesis of abnormal functional integration between brain regions in schizophrenia.
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789. GAD65 and GAD67 Protein Levels in the Dorsolateral Prefrontal Cortex of Subjects with Schizophrenia

Allison A. Curley[1], Dominique Arion[2], David A. Lewis[3]

[1]Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA,[2]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA,[3]Departments of Neuroscience and Psychiatry, University of Pittsburgh, Pittsburgh, PA

Background: Impaired GABA neurotransmission in the dorsolateral prefrontal cortex (DLPFC) may contribute to the cognitive deficits of schizophrenia. Reduced levels of the mRNA encoding the 67-kDa, but not the 65-kDa, isoform of glutamic acid decarboxylase (GAD), the enzyme that synthesizes GABA, have been widely-replicated. However, protein levels of GAD isoforms have only been examined in one study.
Methods: We used antibodies specific for GAD65 and GAD67, and a pan-GAD antibody that also detects a common degradation product, to assess by Western blots the effects of artificially created postmortem intervals (PMI) in monkey DLPFC. The same approach is being used to quantify GAD65, GAD67, and actin (used as a loading control) protein levels in DLPFC area 9 from 20 matched pairs of schizophrenia and control subjects, each of whom has PMI < 20 hrs and RNA integrity number (RIN) > 7.
Results: In monkeys, GAD67 protein was well-preserved, and most GAD65 protein was still detectable, with PMIs < 24 hrs. The band of degraded GAD increased in proportion to the decline in GAD65 levels. In pilot studies, actin-corrected GAD65 levels did not differ between schizophrenia and control subjects, whereas GAD67 levels were reduced in the schizophrenia subjects across a range of PMIs. Blinded analyses of protein levels in the 20 pair cohort are ongoing.
Conclusions: A reduction in the levels of GAD67, but not GAD65, protein in subjects with schizophrenia would parallel the mRNA data and support the hypothesis of reduced GABA synthesis and neurotransmission in the DLPFC in schizophrenia.
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790. The Hippocampus as a Neural Marker of Short-Term Clinical Outcome in First Episode Schizophrenia

Yvonne Czechowska, Michael Bodnar, Ashok Malla, Ridha Joober, Jens Pruessner, Martin Lepage

Psychiatry, Douglas Research Centre-McGill University, Montreal, QC, Canada

Background: In schizophrenia, poor outcome or response to treatment has been related to both cognitive (memory and executive dysfunctions) and neural (enlarged ventricles and reduced occipital-temporal lobes) markers. Although hippocampal volumes are reduced in both first episode and chronic schizophrenia, these deficits have only been related to long-term clinical measures of outcome.
Methods: To determine if volumetric hippocampal differences could identify a poor response to treatment in first episode of schizophrenia (FES) patients. Hippocampi were manually segmented into three parts: the body, head, and tail. Volumes were obtained in 40 FES patients (23 non-responders and 17 responders - separated by six-month therapeutic response to treatment) and 26 matched healthy controls.
Results: Non-responders showed a right tail hippocampal volume deficit compared to responders (NR= 573±134; R= 658±144; t=-1.91, p=0.03). Compared to healthy controls, non-responders displayed bi-lateral hippocampal body reductions (Left Body: NR=1227±176, HC=1333±222, t=-1.83, p=0.03; Left Body: NR=1134±206, HC=1242±192, t=-1.90, p=0.03) while responders showed no differences.
Conclusions: These findings suggest that a volume deficit in the right tail of the hippocampus may be a neural marker in FES patients who will not respond to treatment by six-months. The right hippocampus is suggested to help maintain short-term memory of object-location associations, so a volumetric deficit may affect this ability and ultimately treatment response. The early identification of treatment non-response may have therapeutic implications.
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791. Visual and Verbal Tests of Social Cognition in Patients with Schizophrenia and their Unaffected First-Degree Relatives Delfina de Achával

Cognitive Neurology and Psychiatry Section, FLENI, Buenos Aires, Argentina

Background: Social cognition is affected in individuals with schizophrenia. It is unclear to what extent the deficits are shared by unaffected family members and the nature of the relationship between deficits in different social cognition subcomponents: emotional processing and theory of mind.
Methods: The performance in tests of emotional processing in faces (Baron Cohen, 1997) and eyes (Baron Cohen, 2001), in a test of social faux pas (Stone , 2002) and in theory-of-mind stories (Happé, 1999) were tested in 16 individuals with chronic, stable schizophrenia attending the Cognitive Neurology and Psychiatry Section of FLENI, 19 first-degree relatives, and in 20 healthy persons. A one-way ANOVA was used to compare the groups, followed by a Tukey´s test.
Results: Patients had a poorer overall verbal performance in recognition of faux pas stories (F=4.851, p=0.018) and Happe´s theory-of-mind stories (F=3.411, p=0.032), but in our sample there were no significant differences in the visual emotional processing tested in eyes and faces. First-degree relatives of schizophrenic patients showed an impaired recognition of faux pas stories in comparison with healthy persons (p=0.044). We observed no significant differences in performance in social cognition tests between patients and their relatives. Performance in visual and verbal tests of social cognition were correlated in relatives (r=0.77, p<0.001) and patients with schizophrenia (r=0.493, p=0.052), but not in healthy individuals.
Conclusions: Our results suggest that individuals with schizophrenia and their first degree relatives display a similar pattern of social cognition information processing, although social cognition deficits seem less intense in the latter.

792. Pain Perception in Schizophrenia: An fMRI Longitudinal Study

Camilo De la Fuente-Sandoval[1], Rafael Favila[2], Diana Gomez-Martin[3], Francisco Pellicer[4], Ariel Graff-Guerrero[5]

[1]Laboratorio de Psiquiatria Experimental, Instituto Nacional de Neurologia y Neurocirugia, Mexico, Mexico,[2]Neurologia, GE Healthcare, Mexico, Mexico,[3]Inmunologia y Reumatologia, Instituto Nacional de la Nutricion, Mexico, Mexico,[4]Laboratorio de Neurofisiologia Integrativa, Instituto Nacional de Psiquiatria, Mexico, Mexico,[5]Campus Juriquilla, Universidad Nacional Autonoma de Mexico, Queretaro, Mexico

Background: Several clinical reports suggest a higher threshold to pain sensitivity in schizophrenia; however, the mechanisms and implications of this remain unknown. Therefore, we examined the effect of antipsychotic treatment on blood oxygen level-dependent (BOLD) response to pain tolerance, as obtained by functional magnetic resonance imaging (fMRI) in patients with schizophrenia, before and after 6 weeks of antipsychotic treatment, versus healthy controls
Methods: We studied 12 patients with schizophrenia who were drug free and again after 6 weeks of clinically effective risperidone treatment. Patients were compared with 13 sex-and-age matched controls. fMRI was used to assess BOLD changes in response to a thermal tolerance pain stimulus vs. a non-painful somatosensory stimulus.
Results: Drug-free group showed greater tolerance to higher temperatures than controls, and this tolerance decreased after 6 weeks of treatment with risperidone to levels closer to those observed in control subjects. Moreover, drug-free subjects showed a lack of activation of the posterior cingulate cortex (PCC), Insula (INS), and brainstem, and higher activation in the postcentral gyrus (S1) as compared with controls. Following treatment, patients recovered activity in the INS, but not in the PCC or brainstem. The S1 remained overactive after treatment
Conclusions: A higher pain tolerance is state dependent and it partially responds to effective antipsychotic treatment, though the underlying biological mechanisms may show differential response to treatment. Ongoing studies in subjects at high risk of schizophrenia will help to clarify whether underactivation of the PCC and brainstem and overactivation of S1 reflects a trait in schizophrenia
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793. Evidence of Exacerbated Cognitive Deficits in Schizophrenia Patients with Diabetes

Dwight Dickinson[1], James Gold[2], Faith Dickerson[3], Deborah Medoff[1], Lisa Dixon[1]

[1]Psychiatry, University of Maryland/MIRECC, Baltimore, MD,[2]Psychiatry, University of Maryland/MPRC, Baltimore, MD,[3]Psychiatry, University of Maryland/SEPH, Baltimore, MD

Background: The elevated rates of metabolic dysregulation and disease among individuals with schizophrenia are alarming, with 1.5 to 2 times the normal prevalence of diabetes and more than 40% of schizophrenia patients meeting criteria for the metabolic syndrome. Cognitive impairment in schizophrenia is well established as a critical determinant of disability and reduced role functioning. Less widely studied is the fact that cognition is

also impaired in diabetes. The cognitive impact of diabetes converges with known cognitive deficits in schizophrenia. Although schizophrenia deficits are broadly generalized, the most prominent impairment is in the processing speed domain. Literature suggests that diabetes may exert its largest cognitive effect in this same domain.

Methods: We compared cognitive performance, as measured by the Repeatable Battery for the Assessment of Neuropsychological Status, in three groups: patients with schizophrenia and diabetes (n=97), patients with diabetes only (n=95), and archival data on patients with schizophrenia only (n=575).

Results: Comparisons indicated that the schizophrenia/diabetes group was impaired cognitively relative to both other groups (t's > 2.6, p's < .01), especially in the domains of processing speed and visual/spatial ability (t's > 3.6, p's < .001). Additionally, key impairments were associated with diabetes severity markers in the schizophrenia/diabetes patients, including age of diabetes onset, duration of diabetes, and glycosylated hemoglobin.

Conclusions: Individuals with schizophrenia experience higher diabetes and pre-diabetes prevalence rates. Because either illness alone creates cognitive vulnerability, the two illnesses together are even more likely to result in an increased rate and magnitude of cognitive and functional decline.

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794. Disrupted Resting Functional Connectivity between a Dorsolateral Prefrontal Cortex (DLPFC) Region Showing Catechol-O-Methyltransferase (COMT) Genotype Effects and Inferior Parietal Lobule in Schizophrenia

Daniel P. Eisenberg[1,2], Deepak Sarpal[1,2], Philip D. Kohn[1,2], Andreas Meyer-Lindenberg[3], Dylan Wint[1,2], Bhaskar Kolachana[2], Daniel R. Weinberger[2], Karen F. Berman[1,2]

[1]Section on Integrative Neuroimaging, Intramural Research Program, National Institute of Mental Health, NIH, DHHS, Bethesda, MD,[2]Clinical Brain Disorders Branch, Genes, Cognition and Psychosis Program, Intramural Research Program, National Institute of Mental Health, NIH, DHHS, Bethesda, MD,[3]Unit for Systems Neuroscience in Psychiatry, Neuroimaging Core Facility, Intramural Research Program, National Institute of Mental Health, NIH, DHHS, Bethesda, MD

Background: Cognitive activation fMRI studies in schizophrenia have demonstrated both COMT genotype effects on prefrontal cortical efficiency and functional disconnectivities between prefrontal cortex and diverse brain regions. However, little is known about COMT effects on resting neurofunctional topography or illness-associated prefrontal functional connectivity in the resting state, particularly in medication-free patients.

Methods: Twenty-five participants with schizophrenia (28+6 years, 6 females), withdrawn from medication for four weeks, and 54 healthy participants (28+6 years, 16 females) were genotyped for the COMT Val158Met polymorphism, and underwent two 10 mCi 15O-H_2O PET scans during rest. Using random-effects, general linear modeling, we identified regions where blood flow (rCBF) correlated with number of COMT met alleles. We used significant results ($p<0.05$, corrected) in the prefrontal cortex to functionally define seed-regions, with which we explored functional connectivity.

Results: Five met/met, 12 val/met, and 8 val/val patients and 13 met/met, 25 val/met, and 16 val/val healthy individuals participated. In the schizophrenia group, COMT met (relative to val) carriers had greater right DLPFC, right superior temporal gyrus, and left precuneus rCBF, and less right amygdala rCBF. In healthy participants, met carriers showed less left precuneus rCBF. Between-group comparisons of functional connectivity revealed more robust correlation between right DLPFC and right inferior parietal lobule rCBF in healthy individuals than patients.

Conclusions: These data extend to the resting state previous findings in schizophrenia of both COMT genotype-related DLPFC neural activity changes and altered functional cooperativity of DLPFC with other nodes in key neural circuits, such as the working memory system.

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795. Differential Visual Masking Performance in Individuals at Risk for Schizophrenia Suggests Specific rather than Generalized Information Processing Deficits

Ali Eslami, Kathy Shafer, Kristin Cadenhead

Psychiatry, UCSD, San Diego, CA

Background: Schizophrenia patients have information processing deficits that may be present prior to the onset of florid psychosis. Individuals in the prodromal stage of schizophrenia are a heterogeneous population who has either genetic risk for schizophrenia, with functional decline, and/or subsyndromal psychotic symptoms. One means to understand the pathogenic processes in this population is to use biological markers that are sensitive to these early changes. The Visual Backward Masking (VBM) paradigm has been used to detect deficits in schizophrenia patients, their first degree relatives and schizotypal personality disorder individuals.

Methods: Visual forward and backward masking performance of 39 First Episode Psychosis, 65 At Risk (AR) and 71 Normal Comparison (NC) subjects was assessed in a paradigm that included high and low energy masking conditions.

Results: Significant group-by-direction (forward versus backward) interactions were present across all masking conditions since AR subjects performed better than other groups in the forward direction but showed deficits in low-energy and reduced performance in the high-energy and location conditions relative to NCs. Interestingly, it was AR subjects who later converted to psychosis who had the most prominent VBM deficits across all conditions.

Conclusions: This is the first study to demonstrate VBM deficits in prodromal schizophrenia patients, consistent with those seen in other schizophrenia spectrum groups. The differential deficit in performance between the forward and backward conditions in AR subjects demonstrates that the deficit is not-generalized. More longitudinal studies and larger samples are needed to better study the predictive value of VBM information processing in AR subjects.

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796. Treatment Effect on Attentional Network Functions in Patients with Schizophrenia

Kai Wang[1], Yi Dong[2], Lilin Gao[3], Panpan Hu[1], Kevin G. Guise[4], Laura Martin[4], Philip D. Harvey[5], **Jin Fan**[4,6]

[1]Department of Neurology, Anhui Medical University, Hefei, China,[2]Department of Psychiatry, Anhui Medical University, Hefei, China,[3]Neurology, Anhui Medical University, Hefei, China,[4]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY,[5]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA,[6]Department of Neuroscience, Mount Sinai School of Medicine, New York, NY

Background: Recent theories have conceptualized attention as comprising three separate functional components of alerting, orienting, and executive control. The alerting subsumes the capacity to increase vigilance to an impending stimulus, the orienting component involves the selection of task-specific information from among numerous sensory inputs, and the executive control involves more complex mental operations and has been implicated in conflict processing. Anatomically distinct neural networks and the norepinephrine, cholinergic, and dopamine systems mediate these functions. Many studies on

attention in patients schizophrenia have identified deficits in one or more of these functions and/or related networks. In a previous study, we have shown that hospitalized chronic schizophrenic patients exhibit a robust deficit in the executive network and a smaller but significant deficit in the orienting network as well as in overall RT and accuracy. Although the beneficial effects of treatment with atypical agents, such as clozapine, on cognition are apparent, it is not clear whether this is a global improvement of attention or it is related to improvement of specific attentional functions.

Methods: In this study we examined 21 first-break patients with schizophrenia before and after treatment with clozapine using the Attention Network Test (ANT) to determine whether a 4-week treatment regimen improves attentional functions.

Results: A marginal significant improvement in measures of all three attentional networks was observed, as well as overall improvement in speed and accuracy.

Conclusions: These results may help in better understanding treatment effects on fundamental cognitive functions.

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797. Brain Networks Involved in Spatial Learning: An ICA Analysis of Individuals with Schizophrenia and Healthy Controls

Bradley S. Folley[1,2], Kanchana Jagannathan[1], Robert Astur[1,3], Vince Calhoun[1,4], Godfrey D. Pearlson[1,3]

[1]Institute of Living, Olin Neuropsychiatry Research Center, Hartford, CT,[2]Department of Psychiatry, Vanderbilt University, Nashville, TN,[3]School of Medicine, Yale University, New Haven, CT,[4]Engineering, The MIND Institute, Albuquerque, NM

Background: The Morris Water Maze test has been difficult to translate into human studies of allocentric spatial memory. With virtual reality (VR), it is now possible to examine performance in a computer generated water task. We examined the performance of individuals with schizophrenia (SZ) and healthy controls (HC) in a VR water task during fMRI scanning, analyzing the BOLD signal with ICA, to examine networks involved in allocentric processing in SZ and HC.

Methods: During 3T fMRI, participants (28 HC, 34 SZ) were placed in a virtual 3D pool with 4 balls floating in the water and navigated by manipulating a joystick. During "hidden", the 4 balls were identical, and the participants used distal cues to navigate to the 1 floating above a hidden platform. During "visible", the platform changed locations, one unique ball floated above the platform, and participants navigated to it by moving to the 1 unique ball among the 3 identical ones.

Results: SZ found the platform fewer times, made more errors, and spent more time and distance searching. ICA of fMRI data determined 5 relevant network components including: hippocampal/medial temporal lobe, basal ganglia, and superior temporal gyrus. Hippocampal component activation distinguished the 2 groups, while VBM indicated an inverse correlation between hippocampal grey matter concentrations and fMRI data for SZ only.

Conclusions: These data suggest that SZ perform poorly on the VR water task. Instead of recruiting the hippocampus, they may recruit the dorsal striatum, leading to a procedural learning strategy rather than a navigationally-guided one.

798. In Vivo Measurement of Increased Extracellular GABA with Positron Emission Tomography in Healthy Control Subjects

W. Gordon Frankle[1], Raj Narendran[2], N. Scott Mason[3], Shivangi Vora[4], Maralee Litschge[4], Julie C. Price[3], Chester A. Mathis[3], David A. Lewis[5]

[1]Psychiatry & Radiology, University of Pittsburgh, Pittsburgh, PA,[2]Radiology & Psychiatry, University of Pittsburgh, Pittsburgh, PA,[3]Radiology, University of Pittsburgh, Pittsburgh, PA,[4]Psychiatry, University of Pittsburgh, Pittsburgh, PA,[5]Neuroscience, University of Pittsburgh, Pittsburgh, PA

Background: This study represents the first step in validating a paradigm for measuring GABA transmission in human subjects.

Methods: Eight controls (29 ± 9.6 years, 4M/4F) underwent two [11C] flumazenil PET scans: baseline and 30 minutes after 16 mg PO tiagabine (GABA transporter blocker). The outcome measure was difference in binding potential (BP_{ND}, unitless) between the scans. Regions of interest (ROIs) were applied to the MR co-registered PET data to generate regional time-activity curves. Three cortical ROIs were obtained: Association cortex (DLPFC, orbital frontal, medial prefrontal, anterior cingulate), sensory cortex (parietal, occipital), and limbic medial temporal lobe (MTL; amygdala, hippocampus, enterorrhinal ctx and parahippocampal gyrus). The pons was used as the region of reference.

Results: No difference was observed in V_{ND} (pons VT = 1.0 ± 0.2 mL/g under both conditions). Tiagabine resulted in a significant increase in BP_{ND} in all three cortical areas: Association 5.7 ± 1.3 vs. 6.5 ± 1.3 ($p = 0.05$); Sensory 5.8 ± 1.2 vs. 6.7 ± 1.3 ($p = 0.03$); MTL 4.3 ± 1.0 vs. 4.9 ± 1.1 ($p = 0.03$). BP_{ND} increased post-tiagabine in all component ROIs as well. Results were similar for the arterial input derived BP_{ND}.

Conclusions: BP_{ND} increases in the larger cortical ROIs suggests an acute increase in GABA levels within the cortex may be detectable with this paradigm. This proof of concept study represents the first step towards validating a paradigm for detecting acute fluctuations in GABA in vivo that may explicate the role of GABA in schizophrenia.

799. Working Memory Dysfunction as Phenotypic Marker of Schizophrenic and Bipolar Affective Psychoses: Common and Differential Abnormalities in Brain Activation

Oliver Gruber[1], Ilona Henseler[1], Heike Tost[2], Harald Scherk[1], Thomas Wobrock[1], Marcella Rietschel[3], Peter Falkai[1]

[1]Department of Psychiatry and Psychotherapy, Georg August University Goettingen, Goettingen, Germany,[2]Clinical Brain Disorders Branch, National Institute of Mental Health, Bethesda, MD,[3]Division of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany

Background: Working memory dysfunctions are considered to be promising intermediate phenotypes, i.e. biological markers, which may help to discover genetic and other neurobiological factors involved in the pathogenesis of schizophrenic and affective psychoses. However, little is known about the possible role of these brain dysfunctions for differential diagnosis, for instance between schizophrenia and bipolar affective disorder. In the present study we directly compared brain activation during verbal working memory task performance in matched groups of schizophrenic and bipolar patients as well as healthy controls.

Methods: 12 schizophrenic patients, 14 bipolar patients and 14 healthy controls underwent fMRI during a delayed matching to sample task

requiring the maintenance of verbal information in working memory. Data were preprocessed and statistically analyzed using standard procedures as implemented in SPM2.
Results: Both schizophrenic and bipolar patients exhibited significantly increased activation in bilateral dorsolateral prefrontal cortex and in right intraparietal cortex. Abnormal hyperactivations that were unique to either schizophrenia or bipolar disorder were found in bilateral caudate nucleus and the right amygdala, respectively.
Conclusions: Compatible with findings from genetic research into the pathogenesis of schizophrenia and bipolar disorder, the present data show both similarities and significant differences between these two diagnostic categories regarding the patterns of abnormal brain activation that may underlie verbal working memory deficits in these patients.
Supported by Fritz Thyssen Foundation

800. Effects of Risperidone on Procedural Learning in Antipsychotic-Naive First-Episode Schizophrenia

Margret S. H. Harris[1], Courtney M. Nemeth[1], James L. Reilly[1], Tin T. Khine[1], Matcheri S. Keshavan[2], John A. Sweeney[1]

[1]Center for Cognitive Medicine, University of Illinois at Chicago, Chicago, IL,[2]Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

Background: Studies of procedural learning deficits of medicated schizophrenia patients using predictive saccade paradigms have consistently demonstrated hypometric predictive saccades. However, investigations with antipsychotic-naïve schizophrenia patients have shown inconsistent results. Further, it is unknown whether there is an impact of atypical antipsychotic medications on frontostriatal systems supporting relevant cognitive and motor processes.
Methods: The accuracy and latency of predictive saccades were assessed in 25 antipsychotic-naïve first-episode schizophrenia patients and 22 matched healthy individuals. Patients were tested before and after 6 weeks of treatment with risperidone. Healthy individuals were re-evaluated after a similar time period.
Results: The ability to learn to time response initiation in anticipation of target appearance (target prediction) was not impaired in patients before or after treatment. In contrast, although no deficits were evident before treatment initiation, after treatment patients showed a marked decrease in the accuracy of predictive but not visually guided responses.
Conclusions: The findings from pretreatment testing indicate that procedural learning is a relatively unaffected cognitive domain in treatment-naïve first-episode schizophrenia. The reduced accuracy of predictive saccades after antipsychotic treatment, even in the absence of treatment-emergent extrapyramidal symptoms, suggests that treatment-related D2 antagonism disrupted the balance of "go" and "no go" signaling in striatal systems to disrupt the generation of volitional behavior guided by internalized representations.
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801. Auditory Sensory Gating Deficit to Voice in Schizophrenia: An MEG Study

Yoji Hirano, Toshiaki Onitsuka, Shogo Hirano, Toshihiko Maekawa, Choji Obayashi, Naoya Oribe, Shigenobu Kanba

Department of Neuropsychiatry, Graduate School of Medical Sciences,Kyushu University, Fukuoka, Japan

Background: It has been suggested that schizophrenia patients have dysfunctions to suppress incoming irrelevant sensory input, perhaps related to hallucination or delusion. The dysfunctions have been indexed by a particular neurophysiological phenomenon, P50 sensory gating (assessed via EEG in a paired-click paradigm). Magnetoencephalography (MEG) is complementary to EEG, and superior for localization and analysis of lateralized cortical auditory responses. Furthermore, dysfunctions in early stage of language processing have been demonstrated in schizophrenia. It may therefore be important to investigate auditory sensory gating to the voice using MEG in schizophrenia.
Methods: Auditory-evoked MEG responses using a paired-voice paradigm were obtained from 22 patients with schizophrenia and 28 (age-, gender-, handedness-, and parental socioeconomic status-matched) comparison subjects. P50m and N100m gating ratios were compared and MEG-symptom correlations were investigated with respect to scores on SAPS and SANS.
Results: In the left hemisphere, patients showed significantly larger P50m gating ratios ($p=0.001$) than did comparison subjects, but not in the right hemisphere. There were no significant group differences in N100m for both hemispheres. For MEG-symptom correlations, patients with larger left P50m gating ratios showed more severe auditory hallucinations ($p=0.04$). Patients with larger right P50m gating ratios showed more severe negative symptoms ($P=0.01$).
Conclusions: The present study suggested that schizophrenia patients showed sensory gating deficits to voice especially in the left hemisphere. For MEG-symptom correlations, patients with severe left-hemispheric gating deficits showed more severe auditory hallucinations, while patients with larger right gating ratios showed more severe negative symptoms.

802. P300 Abnormalities in Schizotypal Personality Disorder and Siblings of Schizophrenia Patients revealed by LORETA

Hiroto Hokama[1], Wang Jijun[2], Tsuyoshi Kondo[1]

[1]Department of Neuropsychiatry, Ryukyu University, Okinawa, Japan,[2]Department of EEG Source Imaging, Shanghai Mental Health Center, Shanghai, China

Background: The reduction of P300 component of Event-Related Potentials in schizophrenia is one of the most robust biological findings of schizophrenia. It is also known to exist among subjects at high risk for schizophrenia, including Schizotypal Personality Disorder (SPD) subjects and the first-degree relatives of schizophrenia. However, whether the different groups of high risk subjects have the same or different neural origins of P300 abnormality has not yet been explored.
Methods: The present study examined P300 abnormalities in two high risk groups of schizophrenia with LORETA (low resolution brain electromagnetic tomography). The first group was consisted of nine SPD subjects recruited from university students using Schizotypal Personality Questionnaire (SPQ). The second group was consisted of ten siblings of schizophrenic patients. ERPs were recorded using oddball paradigm.
Results: In both high risk groups, P300 was reduced as compared to their sex/age matched normal controls. Reduction of P300 cortical current density was observed in temporal region with left dominancy in SPD subjects. The siblings of schizophrenia showed reduction of P300 cortical current density in the right frontal region.
Conclusions: These results suggest that P300 reduction in both symptomatological and genetic high risk groups of schizophrenia might have different origin of disturbance in the neural circuitry for P300 generation.

803. Diagnostic Specificity of Auditory ERPs as Endophenotypes for Schizophrenia: Are we Picking the Right Peaks?

Jason K. Johannesen[1], Anantha Shekhar[2], Brian O'Donnell[3], William P. Hetrick[3]

[1]Psychiatry, Yale University, West Haven, CT,[2]Psychiatry, Indiana University, Indianapolis, IN,[3]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN

Background: Event-related potential paradigms are widely investigated as biological endophenotypes of schizophrenia. Abnormalities in P50 suppression,

P300 amplitude, and P300 latency are viable candidates given their reliable expression in schizophrenia, linkage to genes implicated in illness vulnerability, and aggregation among unaffected family members. However, evidence for similar abnormalities in bipolar disorder compromise specificity, and diagnostic utility, of these measures. The use of a multivariate endophenotype, derived from conventional P50 (paired-click) and P300 (standard, target) paradigms, was examined as a method to improve diagnostic efficiency.

Methods: Hierarchical logistic regression was used to classify schizophrenia (SZ; n = 52) against equal numbers of age-matched healthy normal (HN) and bipolar disorder (BP) participants. Predictors were entered as follows: Block 1 - P50 suppression, P300 amplitude, P300 latency; Block 2 - N100 amplitudes; Block 3 - low-frequency (1-20 Hz) and gamma-band (20-50 Hz) spectral power density; Block 4 - P50 and P300 hemispheric asymmetry.

Results: Candidate endophenotypes (Block 1) yielded 71% overall classification accuracy distinguishing SZ from HN. N100 and spectral power measures contributed uniquely to the model and improved accuracy to 79%. The same model classified SZ against BP with 64% overall accuracy, but none of the candidate endophenotypes entered as significant predictors. A model based on N100 amplitudes and gamma spectral power optimally classified SZ and BP with 72% accuracy.

Conclusions: Although schizophrenia and bipolar disorder exhibit dissociable patterns of abnormality on standard ERP paradigms, results suggest that the measures most often assessed as endophenotypes are insensitive to their distinct pathophysiology.

804. Effect of Metabolic Syndrome on Cognition in Older Schizophrenic Patients

Isabella Kanellopoulou[1], Christopher Bowie[1], Hannah Anderson[2], Brooke Halpern[2], Phil D. Harvey[3]

[1]Psychiatry, James J. Peters VAMC/ Mount Sinai School of Medicine, Bronx, NY,[2]Psychiatry, Mount Sinai School of Medicine, New York, NY,[3]Psychiatry, Emory University School of Medicine, Atlanta, GA

Background: Studies have revealed mild cognitive impairment associated with early stage diabetes and hypertension in non-psychiatric populations, particularly in the areas of working memory, attention, and executive functioning. These conditions have been associated with the metabolic syndrome (MS), which is common in schizophrenia, yet their cognitive implications in schizophrenia are not understood.

Methods: Older schizophrenia outpatients on atypical antipsychotic medications with MS (n=58) were matched with those without MS (n=60) on age and education. Univariate analyses of variance were used to examine differences between groups on cognitive domains, with estimated premorbid functioning entered as a covariate.

Results: Effect sizes are presented with positive values representing higher scores for patients without MS. Groups were not significantly different (all p-values > .05) on verbal learning (ES=-.11), memory (ES=.01), attention (ES=.04), processing speed (ES=.32), working memory (ES=.13), or executive functioning (-.21).

Conclusions: In this cross-sectional analysis of older schizophrenia outpatients, there was no evidence for additional cognitive liability associated with symptoms of the metabolic syndrome. It is possible that the magnitude of cognitive impairment in schizophrenia is too large to detect the smaller impairments typically associated with symptoms of the MS. Longitudinal studies will be necessary before causal relationships can be discussed or ruled out.

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805. White Matter Integrity and Prediction of Social and Role Functioning in Subjects at Ultra-High Risk for Psychosis

Katherine H. Karlsgodt[1,2], Tara A. Niendam[1], Russell A. Poldrack[1,3,4], Carrie E. Bearden[4], Tyrone D. Cannon[1,4,5]

[1]Department of Psychology, UCLA, Los Angeles, CA,[2]Semel Institute, UCLA, Los Angeles, CA,[3]Brain Research Institute, UCLA, Los Angeles, CA,[4]Department of Psychiatry and Biobehavioral Science, UCLA, Los Angeles, CA,[5]Department of Human Genetics, UCLA, Los Angeles, CA

Background: Changes in white matter integrity have been observed in patients with schizophrenia, even in the first-episode. However, it is unknown whether these changes exist prior to the onset of schizophrenia or in individuals at clinical or genetic high-risk. Our study sought to determine whether baseline measures of white matter integrity as assessed by diffusion tensor imaging (DTI) were related to measures of global, social and role functioning at follow-up in a sample of individuals at ultra-high-risk (UHR) for psychosis.

Methods: Twenty-four UHR participants completed DTI scans and comprehensive clinical and functional assessments at baseline, and clinical and functional assessments at follow-up, on average, 7.5 months later. DTI data was analyzed with a rigorous registration approach (Tract-Based Spatial Statistics (TBSS); FMRIB Software Library) in order to examine fractional anisotropy (FA). Region of interest analyses focused on the superior longitudinal fasciculus (SLF), which was previously shown to be disrupted in first episode patients.

Results: Robust regression demonstrated that lower FA in the right SLF, indicating reduced white matter integrity, was significantly associated with decline in global and social functioning, with a trend towards a decline in role functioning over the follow-up period. This finding was restricted to the anterior portion of the SLF, potentially representing a more frontally based deficit.

Conclusions: This finding is the first indication that indexes of white matter integrity as assessed by DTI may be predictive of changes in psychosocial functioning in patients at ultra-high risk for psychosis.

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806. Brain Activation Patterns in Schizophrenia after Computerized Cognitive Skills Training

Saurabh Kaushik[1,2], Jean-Pierre Lindenmayer[1,2,3], Craig Branch[4], Susan R. McGurk[5], Anzalee Khan[1,2], Deborah Wance[6], Lisa Hoffman[7], Barbara Simmon[7], Xiaobo Li[4], Sashank Kaushik[1]

[1]Psychopharmacology Research Program, Manhattan Psychiatric Center, Wards Island, NY,[2]Psychopharmacology Research, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY,[3]Psychiatry, New York University School of Medicine, New York, NY,[4]Medical Physics, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY,[5]Psychiatry, Dartmouth College, Concord, NH,[6]Rehabiliation Services, Manhattan Psychiatric Center, Wards Island, NY,[7]Psychology, Manhattan Psychiatric Center, Wards Island, NY

Background: 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 with stimulation with a neurocognitive task after cognitive remediation therapy (CRT).

Methods: Patients with DSM IV schizophrenia were randomized to a 12 week trial of CRT using COGPACK (Marker Software) or to a 12-week control

condition. Patients in the CRT group completed 36 one-hour sessions. Patients received fMRI with the N-back task, the MATRICS battery, functional and symptom assessments at baseline and endpoint.
Results: We present preliminary results of this ongoing study. Patients in CRT showed significantly more improvement in WM functions 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 was not present or only present minimally at baseline (Pre-CRT); however, at endpoint (Post-CRT) there was signal difference in the pre-frontal areas. Patients demonstrated significantly increased activity in the right inferior frontal gyrus and anterior cingulate gyrus.
Conclusions: This study offers an opportunity to examine the underlying neurophysiological effects of neurocognitve treatments of WM deficits. Given the diversity and complexity of brain pathophysiology in schizophrenia, the changes in DLPFC after neurocognitive rehabilitation treatment may be valuable for customizing cognitive treatments for schizophrenia.
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807. Atlas-Based Segmentation of DTI in Schizophrenia

Usman Khan[1], Marek Kubicki[2,3], Carl-Fredrik Westin[4], Steven Pieper[5], Robert McCarley[3], Martha Shenton[1,3,6]

[1]Psychiatry, Brigham and Women's Hospital, Boston, MA,[2]Psychiatry-Psychiatry and Neuroimaging Laboratory, Brigham and Women's Hospital, Boston, MA,[3]Psychiatry, Veterans Affairs Boston Healthcare System, Brockton, MA,[4]Surgical Planning Lab- Laboratory for Mathematical Imaging, Brigham and Women's Hospital, Boston, MA,[5]Surgical Planning Lab- Neuroimage Analysis Center, Brigham and Women's Hospital, Boston, MA,[6]Surgical Planning Lab, Brigham and Women's Hospital, Boston, MA

Background: Diffusion tensor imaging (DTI) allows for a more thorough analysis of anatomical connectivity in schizophrenia. Numerous studies report white matter (WM) abnormalities in schizophrenia, however these studies have either investigated single fiber tracts (region of interest analysis), or relied on error prone DTI normalization to the template space (voxel based morphometry analysis). In this investigation, we attempt to study regional WM alterations in schizophrenia using a WM atlas and individual subject DTI data.
Methods: Sixteen male patients with chronic schizophrenia and seventeen male controls were scanned using high resolution DTI. Fractional Anisotropy (FA) and Trace (Tr) were used to quantify water diffusion within several ROIs derived from an average of manual segmentations of eighty-one subjects selected from the 452 healthy subject MNI population (www.LONI.org). These ROIs were coregistered into subject DTI space using linear and non-linear intensity based algorithms, and FA and Tr within these ROIs averaged, and compared between groups.
Results: Findings revealed reduced FA within left striatum WM (ROI included inferior longitudinal and inferior occipito-frontal fasciculus) in schizophrenia (P=0.011). We also found increased Tr bilaterally in superior longitudinal fasciculus in schizophrenia (t_{33}=2.420, P=0.022). Finally, FA within corpus callosum, showed a significant region by diagnosis interactions (P=0.036), with genu and splenium, but not body, having decreased FA in schizophrenia.
Conclusions: This investigation demonstrates the utility of white matter atlas based segmentation, and suggests regional WM abnormalities in schizophrenia existing in long association tracts interconnecting frontal and temporo-occipital regions, as well as in the corpus callosum.
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808. Neuropsychological Performance at Industry Sponsored Trials and Academic Sites: Do the Results Differ?

Feea R. Leifker, Philip D. Harvey

Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA

Background: Cognitive impairment is a treatment target in schizophrenia. A consensus battery has been developed for clinical trials. Many clinical trials sites lack extensive experience performing neuropsychological (NP) assessments and it is unclear if results of these assessments are the same as would be obtained from assessments performed at academic sites.
Methods: Baseline neuropsychological performance from published papers on pharmaceutical industry sponsored clinical trials was collated. Results from specific tests of processing speed, executive functioning, working and episodic memory, attention, and verbal fluency was compared to performance in published studies conducted by academic sites. Data were examined from first episode patients, nongeriatric chronic patients, and geriatric patients.
Results: For first episode patients, both average performance and variance on all tests sampled was essentially identical across clinical and academic sites. In the analyses of chronic nongeriatric patients, performance in studies reporting industry clinical trials was significantly ($p<.05$) higher on processing speed and executive functioning and significantly lower ($p<.05$) on the CPT than academic studies. There were no significant differences in variance. For geriatric patients there was only one published clinical trial, but performance was significantly ($p<.001$) lower and variance was greater ($p<.001$) on all cognitive domains sampled than academic studies.
Conclusions: These results suggest that NP performance of patients with schizophrenia in industry clinical trials, other than first episode studies, is more variable than that obtained in academic sites, suggesting that increased quality assurance standards may be required to ensure that treatment effects are not obscured by poor assessment quality.

809. The Effects of Context on Schizophrenia Facial Affect Perception

David I. Leitman, Daniel Wolf, James Loughead, Kosha Ruparel, Jeffery N. Valdez, Christian G. Kohler, Mark A. Elliot, Raquel E. Gur, Ruben C. Gur

Brain Behavior Laboratory, University of Pennsylvania, Philadelphia, PA

Background: Facial affect recognition as a process is susceptible to bottom-up sensory and top-down contextual influences that are difficult to disentangle. Such dual influences complicate the interpretation of abnormalities seen in schizophrenia, where affective processing deficits may be attributable to limbic or executive dysfunction as well as sensory disturbance. Here, we examined the effects of context on facial affect processing by measuring the influence of task demand.
Methods: Seventeen controls and sixteen schizophrenia patients performed a facial affect detection task containing four blocks during 4-tesla BOLD fMRI scanning. For each block subjects respond to a particular affective target (e.g. anger) presented alongside foils of differing emotions (e.g. happy, sad, fear) in an "event-related" manner. We hypothesized that affiliative emotion target blocks such as happiness or sadness create one form of context, while threat blocks of emotions such as anger and fear create another. We then contrasted BOLD differences between threat and affiliative foils presented within affiliative or threat target blocks.
Results: Within controls, affiliative foils presented within threat-seeking blocks produced significantly higher bilateral activation in aspects of orbitofrontal (OFC) and ventrolateral prefrontal (VLPFC) cortex than the presentation of identical stimuli within non threat-seeking blocks. However, this contrast revealed no significant change in schizophrenia.

Conclusions: Task demands reveal significant contextual effects during facial affective processing in affect evaluation brain regions. Such contextual modulation is reduced in patients, suggesting that affect detection in schizophrenia may be driven more by bottom-up (stimulus features) than by top-down contextual processing (task demands).
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810. Decreased Fractional Anisotropy in the Anterior Limb of the Internal Capsule in Schizophrenia: A Diffusion Tensor Imaging Study

James Levitt[1,2], Jorge L. Alvarado[2], Marek Kubicki[2], Paul G. Nestor[1], Robert W. McCarley[1], Martha E. Shenton[1,2]

[1]Psychiatry, VA Boston Health Care System, Harvard University, Brockton, MA,[2]Psychiatry, Brigham and Women's Hospital, Psychiatry Neuroimaging Laboratory, Harvard Medical School, Boston, MA

Background: An integral part of higher order cognitive function lies in the cognitive and limbic feedback loops of the frontal-subcortical circuits. The white matter tracts in the anterior limb of the internal capsule (AL-IC) form the last segment of these loops. Using structural MR for volumetric measurements, and diffusion tensor imaging (DTI) for diffusion index analyses, we explored differences in the AL-IC between schizophrenics and normal controls.
Methods: Structural and DT MR images were acquired on a 1.5-T GE scanner for 20 male, chronic schizophrenics and 22 male, normal controls, group matched on age and parental socioeconomic status. The AL-IC was manually delineated on structural images - volume, normalized for head size, and residualized volume were obtained. DTI scans were upsampled to match the structural images' resolution, and then coregistered with their corresponding segmented volumes. Fractional anisotropy (FA), mode, and mean diffusivity (MD) were measured within the AL-IC.
Results: Volumetric measurements revealed no differences between diagnostic groups. The diffusion analyses showed, for schizophrenics: significant bilateral FA decreases ($p = 0.017$ and $p = 0.010$ for left and right AL-IC, respectively), no significant left-sided mode difference, a trend right-sided mode decrease ($p = 0.061$), and trend MD increases ($p = 0.068$ and $p = 0.063$ for left and right AL-IC, respectively).
Conclusions: The FA decrease suggests AL-IC white matter pathology in schizophrenia, possibly associated with disordered fiber networks or decreased neuropil density. These findings provide evidence for structural abnormalities in frontal-subcortical circuitry that may underlie functional deficits characteristic of the disorder.
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811. Predictors of Improvement for a Computerized Cognitive Remediation Program in Psychiatric Inpatients

Jean-Pierre Lindenmayer[1], Susan McGurk[2], Anzalee Khan[3], Lisa Hoffman[4], Frances Alcantara[3]

[1]Psychopharmacology Research Dept., New York University, New York, NY,[2]Psychiatry, Dartmouth University, Concord, NH,[3]Psychopharmacology Research Dept., Nathan Kline Institute for Psychiatric Research, New York, NY,[4]Psychology, Manhattan Psychiatric Center, New York, NY

Background: Cognitive impairments are core to schizophrenia and relate to poor functional outcomes. Cognitive Remediation Therapy (CRT) is designed to improve neurocognitive functioning. With CRT, patients practice cognitive functions using computer exercises and strategy coaching. CRT shows significant benefits on long-term outcomes with moderate effect sizes. Aims include 1) elucidating factors associated with good outcome in CRT and 2) examining baseline differences between 'Improvers' and 'Non-Improvers.'
Methods: 74 schizophrenic/schizoaffective inpatients used COGPACK, computerized software, to practice a range of cognitive functions. 45 patients received 24 sessions and 29 patients received 36 sessions for 12-weeks, with weekly discussions to facilitate cognitive skills and adaptive functioning.
Results: Of 74 patients, 46 were 'Improvers,' 28 were 'Non improvers', based on ≥ 20% improvement in processing speed and executive functioning. Higher scores in measures of attention, WM and WRAT-III reading, more interaction with group leaders, lower PANSS - Positive and Total scores, WCST perseverative errors, and Personal and Social Performance (PSP) for Socially Useful Activities scores were retained at the endpoint, resulting in 81.2% classification accuracy. PANSS-Positive scores, PSP scores, WCST perseverative errors, and attention at baseline significantly predicted improvement with CRT. The overall fit of the 8 predictors was fairly good and reliable in distinguishing between improvers and nonimprovers ($p = .04$).
Conclusions: Baseline characteristics are likely to predict positive response to CRT. These factors cover cognition and psychopathology and must be evaluated during screening to facilitate cognitive and functional improvement. Results support the feasibility of an emergent formula to predict treatment success.

812. Impairment of Associative Recognition with no Response Bias in Schizophrenia

David Luck

Psychiatry, McGill University, Verdun, QC, Canada

Background: Memory is one of the cognitive functions most affected in schizophrenia, but the severity of deficits varies from one task to another. In particular, greater impairments have been reported for associative recognition than item recognition. However, the exploration of decision biases and how it could affect memory dysfunction in schizophrenia has received scant attention.
Methods: In this study, 33 people with schizophrenia and 39 healthy controls were administrated an Association-Item recognition task. During encoding, participants studied pairs of visual objects, and had to memorise objects and their pairing. In a subsequent retrieval task, participants performed an item recognition test (old/ new items) and an associative recognition test (intact/ rearranged pairs).
Results: Results showed that both groups recognized better items than pairs, with overall lower performance in people with schizophrenia. Analyses of response biases revealed that people with schizophrenia had a familiarity response bias for items but not for pairs. A subsequent analysis revealed that relative to controls, patients with a significant familiarity response bias exhibited lower performance for both pairs and items. Individuals with schizophrenia with no response bias showed lower performance for pairs but not for items.
Conclusions: Together, these results confirm the associative recognition dysfunction largely observed in schizophrenia. Furthermore, the study provides evidence that this dysfunction may not result from a decisional bias but rather from cognitive processes impairments.
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813. Attenuated Variation of Late Temporal ERPs to Facial Expressions in Schizophrenia

Spencer K. Lynn, Dean F. Salisbury

Cognitive Neuroscience, McLean Hospital, Harvard Medical School, Belmont, MA

Background: Emotional stimuli elicit amplitude variation in event related brain potentials (ERPs) at temporal sites after circa 500 ms. In psychiatrically-well subjects this variation can distinguish between facial expressions. We sought to characterize this variation in schizophrenia and determine symptom and neurocognitive correlates.
Methods: ERPs were recorded to faces depicting angry, disgusted, fearful, happy, sad, and neutral expressions (the latter a button press target). Twenty-four schizophrenia subjects (nine female) and eight control subjects (three female) participated. EEG was recorded from 60 scalp channels and rerefereced to the average. Mean voltage between 600-800 ms was examined at occipitotemporal electrodes P9 (left) and P10 (right).
Results: Late ERP activity elicited by the neutral target was normal in schizophrenia (P>0.6). However, a marginal emotion x group interaction was observed among the remaining expressions (P=0.059). Among controls, at P10 differences were found for sad vs. disgusted (P=0.003) and fearful (P=0.035), and happy vs. disgusted (P=0.032). P9 showed fewer differences. Patients exhibited no significant ERP variation among non-target faces; however, emotional modulation (indexed by disgusted-sad difference) was associated with better performance on the ERP task (r=0.4, P=0.047) and on immediate and delayed face recognition tests (r=0.4, P=0.04; r=0.6, P=0.005, respectively).
Conclusions: Modulation of the late temporal ERP has been associated with evaluation of a stimulus' emotional significance within the larger behavioral context. Schizophrenia patients may fail to evaluate and integrate the motivational significance of different facial expressions relative to one another, leading to, e.g., reduced emotion-facilitated enhancement of performance in a face recall task.
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814. Altered Visual Attentional System in Schizophrenia: Evidence from an ERP Study

Toshihiko Maekawa[1], Yoji Hirano[1], Shogo Hirano[1], Choji Obayashi[1], Toshiaki Onitsuka[1], Shozo Tobimatsu[2], Shigenobu Kanba[1]

[1]Neuropsychiatry, Kyushu University, Fukuoka, Japan,[2]Clinical Neurophysiology, Kyushu University, Fukuoka, Japan

Background: Cognitive dysfunction of schizophrenia (Scz) may result from abnormal attentional processing in the brain. Attentional processing consists of two streams: One is involuntary attention (automatic) processing and the other is voluntary attention processing. The former is assessed by mismatch negativity (MMN) while the latter is evaluated by P300. The aim of this study was to clarify abnormality of visual attention system in Scz.
Methods: Eighteen Scz were instructed to listen to a story and to also pay attention to a visual target. Black-white circular windmill patterns consisting of a standard, a deviant, and a target stimulus whose ratios were 8:1:1 were presented randomly. The difference in the three stimuli was the number of vanes. Visual MMN (V-MMN) was obtained by subtracting ERPs to the deviant stimulus from that to the standard. P300 was recorded by the response of the target stimulus.
Results: Sixteen Scz completed the experiment. P300 was evoked in all of them but their P300 was smaller than that of normal control (NC). V-MMN was evoked in 12 subjects. The mean amplitude of V-MMN was not significantly different from that of NC, but the latency of V-MMN was more prolonged than that of NC. The latencies of P300 and V-MMN were linearly related to age and dose of antipsychotics. The latency of P300 was related to negative symptoms.
Conclusions: Like the auditory system, visual MMN and P300 were declined in Scz. Our results suggest that there exists common mechanism of the abnormal sensory attentional processing in Scz.

815. Functional MRI of Choice Reaction Time in Schizophrenia

David P. McAllindon[1,2], Alan H. Wilman[1], Philip G. Tibbo[2,3], Scot E. Purdon[2,3]

[1]Biomedical Engineering, University of Alberta, Edmonton, AB, Canada,[2]Bebensee Schizophrenia Research Unit, University of Alberta, Edmonton, AB, Canada,[3]Psychiatry, University of Alberta, Edmonton, AB, Canada

Background: Slower and more variable reaction time (RT) may represent a specific cognitive deficit in schizophrenia. Functional neuroimaging with electroencephalography (EEG) during an auditory choice RT task suggested a relative lack of activation in anterior cingulate cortex in people with schizophrenia compared to healthy volunteers (HV) [1]. We are using functional MRI to better locate the reported EEG results and examining asymptomatic first-degree relatives of people with schizophrenia.
Methods: A 2-choice visual RT task was used contrasting choice (respond) and watch-only conditions. Images were acquired using a GREPI sequence at 1.5T (TR 2s, TE 50ms) and covered the whole brain with 23 slices of thickness 4 mm and 1 mm gap and 3.75x3.75mm inplane resolution. Data were analyzed using standard processing in SPM5.
Results: To date, 5 subjects in each group have been scanned. The behavioural performance is comparable among the groups. The first 8 regions of a fixed effects analysis of the HVs are shown in the table. Group comparisons are not statistically significant, but non-significant trends are evident. First-degree relatives have a trend to a larger activation than other groups in right and left cerebellum, left cingulate gyrus and right medial frontal gyrus.
Conclusions: At this stage, we see some trends toward differences between groups. Additional subjects will be examined.
[1] Mulert, C et al, 2001, Neuroimage 13, 589-600.

Most Significant Activations in HV Group

Anatomical Label	Talairach Coordinates (Center of Gravity)	Size (Voxels)	t-Value
Right Cerebellum	33, -53, -20	1000	9.98
Left Inferior Parietal Lobule	-50, -27, 46	189	8.79
Cingulate Gyrus	0, 5, 44	364	8.72
Left Middle Frontal Gyrus	-33, -3, 61	56	8.39
Left Insula/Superior Temporal Gyrus	-45, -3, 6	57	8.02
Right Precentral/Postcentral Gyrus	39, -41, 60	136	7.94
Right Insula/Superior Temporal Gyrus	48, 3, 3	94	7.05
Right Putamen	21, 12, 2	53	7.03

816. Evidence for Anomalous Network Connectivity during Working Memory in Schizophrenia: An ICA Based Analysis

Shashwath Meda[1], Bradley Folley[1,2], Michael Stevens[1,3], Vince Calhoun[1,3,4], Godfrey Pearlson[1,3,5]

[1]Olin Neuropsychiatry Research Center, Hartford Hospital/IOL, Hartford, CT,[2]Kennedy Center and Department of Psychiatry, Vanderbilt University, Nashville, TN,[3]Department of Psychiatry, Yale University, New Haven, CT,[4]Department of ECE, The MIND Institute, Albuquerque, NM,[5]Department of Psychiatry, Johns Hopkins University, Baltimore, MD

Background: Numerous neuroimaging studies have reported abnormal brain activity during working memory (WM) performance in schizophrenia, but the majority of these studies have not examined brain network integration as determined through 'functional connectivity' analyses. We used independent component analysis (ICA) to identify and characterize dysfunctional spatiotemporal networks in schizophrenia engaged during a Sternberg WM fMRI paradigm.
Methods: 37 chronic schizophrenia and 54 healthy age/gender-matched participants performed a modified Sternberg fMRI task (Johnson et. al. 2006). Timeseries images preprocessed with SPM2 were analyzed using ICA as implemented in the GIFT v1.3c toolbox.
Results: There were 4 functionally-integrated networks whose timeseries were correlated with either the encoding and recognition phases of the task and that differed between schizophrenic and control participants. In particular, schizophrenic patients showed relatively less engagement of several distinct 'normal' encoding-related WM networks compared to controls:
Encoding:
E1. Left Superior Parietal-Left DLPFC-Cingulate (SZ vs HC: p=0.004)
E2. Bilateral Superior Parietal-Right DLPFC (SZ vs HC: p=0.02)
E3. Default Mode Network (SZ vs HC: p=0.009)
Recognition:
R1.PosteriorCingulate-Cuneus-Hippocampus/Parahippocampus (SZ vs HC: p=0.04)
Also, WM task accuracy differed between groups (p<0.0001) and was connected with degree of network engagement, further underscoring the relevance of these profiles of abnormal network integration to well-described schizophrenia WM impairment. During recognition, networks primarily related to motor functionality correlated significantly with task accuracy.
Conclusions: For the first time, we have shown the usefulness/sensitivity of ICA in delineating different WM networks and demonstrating specific network impairments in schizophrenia.

817. Neurocognitive Functioning in First-Episode Schizophrenia: A Meta-Analytic Review

Raquelle Mesholam-Gately[1,2], Anthony J. Giuliano[1,2], Kirsten Plehn[1], Stephen V. Faraone[3], Larry J. Seidman[1,2]

[1]Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA,[2]Department of Psychiatry, Harvard Medical School, Boston, MA,[3]Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY

Background: Compromised neurocognition is a core feature of schizophrenia and related disorders. While individual studies have documented that cognitive deficits are present at the first episode (FE), the magnitude of deficits varies among cognitive domains and between studies. The aim of this study is to provide a meta-analysis of neurocognitive findings in FE schizophrenia.
Methods: A systematic literature search yielded 47 studies meeting inclusion criteria for meta-analysis. Inclusion criteria were publication in English, diagnoses of schizophrenia, schizoaffective or schizophreniform disorder, a healthy comparison group, and sufficient data for calculating effect sizes (ES). Meta-analytic procedures in STATA were used to model between-study variance across ten cognitive domains. Following Heinrichs & Zakzanis' (1998) meta-analysis of older mixed schizophrenia samples, the 10 cognitive domains included general cognitive ability, verbal-language ability, global and selective verbal memory, nonverbal memory, attention, executive functioning, motor skills, visuospatial abilities, and social cognition.
Results: FE schizophrenia samples demonstrated medium-to-large impairments across the ten neurocognitive domains (ds = -0.44 to -1.79). Deficits were maximized in verbal memory and processing speed. However, heterogeneity of ES was considerable, with degree of variation in ES attributable to heterogeneity often exceeding 55% and up to 93%.
Conclusions: Findings support the notion that cognitive symptoms are well-developed by the FE, approach the magnitude of deficit shown by individuals with well-established illness, and are maximized in verbal memory and processing speed. However, the magnitude of deficit varies considerably across studies, and important features of study samples and designs require careful consideration in reviews of this literature.
Supported by NARSAD

818. Direct Comparison of fMRI of Working Memory in Schizophrenia and Psychotic Bipolar Disorder

Snezana M. Milanovic[1,2,3], Heidi W. Thermenos[4,5], Jill M. Goldstein[1,6,7], Susan W. Gabrieli[3,8], Nikos Makris[9], Ariel Brown[6,10], Peter LaViolette[2], Jennifer K. Koch[1], Ming T. Tsuang[1,2,11], Stephen L. Buka[12], Larry J. Seidman[1,2,3]

[1]Department of Psychiatry, Harvard Medical School, Massachusetts Mental Health Center in the Division of Public Psychiatry, Boston, 02115, MA,[2]Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital,, Boston, 02114, MA,[3]Department of Psychiatry, Massachusetts General Hospital/ Martinos Center for Biomedical Imaging, Charlestown, 02129, MA,[4]Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Massachusetts Mental Health Center in the Division of Public Psychiatry, Boston, 02115, MA,[5]Department of Psychiaty, Massachusetts General Hospital/ Martinos Center for Biomedical Imaging, Charlestown, 02129, MA,[6]Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital, Boston, 02114, MA,[7]Departments of Medicine, Brigham and Women's Hospital, Harvard Medical School, Division of Women's Health, Connor's Center for Women's Health & Gender Biology, & Department of Psychiatry, Boston, 02115, MA,[8]Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, 02139, MA,[9]Center for Morphometric Analysis, Massachusetts General Hospital, Charlestown, 02129, MA,[10]Department of Psychology, Boston University, Ph.D. Program in Behavioral Neuroscience, Boston, MA,[11]Department of Psychiatry, University of California, San Diego, Center for Behavioral Genomics, La Jolla, 92093, CA,[12]Department of Community Health, Brown University, Providence, 02912, RI

Background: We used a 2-back working memory (WM) task to directly examine the performance and brain activation differences in patients with SCH and BPp. We hypothesized that SCH and BPp will demonstrate reduced WM performance correlating with impaired control over switching from rest to the WM task mode. We predicted that the impairment will be observed through interactions of the medial prefrontal cortex (BA10) and anterior cingulate (AC) for BPp and BA10 and superior temporal gyrus (STG) for SCH.
Methods: Controls (CON), BPp or SCH were scanned using functional magnetic resonance imaging (fMRI) while performing X or 2-back memory tasks. All analysis were done on the 2-back>X contrasts using Statistical

Parametric Analysis-2.
Results: CON and BPp showed consistent suppression of BA10 and AC during the first and second runs of WM performance. In contrast, SCH demonstrated suppression in the first, followed by activation of the same regions in the second run. CON suppressed the STG during both runs, while BPp and SCH showed the first run suppression, followed by activation.
Conclusions: 1) Good memory performance in CON is associated with successful transition from rest to the WM mode as observed by BA10 and AC suppression, 2) SCH performance decline is associated with the failure of suppression in the BA10, AC, STG and possibly effort-related attenuated control over switching from rest to the WM mode, 3) BPp execute the switching process well but demonstrate STG suppression/activation patterns similar to SCH and possibly related to lower 2-back performance.
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819. Meta-Analysis of 41 Functional Neuroimaging Studies of Executive Cognition Reveals Dysfunction in a General Purpose, Frontal Cortex-Dependent Cognitive Control System in Schizophrenia

Michael J. Minzenberg[1], Angela R. Laird[2], David C. Glahn[2], Cameron S. Carter[1]

[1]Psychiatry, University of California Davis, Sacramento, CA,[2]Psychiatry, University of Texas Health Science Center, San Antonio, TX

Background: It remains unclear whether the prefrontal dysfunction observed in schizophrenia represents the coincidence of several PFC region- and task-specific impairments, or rather the expression of a more unitary dysfunction in a distributed neocortical network mediating a superordinate cognitive control function. We used quantitative meta-analysis to test whether common nodes of this network would be identified with altered activity across a large set of functional neuroimaging studies of executive cognition in schizophrenia.
Methods: 41 reports were included. Tasks included Delayed Match to Sample, N-Back, AX-CPT, and Stroop. Activation Likelihood Estimation (ALE) modeled reported activation maxima as the center of a 3D Gaussian function, to integrate studies in the meta-analysis.
Results: Within-group analyses showed the Healthy Control group to activate a distributed cortical-subcortical network that prominently included the DLFPC, VLPFC, ACC and thalamus. The Schizophrenia group exhibited a similar network (varying modestly across task types), however with altered activation in various regions revealed in the between-group analysis as reduced activation in left DLPFC, rostral/dorsal ACC, left thalamus; and increased activation in left VLPFC, pre-supplemental motor area (SMA), left angular gyrus, SMA and orbitofrontal cortex (OFC).
Conclusions: Healthy adults and schizophrenia patients activate a qualitatively similar network during PFC-dependent executive task performance, consistent with a superordinate, general-purpose cognitive control network, with critical nodes in the DLPFC and ACC. In addition, schizophrenia patients show altered activity with deficits in DLPFC, ACC and thalamus, which could be associated in turn with compensatory increases in activity elsewhere in the network, such as VLPFC and OFC.
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820. First-Break Schizophrenia Patients Exhibit Impaired Context-Related Gamma Oscillatory Activity Over Frontal Sites Measured by Scalp Electroencephalography During Cognitive Control Performance

Michael J. Minzenberg, Jong H. Yoon, Alana Firl, Celeste Reinking, Andrew Watrous, Cameron S. Carter

Psychiatry, University of California Davis School of Medicine, Sacramento, CA

Background: Schizophrenia patients exhibit impaired prefrontal cortex (PFC) activity during cognitive control processes. We hypothesized impaired frontal gamma oscillatory activity in patients during the delay period of a cognitive control task.
Methods: 30 first-year schizophrenia patients (SZ) and 30 healthy control subjects (HC) (mean age 20.0 vs. 21.3 years; 76% vs. 57% male) performed a task contrasting cued incongruent stimulus-response mapping with cued congruent S-R mapping. Scalp gamma was measured at 1000 Hz (Neuroscan 4.3) using 132-channel, NSL layout Quik-Cap. Signals were resampled in EEGLab at 250Hz, average reference computed, baseline-subtracted and epoched. Noisy leads were excluded, and probability-based artifact rejection. ICA was performed to subtract blink components, then Morlet wavelet coefficients with baseline window 100 ms preceding cue onset. For each subject, mean gamma power difference was computed between high (incongruent) and low (congruent) control conditions, at each 10 Hz-subband within the 30-80Hz range in early (0-500 ms) and late (500-1000 ms) cue-probe delay periods, at each channel over the frontal scalp.
Results: SZ and HC groups were similar in the numbers of trials or channels retained for analysis. The SZ group exhibited significantly impaired power (compared to HC) across the full set of frontal channels, in all gamma subbands at both delay periods.
Conclusions: These results suggest that schizophrenia patients are deficient in mounting gamma-range cortical oscillatory activity to support context-dependent cognitive control processes. This phenomenon may serve as a mechanistic basis for the PFC dysfunction observed in fMRI studies, and may reflect impaired local cortical network activity.
Supported by NIMH

821. ERP Evidence of Overactivated Semantic Networks in Chronic Schizophrenia

Margaret A. Niznikiewicz[1], Moneeshidra Singh[2], Paul Nestor[3], Robert W. McCarley[2]

[1]Psychiatry, Harvard Medical School, Brockton, MA,[2]Psychiatry, harvard medical school, Brockton, MA,[3]Psychology, University of Massachusetts, Brockton, MA

Background: Abnormal language processing has been recognized as a hallmark of schizophrenia. Recent studies using event related potential (ERP) technique documented abnormalities in context and working memory utilization. However, there are few ERP studies of initial activation in semantic networks also proposed to be abnormal in schizophrenia (SZ) (Niznikiewicz et al., 2002; Mathalon et al., 2002). If the hypothesis of overactivation in semantic networks is correct, the N400 ERP, indexing an ease of forming semantic links, is expected to be less negative in SZ when recorded in short stimulus asynchrony (SOA) paradigms.
Methods: We have conducted a short SOA word-pair priming study in 21 chronic SZ and 23 normal control (NC) individuals matched on age, handedness and PSES, with English as first language, in a lexical decision task. EEG was recorded from 64 electrodes. Separate averages were made to related and not-related word targets.
Results: The N400, measured within 350-450 msec latency window was

found less negative in the unrelated word-pair condition in SZ relative to NC ($p < 0.04$). The N400 priming effect was found in NC ($p < 0.01$) but not in the SZ.
Conclusions: These results suggest over-activation in semantic networks in SZ that may be attributable to faulty inhibitory processes as suggested by significantly reduced N400 in unrelated but not related word condition. This is one of the first studies to provide evidence for overactivated semantic networks in SZ using word-pair stimuli.
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822. Abnormal N170 Modulation to Frequency Change in Male Patients with Chronic Schizophrenia

Choji Obayashi[1], Taisuke Nakashima[2], Toshihiko Maekawa[1], Yoji Hirano[1], Shogo Hirano[1], Naoya Oribe[1], Shozo Tobimatsu[2], Shigenobu Kanba[1], Toshiaki Onitsuka[1]

[1]Neuropsychiatry, Graduate School of Medical Sciences,Kyushu,University, Fukuoka, Japan,[2]Clinical Neurophysiology, Graduate School of Medical Sciences,Kyushu,University, Fukuoka, Japan

Background: Impaired processing of faces in schizophrenic patients may underlie some aspects of their disturbance in social functions. The present study investigated whether or not schizophrenics modulate their N170 in response to different type of visual stimuli [faces vs. non-faces or high spatial frequency (HSF) vs. low spatial frequency (LSF) or positive vs. negative emotional faces]. This study also investigated whether or not schizophrenics show N170 reduction specific to faces in Japanese sample, and examined associations between face N170 reduction and reduced social function.
Methods: Sixteen male chronic schizophrenia patients and 24 age-, gender-, handedness-, and parental socioeconomic status-matched normal controls participated in this study. Event-related potentials were recorded to the filtered (HSF or LSF) and the unfiltered (broad spatial frequency: BSF) pictures of houses and, neutral, happy, anger and fearful faces.
Results: Normal controls exhibited the HSF>BSF>LSF N170 amplitude differences ($p<0.001$), while schizophrenics did not modulate their N170 in response to different frequency stimuli ($p=0.27$). For N170 amplitude differences, there were significant group differences in neutral ($p=0.003$), happy ($p=0.001$), anger ($p=0.001$), and fearful ($p=0.002$) faces. However, there was no significant group difference in the house stimulus ($p=0.51$), indicating that schizophrenia patients showed bilateral face-specific N170 reduction. There were significant negative correlations between GAF scores and N170 to faces in schizophrenia.
Conclusions: These results suggest that abnormal N170 modulations to frequency change may underlie at least some of the deficits associated with visual perception in schizophrenia.

823. Abnormal Parietal Activation during Recognition of Old/New Items in Schizophrenia

Marc Pelletier, Alonso Montoya, Amélie Achim, Matthew Menear, Samarthji Lal, Martin Lepage

Psychiatry, McGill University, Verdun, QC, Canada

Background: Memory deficits affect schizophrenia subjects. Studies repeatedly report the prefrontal cortex (PFC) and the medial temporal lobes (MTL) as the neural correlates for these deficits but these correlates may simply be the consequence of schizophrenia subjects performing at a suboptimal level. In contrast, few studies have explored whether schizophrenia affects brain activation in the parietal cortex, a region that is reliably activated when contrasting old items recognition from new items in healthy subjects.
Methods: We used an event-related functional Magnetic Resonance Imaging (fMRI) to examine brain activation in fifteen chronic, medicated schizophrenia subjects and eighteen control subjects during the retrieval part of a recognition memory test that required subjects to make old/new judgments. We investigated both the neural correlates that were commonly activated while performing this task and the neural correlates that distinguished the two groups, with a random effects model and statistical significance set at $p<0.001$.
Results: At the behavioral level, both groups performed equally well. At the brain level, both groups commonly activated regions in the PFC, MTL, and the precuneus. Examining group differences for the old/new contrast revealed a deactivation in the schizophrenia group restricted in the left parietal lobule.
Conclusions: At equal performance for recognizing old and new items, schizophrenia subjects demonstrate apparently normal modulation of the PFC and MTL, but abnormal modulation of the left parietal lobule. The partially distinct network of activations underlies the role of the parietal cortex in the possible use of distinct cognitive strategies by schizophrenia subjects during memory recognition.
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824. Prefrontal Control of Item-Specific versus Relational Working Memory and Long-Term Memory Encoding in Schizophrenia

J. Daniel Ragland[1], Robert S. Blumenfeld[2], Jong H. Yoon[1], Michael Minzenberg[1], Stefan Ursu[1], Marjorie Solomon[1], Cameron S. Carter[1], Charan Ranganath[2]

[1]Psychiatry and Behavioral Sciences, University of California at Davis, Sacramento, CA,[2]Psychology, University of California at Davis, Davis, CA

Background: Ventrolateral PFC (VLPFC) is critical for attending to relevant items ("item-specific" WM), whereas dorsolateral PFC (DLPFC) is critical for building relationships between items ("relational" WM). This fMRI study tests the prediction that DLPFC control of relational memory is disproportionately impaired in schizophrenia.
Methods: VLPFC and DLPFC function was examined while patients and controls performed item-specific versus relational WM tasks: on item-specific 'rehearse' trials subjects maintained a set of 3 objects across a 12 second delay in anticipation of a memory probe for serial position of the items; on relational 'reorder' trials participants rearranged a set of 3 items based on perceived weight and maintained this information in anticipation of a memory probe for serial order of items in the rearranged set. Following scanning, subjects were given a recognition test and fMRI responses during each trial type were averaged as a function of subsequent memory.
Results: There was a larger effect of schizophrenia on reorder versus rehearse performance. Both tasks engaged prefrontal, mesial temporal, and parietal regions. Region of interest analysis revealed predicted reductions in DLPFC versus VLPFC activation in patients. Functional connectivity analysis showed enhanced DLPFC connectivity with the PFC in patients and with posterior association cortices in controls.
Conclusions: Results support the conclusion that patients with schizophrenia have a specific deficit in DLPFC function that contributes to memory impairment, whereas the VLPFC is less disrupted and may play a compensatory role. Future remediation may build on preserved item-specific processing, whereas treatment development may target DLPFC dysfunction.

825. Reduced Attentional Engagement Contributes to Deficits in Prefrontal Inhibitory Control in Schizophrenia

James L. Reilly[1], Margret S. H. Harris[1], Tin T. Khine[1], Matcheri S. Keshavan[2], John A. Sweeney[1]

[1]Center for Cognitive Medicine, University of Illinois at Chicago, Chicago, IL,[2]Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI

Background: Problems with the voluntary control of behavior, such as those leading to increased antisaccade errors, are accepted as evidence of prefrontal dysfunction in schizophrenia. We previously reported that speeded prosaccade responses, i.e. shorter response latencies for automatic shifts of attention to visual targets, were associated with higher antisaccade error rates in schizophrenia. This suggests that dysregulation of automatic attentional processes may contribute to disturbances in prefrontally-mediated control of voluntary behavior.
Methods: Twenty-four antipsychotic-naïve schizophrenia patients and 30 healthy individuals completed three tasks: a no-gap prosaccade task in which subjects shifted gaze toward a peripheral target that appeared coincident with the disappearance of a central fixation target, and separate prosaccade and antisaccade tasks in which a temporal gap or overlap of the central target offset and peripheral target onset occurred. Sixteen patients were retested after 6-weeks of antipsychotic treatment.
Results: Patients' prosaccade latencies in the no-gap task were speeded compared to healthy individuals. While patients were not atypical in the degree to which response latencies were speeded or slowed by the gap and overlap manipulations, those patients with diminished attentional engagement on the prosaccade task (i.e., reduced overlap effect) had significantly elevated antisaccade error rates. This effect persisted in patients evaluated after antipsychotic treatment.
Conclusions: This study provides evidence that a reduced ability to engage attention may render patients more distracted by sensory inputs, thereby further compromising impaired executive control during antisaccade tasks. Thus, alterations in attentional and executive control functions can synergistically disrupt voluntary behavioral responses in schizophrenia.
Supported by MH62134, MH01433, NIH/NCRR/GCRC Grant M01 RR00056, and NARSAD

826. Remembering Familiar and Novel Stimuli in Schizophrenia: Evidence for Lack of Automaticity using Functional MRI

Jennifer L. Robinson, Jennifer Barrett, Dawn I. Velligan, David C. Glahn

Psychiatry, University of Texas Health Science Center, San Antonio, TX

Background: Although working memory (WM) deficits are prevalent in schizophrenia, questions remain about the neural networks involved in familiar versus novel stimuli encoding/maintenance, and how these networks are compromised in schizophrenia. While the maintenance of familiar memoranda is typically associated with less mental effort and lower levels of activation throughout the WM network, we anticipate that patients with schizophrenia will not benefit from being exposed to stimuli, thus showing more activity when remembering familiar stimuli.
Methods: Seventeen schizophrenics (SZ) and twenty-five controls underwent fMRI while performing a delayed-non-match-to-sample task. This WM task involves two conditions, one using familiar stimuli (FAM), and one using novel stimuli (NOV). Activation patterns associated with task activity were examined for both conditions.
Results: SZ performed significantly worse than controls during FAM ($F(1,41)=35.80, p<0.001$) and NOV($F(1,41)=30.72, p<0.001$). Controls show relatively more activity during NOV relative to the FAM, particularly within the bilateral inferior and left middle frontal gyri. In contrast, SZ did not show any differences between conditions. In comparison to controls, SZ had less activation in regions of the right inferior frontal, left middle frontal, bilateral precentral gyri, and right parietal lobule during FAM. Similar regions of hypoactivation were also noted in NOV.
Conclusions: Condition specific differentiation in the inferior frontal gyrus associated with the FAM may be indicative of a neural correlate for automaticity, in which schizophrenics have less activation. Furthermore, our findings suggest that disruption in other prefrontal and parietal cortices associated with both familiarity and novelty encoding may underlie memory difficulties observed in schizophrenia.
Supported by NARSAD

827. Frontal-Temporal Connectivity and Cognitive Dysfunction in Schizophrenia

Katherine V. Roe[1,2], Eric A. King[1,2], Deepak K. Sarpal[1,2], Aaron Bonner-Jackson[1,2], Terry S. Goldberg[2], Andreas Meyer-Lindenberg[2], Daniel R. Weinberger[2], Karen F. Berman[1,2]

[1]Section on Integrative Neuroimaging, Intramural Research Program, NIMH, NIH, DHHS, Bethesda, MD,[2]Clinical Brain Disorders Branch, Genes Cognition and Psychosis Program, Intramural Research Program, NIMH, NIH, DHHS, Bethesda, MD

Background: Cognitive and language dysfunction are core characteristics of schizophrenia. Numerous structural and functional findings suggest these symptoms are based in complex, network-level dysfunction that particularly impacts prefrontal as well medial and lateral temporal brain regions. To explore the role this neural system dysfunction has in cognitive and linguistic symptoms in schizophrenia, the current study assessed whether patients displayed atypical fronto-temporal connectivity during two paced fluency tasks believed to differentially tap language and executive functions (Baldo et al, 2006) and differentially rely on frontal-temporal interactions (Friston et al, 1995).
Methods: Regional cerebral blood flow (rCBF) was measured using oxygen-15 water PET in 25 patients with schizophrenia (31.5±8.5 years, 5 females) and 25 matched healthy controls (29.6±6 years, 10 females) performing paced Letter and Category Fluency tasks. To measure functional connectivity, scan by scan rCBF values were extracted from seeds in left hippocampus, Broca's area, and Wernicke's area and entered into a brain-wide cross-correlation analysis. Correlation maps for the two fluency conditions were compared across groups.
Results: Patients exhibited reduced positive intrahemispheric connectivity between left frontal and temporal regions during Letter fluency, and reduced negative interhemispheric fronto-temporal connectivity during Category fluency. Additionally, positive ipsilateral prefrontal-hippocampal connectivity and negative contralateral prefrontal-hippocampal connectivity was reduced in patients during both fluency tasks.
Conclusions: These data support previous evidence of altered fronto-temporal functional connectivity patients with schizophrenia, document inefficient cooperativity between these regions, and indicate that this system-level dysfunction plays a critical role in both the language and executive processing symptoms prevalent in this population.
Supported by DHHS, NIMH, NIH, IRP

828. The Relationship between Visual Processing and Performance on the CPT-IP in Schizophrenia

Erica Saccente[1], Pam Butler[1,2], Rachel Ziwich[1], Gail Silipo[1], Daniel C. Javitt[1,2]

[1]Program in Cogntiive Neuroscience and Schizophrenia, Nathan Kline Institute, Orangeburg, NY,[2]Psychiatry, New York University School of Medicine, New York, NY

Background: The Continuous Performance Test - Identical Pairs Version (CPT-IP) has been used extensively to study attention in schizophrenia. Despite its apparent connection with visual components, performance on the task has not yet been compared to visual processing measures. Schizophrenia is associated with deficits in early visual performance, as reflected in reduced sensitivity to visual contrast. As opposed to CPT-IP, visual contrast tests do not require sustained attention or comparison between successive stimuli.
Methods: Performance on the CPT-IP was assessed in twenty-five patients with schizophrenia relative to matched controls. Participants were also given a behavioral measure of contrast sensitivity, which reflects early visual processing.
Results: Patient performance was significantly worse ($p<0.05$) on the CPT-IP than the healthy controls. Further, patient performance on the CPT-IP, as measured by d', significantly correlated ($r=.6$, $p=.001$) with contrast sensitivity, particularly at low spatial frequency (1 cycle/degree) and short stimulus duration (32 ms), suggesting involvement of magnocellular dysfunction. Correlations were also observed between CPT-IP and measures of working memory, speed of processing, problem solving and reasoning, verbal learning, visual learning, attention/vigilance, and social cognition, but no correlations were observed between CS and cognitive tests other than CPT-IP.
Conclusions: These results suggest that impaired performance on the CPT-IP in schizophrenia might be indicative of a visual processing deficit, particularly involving the magnocellular system. The CPT-IP, while conceptualized as a measure of attention, might also reflect early visual processing dysfunction. These findings suggest that the construct of attention, as currently measured, might also reflect early visual dysfunction.
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829. Sensory Gating Deficit in Schizophrenia is not a Result of Lowered Response to S1

Monica P. Sangal, Ryan Mears, Nash Boutros

Psychiatry, Wayne State Universtiy School of Medicine, Detroit, MI

Background: Sensory gating deficit is becoming recognized as a major endophenotype for schizophrenia and schizophrenia spectrum disorders. Sensory gating is assessed via an evoked potential paradigm where two identical stimuli (S1-S2) are delivered in rapid succession (500 ms apart) with a longer inter-pair interval of 8-10 seconds. The lower the ratio of the response to S2 to the response to S1, the better is the inhibitory capacity of the brain (more intact sensory gating). The interrelationship between the responses to S1 and S2 have created questions about the value of the measurement, specifically whether a low amplitude response to S1 is the origin of the gating deficit in schizophrenia patients.
Methods: A comprehensive literature review was performed to examine the reported relationship between these variables. 35 datasets in 25 papers (because some papers had multiple schizophrenia groups) examining sensory gating in schizophrenia spectrum patients compared to healthy control subjects were identified and reviewed.
Results: 12 datasets found the responses to S1 to be lower (< 80%) in schizophrenia compared to controls, with ten finding a gating deficit (S2:S1 ratio >0.6). Among the other 23 datasets, 15 found a gating deficit. Fisher's exact test examining the effect of the amplitude of the response to S1 on finding a gating deficit found no difference.
Conclusions: Sensory gating deficit in schizophrenia patients is found with similar prevalence whether S1 response is affected or not. This suggests the validity of the sensory gating measure as an independent physiological abnormality in schizophrenia patients.

830. Perceptual Closure Processes in Schizophrenia

Pejman Sehatpour, Elisa Dias, John J. Foxe, Daniel C. Javitt

Program in Cognitive Neuroscience and Schizophrenia, Nathan Kline Institute, Orangeburg, NY

Background: The term "perceptual closure" has been used to refer to the neural processes responsible for "filling-in" missing information in the visual image under adverse viewing conditions such as occlusion, poor lighting or novel orientations.
Methods: Here, we investigated the spatio-temporal dynamics of perceptual closure processes in schizophrenia using an integrative approach by co-registering data from high-density scalp electrical recordings (ERPs) and functional magnetic resonance imaging (fMRI), while patients and controls participated in a perceptual closure task. Participants were presented with highly fragmented images and control scrambled images. Fragmented images were calibrated to be 'just' recognizable as objects (i.e., perceptual closure was necessary), whereas the scrambled images were unrecognizable. Previous electrophysiological studies of closure comparing the responses to these two stimulus classes have revealed the neural processes underlying perceptual closure. Preliminary results obtained by comparison of responses between the two populations are presented.
Results: These results revealed an object recognition system consisting of a network of areas including the LOC, the hippocampal formation and frontal regions mediating closure processes.
Conclusions: Preliminary results indicate significant task-dependant deficits in schizophrenia beginning as early as 100 ms post stimulus onset, accompanied by a secondary dysregulation of the neurocognitive network of brain regions engaged in closure processes.
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831. Correlation between Tests on the MATRICS Consensus Cognitive Battery (MCCB) and the IntegNeuro Computerized Battery in Schizophrenia and Healthy Controls

Steven M. Silverstein[1], Judith Jaeger[2], Anne-Marie Donovan Lepore[3], Sandra Wilkniss[4], Adam Savitz[5], Igor Malinovsky[1], Danielle Hawthorne[1], Shane Raines[2], Stephen Furlong[2], Steven Zukin[2], Gersham Dent[2]

[1]University Behavioral HealthCare, University of Medicine and Dentistry of New Jersey, Piscataway, NJ,[2]Discovery Medicine Neuroscience, AstraZeneca Pharmaceutical Company, Wilmington, DE,[3]Psychiatry, Zucker Hillside Hospital, Queens, NY,[4]Research, Thresholds, Inc., Chicago, IL,[5]Psychiatry, Weill Medical College of Cornell University, White Plains, NY

Background: The aim of this study was to measure the level of agreement between two alternative methods of assessing cognition in schizophrenia: the computerized IntegNeuro battery and the primarily paper and pencil MATRICS Consensus Cognitive Battery (MCCB).
Methods: Methods: In a 5-site study, 150 clinically stable patients with SCID-confirmed schizophrenia and 75 healthy controls took both the MCCB and IntegNeuro batteries. Pearson correlation coefficients were computed between homologous measures on IntegNeuro and each of the 10 MCCB tests. These pairs were selected a-priori as the best match on the basis of similarity of test parameters/characteristics. As a second step, that IntegNeuro test which was most highly correlated with each MCCB test was identified.
Results: Correlation coefficients among predicted IntegNeuro measures for each of the 10 MCCB tests ranged from 0.40 (MSCEIT Social Cognition with Gur Facial Recognition Test) to 0.75 (each battery's test of Letter

Number Sequencing). All p values were <.0001. In 7 out of 10 cases, the highest IntegNeuro/ MCCB correlation pair was the same one predicted by a priori judgement. Interestingly, among all IntegNeuro measures, the highest correlation for the only computerized measure in the MCCB (the CPT-IP) is the IntegNeuro Letter Number Sequencing test (r=0.57). The highest correlation for the MSCEIT on the MCCB is with the IntegNeuro Mazes test gradient of errors over completion time (r=-0.48) suggesting that attributes other than social cognition are important for MSCEIT performance.
Conclusions: Results from these interim analyses suggest comparability between the IntegNeuro computerized test battery and the MCCB
Supported by AstraZeneca

832. Impaired Learning and Memory on the California Verbal Learning Test in Persons with Schizophrenia, but not their First-Degree Relatives: Findings from the Consortium on the Genetics of Schizophrenia (COGS)

William S. Stone[1], Anthony J. Giuliano[1], Stephen J. Glatt[2], Stephen V. Faraone[2], Ming T. Tsuang[3], Larry J. Seidman[1]

[1]Psychiatry, Harvard Medical School / Beth Israel Deaconess Medical Center, Boston, MA,[2]Psychiatry, SUNY Upstate Medical University, Syracuse, NY,[3]Psychiatry, University of California, San Diego, La Jolla, CA

Background: Patients with schizophrenia are robustly impaired on measures of Verbal Declarative Memory (VDM), including the California Verbal Learning Test (CVLT). Reports of CVLT performance in first-degree relatives, however, are inconsistent.
Methods: The Consortium on the Genetics of Schizophrenia (COGS) aims to identify the genetic basis of common endophenotypes in schizophrenia, including VDM. This report presents data on the CVLT-II in probands with schizophrenia (n=253), their biological full siblings (n=353) and parents (n=202), and community comparison subjects (CCS; n=465) across seven geographically diverse sites. Stringent quality assurance protocols assured procedural uniformity.
Results: Probands learned significantly fewer words (Total Trials 1-5) than all other groups after controlling for significant effects of age, gender, and WRAT3 Reading level, but the relative groups did not differ significantly from the CCS group. Follow-up analyses showed a significant group x site interaction, plus a significant difference between CCS and sibling relatives at one site and trends toward significance at two others. The significant difference resulted from a high-performing control group (0.95 SD above the CVLT-II standardization mean) rather than a low performing sibling group (z=0.17 above the mean of all the sites). Notably, significant site differences were limited to the CCS and sibling relative groups, with the larger differences occurring in the CCS group.
Conclusions: Based on the largest sample to date, the results show that relatives of probands with schizophrenia are not generally impaired on the CVLT-II. They also shed light on previous inconsistent findings by highlighting site differences, particularly in control subjects.
Supported by RO1-MH065562

833. Multisensory Mental Rotations are not Impaired in Schizophrenia

Cenk Tek, Pamela C. DeGeorge, Bruce E. Wexler

Psychiatry, Yale University School of Medicine, New Haven, CT

Background: Mental rotation of objects is an operation in which a mental image is rotated on a three dimensional axis. This mental operation has near-perfect psychophysical properties: the time to make a judgment increases proportionally to the angle of rotation. Mental rotations can be reliably mapped to posterior parietal cortex, associated with dorsal visual pathway, and appear to be dependent on analog spatial representations. Furthermore, this function appears to be independent of sensory modality of the input. Patients with schizophrenia are generally impaired in various spatial tasks. We have utilized mental rotation paradigms to test the integrity of posterior parietal lobe function in schizophrenia.
Methods: 16 outpatients with schizophrenia and 10 healthy controls have been tested with a standard cognitive battery as well as four different mental rotation paradigms: 1) Visual three dimensional Shepard-Metzler figures, 2) Haptic Shepard-Metzler figures built from wooden blocks, 3) Visual letters and numbers, 4) Haptic letters and numbers.
Results: As expected, patients performed worse in the cognitive battery compared to healthy controls. On the rotation tasks patients were slightly slower and less accurate than controls, especially as the task became more difficult. However, their overall accuracy, and rotation angle-reaction time proportion was not significantly different than controls.
Conclusions: The results of this preliminary study do not point to a specific impairment in the parietal areas that are responsible for mental rotation operations in schizophrenia. The findings also did not support a presence of any earlier perceptual impairment that might affect later more complex operations negatively.
Supported by NARSAD Young Investigator Award

834. Associations between Childhood Trauma and Psychotic-Like Symptoms among Individuals at Clinical High Risk for Psychosis

Judy L. Thompson[1], Meredith Kelly[1], David Printz[1], David Kimhy[1], Shamir Khan[1], Julie Walsh[1], Jill Harkavy-Friedman[1], Dolores Malaspina[2], Cheryl Corcoran[1]

[1]Psychiatry, Columbia University, New York, NY,[2]Psychiatry, New York University, New York, NY

Background: Population-based and clinical-sample studies suggest that childhood trauma is associated with later psychosis, and it has been proposed that early trauma may play a causal role in the development of psychosis. The current study examined whether childhood trauma was associated with the severity of symptoms experienced by individuals considered to be at heightened clinical risk for psychotic illness.
Methods: Thirty participants, ages 13-25, who met prodromal research criteria were assessed with the Early Trauma Inventory (ETI). The ETI probes for experiences of varying degrees of severity within the domains of general trauma and physical, emotional, and sexual abuse.
Results: When including all events assessed by the ETI, 77% of the sample reported a history of physical punishment or abuse, 67% endorsed childhood emotional abuse, and 27% reported childhood sexual abuse; these rates are similar those obtained using the ETI with schizophrenia patients (Corcoran, unpublished data). Trauma scores were significantly associated with positive and disorganized symptoms. Specifically, physical punishment/abuse was associated with positive and disorganized symptoms and emotional abuse was related to disorganized symptoms (all rs>.43); further, sexual abuse (dichotomized) was related to positive symptoms (χ^2=5.87, p=.015). These associations were generally stronger for the ethnic minority (n=17) compared to Caucasian participants (n=13).
Conclusions: Results suggest that among individuals at heightened clinical risk for psychosis, childhood abuse is associated with severity of psychotic-like symptoms. Thus childhood abuse may contribute to more severe psychotic-like symptoms; conversely, childhood abuse may index psychosis risk but not play an etiological role in symptom development.
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835. Self-Assessment of Negative Affect and Stress Sensitivity in Schizophrenia: Reliability and Predictive Validity

Ivy F. Tso[1,2], Tyler B. Grove[1], Ashley C. Chen[3], Patricia J. Deldin[1,2], Stephan F. Taylor[1]

[1]Psychiatry, University of Michigan, Ann Arbor, MI,[2]Psychology, University of Michigan, Ann Arbor, MI,[3]Neuroscience Program, University of Michigan, Ann Arbor, MI

Background: Anxiety, depression, and heightened stress sensitivity are predictive of onset and course of schizophrenia, but systematic assessments are not a part of routine clinical practice. This study sought to investigate the reliability and predictive validity of a battery of self-report scales assessing negative affect in schizophrenia.
Methods: Thirty-seven schizophrenic/schizoaffective patients (17 females), 27 bipolar patients (13 females) and 30 healthy controls (13 females) matched for age, sex, reading level, and parental education participated. At baseline, subjects completed tests of neurocognition (BACS) and questionnaires measuring stress sensitivity (Perceived Stress Scale; Psychological Stress Index), anxiety (State/Trait Anxiety Inventory), depression (Beck Depression Inventory), hedonic capacity (Physical and Social Anhedonia Scales; Temporal Experience of Pleasure Scale), and social functioning (Social Adjustment Scale). Patients were also assessed for clinical symptomatology. Test-retest reliability for stress scales was obtained at 4 to 8 weeks. Thirty schizophrenic/schizoaffective patients were followed up at 12 months.
Results: Self-report measures of negative affect demonstrated satisfactory to good internal consistency, test-retest reliability, and convergence with clinician assessments. Schiz and bipolar groups performed more poorly on neurocognition, scored higher on stress sensitivity, anxiety, depression, anhedonia, and social maladjustment than controls. Schiz patients scored lower on anticipatory but not consumatory pleasure than bipolar and control groups. In schizophrenia, baseline anxiety (r=.48-.61), depression (r=.53-.73), stress sensitivity (r=.56-.66), and social anhedonia (r=.21-.51) were the strongest correlates of baseline and 12-month social functioning.
Conclusions: Heightened negative affect can be reliably assessed by self-report in schizophrenia, and may have clinical utility as robust predictors of functional outcome.
Supported by Palencsar Family; NIMH

836. Remission in Schizophrenia Patients Treated with Long Acting Risperidone: 12-Month Results of Electronic Schizophrenia Treatment Adherence Registry

Ivan Tuma[1], Jos Peuskens[2], Jan Pecenak[3], Lars Eriksson[4], B. Bork[5], Michael Povey[6], Annette Lam[7], Zhongyun Zhao[8]

[1]Medical School and Teaching Hospital Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic,[2]KU Leuven campus UC St. Jozef Kortenberg, Universitair Psychiatrisch Centrum, Leuven, Belgium,[3]Psychiatry, FNSP Bratislava, Bratislava, Slovakia,[4]Psychiatry, SU/Östra RPV, Hisings-Backa, Sweden,[5]Psychiatry, DP Tønder, Tønder, Denmark,[6]Statistics, SGS Life Science Services,, Wavre, Belgium,[7]Health Economics, Johnson & Johnson Pharmaceutical Services, Toronto, ON, Canada,[8]Health Economics, Johnson & Johnson Pharmaceutical Services, Raritan, NJ

Background: To assess remission in patients with schizophrenia treated with risperidone long-acting injection (RLAI) and enrolled in the electronic-Schizophrenia Treatment Adherence Registry (e-STAR) from Belgium, Czech Republic, Denmark, Slovakia, Sweden.
Methods: e-STAR is an international, long-term, prospective, observational study of patients with schizophrenia who commence RLAI. Remission was evaluated at baseline and every 3-months prospectively based on the following symptoms: delusions, conceptual disorganization, hallucinatory behavior, mannerisms and posturing, unusual thought content, blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation. Patients in whom all of these symptoms are absent/minimal/mild were considered to be in cross-sectional remission and if this persisted for at least 6 months, they were considered to be in symptomatic remission. Results presented are based on data from patients who have completed their 12-month follow-up visit.
Results: To date, 2,157 patients have been enrolled from the 5 countries and 1,092 patients have been followed for at least 12 months. Most were male (59.5%) with mean age of 38.9±12.7 years and mean time since diagnosis of 9.4±9.4 years. At 12 months, 92.5% of patients are still on RLAI. Proportion of patients was in cross-sectional remission increased from 4.3% at baseline to 36.1% at 12 months ($p<0.001$). Proportion of patients who achieved symptomatic remission was 2.1% at 6 months and 17.2% at 12 months ($p<0.001$).
Conclusions: This pooled interim data indicate that over one-third of patients met the criteria for cross-sectional remission and some even achieved symptomatic remission after 1-year treatment with RLAI.
Supported by Johnson & Johnson

837. The Neural Substrates of Emotional Processing in Schizophrenia: An Event-Related fMRI Study

Stefan Ursu[1], Ann M. Kring[2], Shauna Gordon-McKeon[1], Michael J. Minzenberg[1], Jong H. Yoon[1], J. Daniel Ragland[1], Marjorie Solomon[1], Cameron S. Carter[1]

[1]Psychiatry and Behavioral Sciences, UC Davis, Sacramento, CA,[2]Psychology, UC Berkely, Berkeley, CA

Background: Impairments in emotional processing in schizophrenia have long been described, but the precise mechanisms underlying these impairments, and especially their neural substrates, are still poorly understood. In an effort to further our understanding of these issues, we used event-related fMRI to study the neural circuitry involved in evaluating and responding to emotionally valenced stimuli.
Methods: Chronic schizophrenia patients and control subjects were scanned while viewing and rating their subjective reaction to images from the International Affective Picture System (IAPS).
Results: Data from 13 patients and 9 control subjects suggested that, across the two groups, a network of brain areas frequently implicated in processing of emotional information was robustly activated in response to positively and negatively valenced IAPS stimuli, relative to neutral ones. These areas included ventromedial prefrontal cortex, orbitofrontal cortex, ventral striatum, extended amygdala and insula.
Conclusions: This pattern of activation is consistent with the framework of Kring et al., which proposes that the ability of patients to directly experience affect is largely intact, and that abnormalities in the affective domain are, in fact, manifestations of altered representations of the anticipated effects of emotional stimuli. Results form a larger sample of subjects will be presented, including correlations of brain activity with measures of reactivity to emotional stimuli collected during scanning (i.e. subjective ratings and skin conductance response).
Supported by NARSAD

838. Genetic Influences on Reinforcement Learning Performance in Schizophrenia

James A. Waltz[1], Ikwunga Wonodi[1], Amie Elliot[1], Ping-I Lin[1,2], L. Elliot Hong[1], James M. Gold[1], Gunvant Thaker[1]

[1]Dept. of Psychiatry, Univ. of Maryland School of Medicine, Baltimore, MD,[2]Dept. of Medicine, Univ. of Maryland School of Medicine, Baltimore, MD

Background: Recent findings of genetic influences on reinforcement learning performance suggest that measures of reinforcement learning could serve as markers for dopamine dysfunction in patients with schizophrenia (SZ).
Methods: We administered 95 SZ patients, 68 first-degree relatives of patients, and 82 controls a reinforcement learning task involving either a left or right button-press to 6 stimuli, each presented individually 33 times. For 2 stimuli (100% valid), one of the responses was always reinforced. For another 2 stimuli (80% valid), the "correct" response was reinforced 80% of the time. For a further 2 stimuli, left and right button-presses were reinforced equally. For the 4 stimuli involving a correct (more-frequently-reinforced) response, we computed subjects' rates of choosing that response.
Results: Using ANOVAs, we observed main effects of both group ($F=16.54$; $p<0.001$) and reinforcement probability ($F=65.48$; $p<0.001$), as well as a trend toward a group x probability interaction ($F=3.08$; $p<0.06$). Post-hoc LSD tests revealed that patients' combined performance on both 100% and 80% valid items (59+2%) was worse than that of their first-degree relatives (65+2%), which was in turn worse than that of controls (70+2%). When we assessed a subgroup of subjects for whom we had genetic data, we found that 16 patients with the Met-Met type of the COMT gene showed significantly better end performance (72+5%; $t=2.50$; $p=0.013$) than 63 patients with at least one valine allele (59+2%).
Conclusions: These results suggest that genes related to dopamine function contribute to learning impairments in SZ patients.
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839. Functional Connectivity of Thalamo-Cortical Projections is Altered in Schizophrenia

Robert C. Welsh[1], Ashley Chen[2], Stephan F. Taylor[3]

[1]Radiology and Psychiatry, University of Michigan, Ann Arbor, MI,[2]Neuroscience, University of Michigan, Ann Arbor, MI,[3]Psychiatry, University of Michigan, Ann Arbor, MI

Background: Post-mortem data, structural neuromaging and functional neuroimaging have implicated the medial-dorsal nucleus (MDN) of the thalamus in schizophrenia. Reciprocal thalamo-cortical projections from the MDN to frontal cortex, including the anterior cingulate cortex, carry out higher level integration of cognition, emotion and motivation, functions disturbed in schizophrenia. As evidence has begun to accumulate that schizophrenia involves disturbances in connectivity, we used a resting state paradigm to analyze the functional connectivity of thalamo-cortical projections from the MDN.
Methods: Resting state fMRI data (6 min) was collected from 11 schizophrenia/schizo-affective patients and 12 healthy, age-matched controls. High-resolution structural T1 images were also obtained. fMRI time-series data were reconstructed off-line and corrected for physiological variance. Slice-timing and motion detection were done using FSL. Using anatomic atlases a seed region (2x2x2 3mm voxels) was identified in the MDN and correlation coefficients calculated for the extracted time-series with all other voxels of the brain.
Results: The functional connectivity analysis for the right and left MD thalamus revealed correlations with frontal cortical targets, including dorsal anterior cingulate cortex (ACC), rostral ACC, and dorsolateral PFC, whereas the schizophrenia group showed reduced connectivity throughout, significantly in rostral ACC. Gray matter signal from T1 images did not differ between groups for the seed region.
Conclusions: The results demonstrate the possibility of using resting state paradigms to analyze functional connectivity for thalamo-cortical projections. To our knowledge, this is the first demonstration of altered functional connectivity of the MDN in schizophrenia.
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840. Impaired Forward Models in Schizophrenia as Assessed by the Size-Weight Illusion

Lisa E. Williams[1], Vilayanur S. Ramachandran[1], David Braff[2], Gregory A. Light[2]

[1]Psychology, University of California, San Diego, La Jolla, CA,[2]Psychiatry, University of California, San Diego, La Jolla, CA

Background: The size-weight illusion (SWI) is a strking perceptual effect wherein an individual asked to compare the weight of two objects of identical physical weight but different sizes will feel the smaller object is substantially heavier. The forward model of motor control proposes that when a motor act is initiated an efference copy of the action is also generated. Comparisons between this copy and actual sensory feedback are used for online movement adjustments, cancelling sensory reafference, and movement prediction and planning. Previous research has suggested the source of the SWI may be a central mismatch between expected sensory feedback - efference copy - and actual proprioceptive feedback of the two stimuli. Disruptions in this mechanism have also been proposed to explain various positive symptoms of schizophrenia, including auditory hallucinations and delusions of control.
Methods: Schizophrenia patients (n=17) and nonpsychiatric comparison subjects (n=14) were asked to compare and report which of two grey disk stimuli was heavier. Disks were large (5 inches diameter) or small (2 inches diameter), and weighed 90, 120, 150, 180 or 210 grams. Testing included illusion trials (90 small vs. 120-210 large) and control trials (comparisons between same size weights).
Results: We found that on the two most difficult size-weight discriminations (90 small vs. 120 and 150 large), as a group, individuals with schizophrenia experience the size-weight illusion on fewer trials than control participants, despite demonstrating comparable weight discrimination.
Conclusions: This finding offers further support to the idea of a dysfunctional motor control comparator mechanism in schizophrenia.
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841. Profile of Neuropsychological Functioning during the Prodrome to Psychosis

Kristen A. Woodberry[1,2,3], Anthony J. Giuliano[2,4], Mary Verdi[3], Larry J. Seidman[2,4]

[1]Psychology, Harvard University, Cambridge, MA,[2]Department of Psychiatry and the Massachusetts Mental Health Center Division of Public Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA,[3]Center for Psychiatric Research, Maine Medical Center, Portland, ME,[4]Psychiatry, Harvard Medical School, Boston, MA

Background: While previous studies have identified verbal memory and olfactory deficits in putatively prodromal subjects as potential predictors of later illness, there are limited data on whether the neuropsychological (NP) profiles of these individuals differ significantly from controls.
Methods: We compare NP data from a sample of 39 putatively prodromal youth (participants in the Portland Identification and Early Referral [PIER] program, NIMH RO1 MH065367, Robert Wood Johnson Foundation, William McFarlane, PI) to NP data from a demographically-matched healthy control sample (N = 33). Profile analysis is used to compare NP profiles based on eight cognitive domains: verbal and nonverbal IQ, verbal and visual

sustained attention and working memory, executive functions, learning and memory, motor functioning, and olfactory functioning.
Results: Preliminary analyses show that the NP profile of the prodromal sample is significantly different in magnitude from that of controls; prodromal subjects demonstrate overall deficits. While NP domain scores differ significantly from each other, we do not find evidence for a significant domain-by-group interaction. However, significant group effects for executive and olfactory functioning, verbal IQ and memory suggest that this may be primarily an issue of power. We plan to test this in ongoing analyses with a larger sample.
Conclusions: This prodromal sample demonstrates a moderate overall NP deficit, consistent with previous literature. Moderate effect sizes for executive, olfactory, and memory deficits suggest these domains may be particularly impaired relative to controls.
Supported by NIMH RO1 MH065367; Harvard Graduate Society Dissertation Completion Fellowship; Sackler Scholar Programme in Psychobiology; Commonwealth Research Center of the Massachusetts Department of Mental Health

842. Neuropsychological Functioning in Schizophrenia Patients with Average or Below Average Intellectual Abilities

Neil D. Woodward[1], Herbert Y. Meltzer[2], Karuna Jayathilake[2]

[1]Psychiatric Neuroimaging Program, Vanderbilt University Medical Center, Nashville, TN,[2]Dept. of Psychiatry, Vanderbilt University Medical Center, Nashville, TN

Background: Patients with schizophrenia demonstrate significant impairments in cognitive function. The deficits are often observed within the context of impaired general intellectual abilities. Consequently, it remains unclear if neuropsychological impairment in schizophrenia results from dysfunction in specific cognitive abilities and associated neural systems or deficient general intellectual ability and widespread alterations in cerebral function.
Methods: To better understand the profile of cognitive impairment in schizophrenia, 93 predominantly treatment resistant patients were classified on the basis of their estimated Wechsler Adult Intelligence Scale-Revised (WAIS-R) intelligence quotient (IQ) into average (IQ=85-115) and below average (IQ=70-85) groups and compared on a battery of neuropsychological tests to a sample of 20 control subjects matched for age, gender, and ethnicity.
Results: Compared to IQ matched controls and their own IQ, patients within the average IQ group demonstrated a moderate impairment in overall neuropsychological functioning (Z-score=-0.97) that was characterized by disproportionately worse verbal memory (Z-score=-1.57) and semantic verbal fluency (Z-score=-1.43). Patients within the below average IQ group demonstrated greater overall neuropsychological impairment (Z-score=-1.78) than both controls and average IQ patients, but did not demonstrate a deficit relative to their IQ.
Conclusions: Patients with an average IQ demonstrate neuropsychological impairment characterized by disproportionately worse performance on tests of verbal learning and semantic fluency. In contrast, patients with below average IQ do not perform disproportionately worse on neuropsychological testing, relative to their IQ, despite demonstrating greater impairment compared to a control sample. These findings indicate that neuropsychological functioning in schizophrenia varies as a function of overall intellectual ability.
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843. Reduced Early Visual Processing in Drug-Naive First Episode Schizophrenia

Sherlyn Yeap[1], Simon P. Kelly[2], Jogin H. Thakore[3], John J. Foxe[2]

[1]Psychiatry, Royal College of Surgeons Ireland, Dublin, Ireland,[2]Psychiatry, Nathan Kline Insitute for Psychiatric Research, New York, NY,[3]Psychiatry, St. Vincent's Hospital Fairview, Dublin, Ireland

Background: Patients with schizophrenia show alterations in early visual information processing as indexed by the P1 visual evoked potential. Previous studies looking at chronic patients as well as first-degree relatives have shown marked reductions in P1 amplitude when compared to controls.
Methods: High-density electrical scalp recordings of drug-naive patients with DSM-IV diagnosed first episode schizophrenia (N=20) and healthy age-matched controls (N=20) were recorded using simple isolated check stimuli.
Results: Preliminary results indicate a substantially reduced P1 amplitude in the patient group compared to controls.
Conclusions: In addition to well-documented deficits in chronic patients, first episode patients with schizophrenia also show deficits in early visual information processing suggesting that it may be longitudinally robust. We suggest that these deficits may further confirm that the P1 is a trait rather than a state marker.
Supported by Health Research Board, Ireland

844. Automated Diagnosis of Schizophrenia using Multivariate Pattern Analysis of fMRI Data

Jong H. Yoon, Diana Tamir, MIchael J. Minzenberg, J. Daniel Ragland, Stefan Ursu, Cameron S. Carter

Psychiatry, Univ Cal Davis, Sacramento, CA

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 activation patterns from individuals with schizophrenia from healthy subjects.
Methods: 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 procedure in which the subject 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.
Conclusions: 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.

845. Knowing What to do and doing What you Know: A Comparison of Daily Living Skills Measures in Schizophrenia

Rachel Ziwich, Maria Jalbrzikowski, Erica Saccente, Gina Forchelli, Daniel C. Javitt, Nadine Revheim

Cognitive Neuroscience, Nathan Kline Institute, Orangeburg, NY

Background: Individuals with schizophrenia have difficulties navigating the tasks of everyday living, which result in poor community adjustment and inability to live independently. While these problems are associated with

neurocognitive deficits, they can be measured independently as functional outcomes. Daily problem-solving skills have been measured using the semi-structured interview format of the Independent Living Scales (ILS), with 33-items comprising the problem-solving factor score, which evaluates abstract reasoning and judgment. The UCSD Performance-Based Skills Assessment (UPSA) has utilized a performance-based format to assess functional capacity using five domains of functioning. Recent reports for an UPSA-Brief measure have also suggested its validity for prediction of residential independence.
Methods: The purpose of this study was to examine individuals with persistent schizophrenia and compare the results of their ILS, UPSA and UPSA-Brief scores to each other and in relation to current community status. The instruments were administered to 45 inpatients and outpatients (35.5±11.3 y.o.; 15.8±9.6 years illness duration.)
Results: ILS, UPSA and UPSA-Brief scores were found to be significantly correlated (ILS and UPSA, r=.70,p<.001,n=45; ILS and Brief-UPSA, r=.66,p<.001,n=45). Based on current residential placement, between group comparisons were made for patients requiring moderate-maximum supervision (n=40) with those requiring minimum-no supervision (n=5). Significant differences were found for ILS (t=-4.55,df=9.65,p=.001) and UPSA (t=-2.49,df=43,p=.02), but not for UPSA-Brief (t=-1.68,df=43,p=.10). Mean scores are discussed in relation to "passing" scores for independent living. UPSA scores are also presented vis-a-vis 3 levels of supervision categorized by ILS.
Conclusions: Results suggest the interview-based ILS and performance-based UPSA are comparable functional outcome measures.
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846. Motor-Behavior Abnormalities and Schizophrenia-Prodrome Symptoms in Adolescents and Young Adults with 22q11 Deletion Syndrome

Joseph F. Cubells[1], Opal Y. Ousley[2], Kimberly Rockers[1], Amanda McMillan[3], Evan Schoenberg[1], Thomas J. Sutton[1], Sang-Hee Kim[2], Karlene Coleman[1], Elaine F. Walker[4]

[1]Human Genetics, Emory Univ. Sch. Med., Atlanta, GA,[2]Psychiatry and Behavioral Sciences, Emory Univ. Sch. Med., Atlanta, GA,[3]School of Medicine, Mercer University, Macon, GA,[4]Psychology, Emory University, Atlanta, GA

Background: The 22q11 deletion syndrome (22q11DS) strongly associates with risk for schizophrenia. Abnormal motor movements (AMM) of the extremities, face, neck and oral region are common in schizophrenic patients, and associate with risk for development of schizophrenia in pre-morbid studies of children and adolescents. We tested the hypotheses that 22q11DS patients exhibit AMM, and that such movements associate with prodromal symptoms of schizophrenia.
Methods: 22q11DS patients (N = 26; 17-30 years old) were ascertained from a case registry at Children's Healthcare of Atlanta. Consenting participants underwent evaluation using the Structured Interview for Prodromal Symptoms (SIPS), and videotapes of participants were rated using the Dyskinesia Identification System: Condensed User Scale (DISCUS). Data from 22q11DS patients were compared to those from previously-assessed non-22q11DS subjects with schizotypal personality disorder (SPD; N = 34), or no personality disorder (NPD; N = 46).
Results: Facial, oral, head/neck and upper-limb MMA scores were significantly higher in 22q11DS patients than in non-22q11DS subjects with NPD (all p <.001). Scores of oral, head/neck and upper-limb MMA were also significantly higher in 22q11DS patients than in SPD patients (all P .05). MMA scores in 22q11DS patients significantly associated with severity of positive, negative and general-symptom SIPS scores (r = 0.39, 0.32 and 0.30, respectively, all p < 0.05).
Conclusions: 22q11DS patients exhibit elevated MMA, and severity of MMA in 22q11DS associates with severity of schizophrenia-prodrome symptoms.
Supported by The Predictive Health Institute and Robert W. Woodruff Fund, Emory University.

847. Effect of COMT Val158Met Genotype on Hippocampal Physiology in Schizophrenia

Annabella Di Giorgio[1], Grazia Caforio[1], Giuseppe Blasi[1], Raffaella Romano[1], Giuseppe De Simeis[1], Simona Aquilino[1], Leonardo Fazio[1], Paolo Taurisano[1], Barbara Gelao[1], Marcello Nardini[1], Teresa Popolizio[2], Alessandro Bertolino[1]

[1]Psychiatric Neuroscience Group, Department of Psychiatry and Neurology, University of Bari, Bari, Italy,[2]Section of Neuroradiology, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo (FG), Italy

Background: Catechol-O-Methyltransferase (COMT) Val[158]Met is thought to modulate dopamine regulated hippocampal activity during episodic memory, and to weakly increase risk for developing schizophrenia. Aim of the present study with fMRI was to evaluate the potential association between this COMT polymorphism and hippocampal physiology during recognition memory encoding in schizophrenia.
Methods: 28 schizophrenic patients (DSM-IV criteria, 25 males, mean age ±SD 30.3 ± 9.3 yrs) and 33 healthy subjects matched for a series of socio-demographic variables were recruited. All participants were genotyped for COMT Val[158]Met genotype and underwent fMRI at 3T (gradient-echo EPI, TE 3000 ms, TR 20 ms) during a recognition memory task, that has previously been associated with robust activation of the hippocampal memory system. SPM5 and random effects models were used for statistical analyses (all p<0.005).
Results: The two groups did not differ in COMT genotype distribution which was in Hardy Weinberg equilibrium. ANOVA of behavioral performance data demonstrated a main effect of diagnosis on encoding accuracy, with patients performing worse than healthy subjects (p<0.02). A Full Factorial ANOVA of the imaging data (including accuracy as a covariate) indicated a main effect of diagnosis, with healthy subjects showing greater hippocampal activity during memory encoding compared to patients; no main effect of genotype; and a significant genotype by diagnosis interaction, in that the effect of diagnosis on hippocampal engagement was evident only in Met/Met subjects.
Conclusions: These results suggest that modulation of dopamine signaling may be important in determining the phenotype of hippocampal physiology during recognition memory in schizophrenia.

848. Do Probands with First Episode Psychosis have Relatives with Specific or Non-Specific Psychopathology?

Kia Faridi[1,2], Nicole Pawliuk[2], Suzanne King[1,2], Ridha Joober[1,2], Ashok K. Malla[1,2]

[1]Department of Psychiatry, McGill University, Montreal, QC, Canada,[2]Douglas Research Centre, Douglas Mental Health University Institute, Montreal, QC, Canada

Background: It is well established that family members of individuals with schizophrenia suffer from elevated rates of schizophrenia-spectrum disorders (SSD) and other forms of psychopathology. However, few studies have examined familial psychopathology in first episode psychosis (FEP). In this study we systematically evaluated family history in patients experiencing an affective or non-affective FEP.
Methods: The Family Interview for Genetic Studies was used to obtain diagnostic information on all first- and second-degree relatives of probands admitted to a specialized FEP program. Probands were 93 previously untreated patients suffering from FEP, aged 14 to 30. Diagnoses ascertained included psychotic disorders, affective disorders, and substance use disorders (SUD).
Results: One in five probands (19.4%) had a history of psychosis among their first-degree relatives, while 34.5% had any family history of psychosis.

Fewer had a family history of SSD (7.5 % and 18.3% first-degree and any relatives, respectively). Over half of probands had a first-degree relative with Major Depressive Disorder, and 38.7% had a first-degree relative with a SUD. Overall, 69.9% of probands had a first-degree relative with a mental disorder. The proportion with a family history of any of these diagnoses did not vary by proband diagnosis.

Proportion of Probands with a Family History of Various Forms of Psychopathology

Diagnosis	Probands with Family History Amongst First Degree Relatives n = 93		Probands with Family History Amongst Any Relative (1st or 2nd Degree) n = 93	
	n	%	n	%
Schizophrenia Spectrum Disorder	7	7.5%	17	18.3%
Any Psychosis	18	19.4%	32	34.5%
Major Depressive Disorder	49	52.7%	60	64.5%
Bipolar Disorder	7	7.5%	11	11.8%
Substance Use Disorder	36	38.7%	55	59.1%
Any Psychopathology	65	69.9%	78	83.9%

Conclusions: Diverse psychopathology is common in families of FEP patients. A family history of psychosis, depression, or SUD was common, while a family history of SSD was relatively less so.

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849. COMT Val/Met (158/108) Polymorphism and Schizophrenia: a Case-Control and Family Based Association Study

Ferid Fathalli[1], Guy A. Rouleau[2,3], Karim Tabbane[4], Alain Labelle[5], Pierre Lalonde[6], Chawki Benkelfat[7], Samarthji Lal[7], Zoltan Danics[8], Ridha Joober[7,9]

[1]Research Center (FBC), Douglas Hospital, Montreal, QC, Canada,[2]Research Center, Saint-Justine University Hospital, Montreal, QC, Canada,[3]Notre Dame Hospital, Notre Dame Hospital, Montreal, QC, Canada,[4]Department of Psychiatry, University of Tunis, Tunis, Tunisia,[5]Ottawa Royal Hospital, Ottawa Royal Hospital, Ottawa, ON, Canada,[6]Department of Psychiatry, University of Montreal, Montreal, QC, Canada,[7]Department of Psychiatry, McGill University, Montreal, QC, Canada,[8]National Institute of Psychiatry, National Institute of Psychiatry, Budapest, Hungary,[9]Research center (FBC), Douglas Hospital, Montreal, QC, Canada

Background: The COMT gene is of particular interest in schizophrenia since corticostriatal dopamine dysregulation is believed to be an important contributor to the pathogenesis of schizophrenia

Methods: A case-control study was performed with a sample of 292 schizophrenic patients and 158 control subjects assessed for the COMT Val/Met (158/108) variant. In addition, we carried out a family-based association study with 174 nuclear Caucasian families including 570 persons (133 European ancestry families with 417 individuals and 41 Tunisian -Arab Mediterranean-families including 153 individuals). For the case-control study, we compared allelic and genotype distribution between patients and controls. For the family based study, we used the transmission disequilibrium test as implemented in the Fbat program.

Results: No differences between patients and control subjects regarding genotype (χ^2=0.49; df = 2; p=0.78) and allelic frequencies (χ^2 = 0.07; df = 1; p = 0.78) were observed. However, in patients with European ancestry, later age at onset (> 25 years) was associated with heterozygosity in males. No difference in genotype and allelic frequencies was found between patients separated according to the quality of their response to conventional neuroleptic. In the family study there was a preferential transmission of the Val allele (high activity) in Tunisian (additive model: Z= 2.2, p= 0.02; dominant model: Z=3.5, p=0.0003) but not in European families.

Conclusions: The COMT Val/Met (158/108) polymorphism may play a role in increasing the risk for schizophrenia in some populations. It also could play a role in modulating disease characteristics such as age at onset.

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850. Reduced Acetylated Histone 3 (acetylH3) Levels and Impaired TSA-Induced Increases in Acetylation in Schizophrenia

David P. Gavin, Cherise Rosen, Saritha Kartan, Dennis R. Grayson, Rajiv P. Sharma

Psychiatry, University of Illinois at Chicago, Chicago, IL

Background: Histone deacetylases (HDAC) induce a restrictive chromatin state which has been implicated in schizophrenia. GAD1 is an epigenetically regulated schizophrenia candidate gene. HDAC inhibitors, such as trichostatin A (TSA), increase acetylated histone 3 (acetylH3) protein levels and GAD1 mRNA expression in patients and in cultured lymphocytes.

Methods: Lymphocytes were isolated from 21 normal and 23 schizophrenia subjects. Diagnoses were confirmed using SCID and symptoms rated with PANSS. Cells were incubated with 100 nM TSA or vehicle (DMSO) for 24 hours. GAD1 mRNA expression was measured using realtime RT-PCR, and acetylH3 by Western blot analysis.

Results: Schizophrenia subjects had significantly lower baseline acetylH3 levels compared with normal subjects ($p<0.04$) and showed significantly smaller increases in acetylH3 after TSA treatment than normal subjects (11% vs. 60%; $p<0.01$). There was a trend for smaller increases in GAD1 mRNA expression after TSA treatment in schizophrenia compared with normal subjects (-18% vs. 134%; $p<0.08$). GAD1 and acetylH3 were significantly correlated in TSA-treated cells among normal subjects ($r=0.692$; $p<0.01$), but not among those with schizophrenia. There was a significant negative correlation between thought disorder symptoms and TSA-induced increases in GAD1 expression ($r=-0.764$; $n=7$; $p<0.05$).

Conclusions: Our results confirm previous findings that schizophrenia chromatin is generally more "rigid," and that HDAC inhibitors are less effective at inducing chromatin remodeling. These results provide further evidence of the association between schizophrenia and chromatin remodeling abnormalities, and suggest these differences are more profound in a subset of schizophrenia patients.

851. Prepulse Inhibition and Baseline Startle are Heritable in Families of Schizophrenia Patients and Healthy Controls

Wendy Hasenkamp[1], Michael Epstein[2], Amanda Green[1], Lisette Wilcox[1], William Boshoven[1], Erica Duncan[1,3]

[1]Mental Health Service, Atlanta Veterans Affairs Medical Center, Atlanta, GA,[2]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA,[3]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA

Background: Prepulse inhibition of the acoustic startle reflex (PPI) is a measure of sensorimotor gating that has been proposed to be an endophenotype in schizophrenia. If this measure proves to have significant heritability, it may advance studies of the genetics of schizophrenia.

Methods: We evaluated baseline startle magnitude and PPI at 30, 60 and 120-ms intervals between prepulse and startling stimuli in 181 subjects from 75 families (38 families ascertained via a schizophrenic proband, 37 non-psychiatric families ascertained at random). To assess whether PPI possessed

a significant genetic component, we conducted a heritability analysis using the popular variance-component approach, adjusting for the effects of age, gender and race. We conditioned these variance-component analyses on the outcome values of the 38 schizophrenic probands to remove any potential bias resulting from the non-random ascertainment of these families. Outcomes were transformed to normality to make the variance-component analyses robust to potential heavy tails in the outcome distribution. We based inference on likelihood-ratio statistics derived from the MENDEL software package.
Results: We estimated the heritability of baseline startle magnitude to be 69% (p=0.0004), and the heritability of PPI at 60-ms to be 42% (p=0.015). Heritability estimates of PPI at 30 and 120-ms were moderately significant.
Conclusions: These data support the concept of PPI as a heritable endophenotype in schizophrenia, and agree with previous estimations of PPI and baseline startle heritability. Hopefully, future research will identify specific genes underlying PPI phenotypes, which will assist in the understanding of the genetic basis of schizophrenia.
Supported by Department of Veterans Affairs Merit Review Program

852. Protective and Risk Functional Diplotypes of PRODH Schizophrenia Risk Gene on 22q11, Impact on Brain Structure, Function and Clinical Risk

Lucas Kempf[1], Kristin K. Nicodemus[1], Bhaskar Kolochana[1], Radhakrishna Vakkalanka[1], Beth Verchinski[1], Michael Egan[2], Richard Straub[1], Venkata Mattay[1], Joseph Callicott[1], Daniel Weinberger[1], Andreas Meyer-Lindenberg[3]

[1]USNP/GCAP, NIMH, Bethesda, MD,[2]Clinical research, Merck and Co, West Point, PA,[3]Department of the Director, Central Institute of Mental Health, Mannheim, Germany

Background: Proline Dehydrogenase (PRODH) on 22q11.2 has been implicated in susceptibility to schizophrenia. Several functional changes in the enzyme have been characterized. Since interacting effects of common polymorphisms on enzyme activity are a likely pathophysiological mechanism, diplotypes are useful to separately characterize effects of interacting functional variants.
Methods: Clinical association for haplotypes in the GCAP sibling study was done with TDT. Imaging: We studied 144 healthy volunteers of European ancestry in a multimodal fashion using functional, connectivity and structural data. Diplotypes were constructed with Phase 2.1 and second level imaging analysis was conducted using a regression approach with probabilistic diplotypes in the design matrix.
Results: Clinical association was positive for the fast metabolizing haplotype and negatively for the slow metabolizing haplotype. Imaging results showed a significant effect of risk haplotype compared to the reference haplotype, on the structure of the striatum cluster maximum 21, 22, -6 T=3.36, FDR=0.038. The protective haplotype showed an increase in regional volume in the left superior prefrontal cortex (-20 60 1, Z=4.38, p<0.001) and right occipital lobe (FDR 0.033, 21 -86 17, Z=5.00, p<0.001). PRODH risk diplotype showed effects in activation of the inferior frontal and parietal lobes in the working memory network. Functional connectivity analysis with the striatum showed a diplotype dependant connectivity pattern.
Conclusions: Our data suggest that PRODH risk haplotype impacts on striatal function and structure, confirming previous results using single SNPs and suggesting a risk mechanism for schizophrenia involving neostriatum and the protective haplotype increases the left dorsal lateral prefrontal cortex.
Supported by NIH

853. Family History and Paternal Age-Related Gender Effects on Schizophrenia Reoccurrence in the Jerusalem Cohort.

M. C. Perrin[1], S. Harlap[2], K. Kleinhaus[3], M. Opler[4], P. Lichtenberg[5], B.G. Draiman[6], O. Manor[6], D. Malaspina[4]

[1]Departments of Psychiatry and Environmental Medicine, New York University School of Medicine, New York, NY,[2]Departments of Psychiatry and Obstetrics and Gynecology, New York University School of Medicine, New York, NY,[3]Department of Psychiatry, Columbia University, New York, NY,[4]Department of Psychiatry, New York University School of Medicine, New York, NY,[5]Hadassah Medical School, Herzog Hospital and Hebrew University, Jerusalem, Israel,[6]School of Public Health, Hebrew University, Jerusalem, Israel

Background: Family history of schizophrenia is an established risk factor for schizophrenia. It has rarely been estimated using a prospective cohort and described in relation to sex of affected individuals, their relatives and paternal age.
Methods: We measured the incidence of schizophrenia associated with a history of a psychiatric hospitalization in first-degree relatives, using the Jerusalem Perinatal Study, a population-based cohort of 92,408 offspring. Families were traced in the Population Registry and linked by identity number to the Psychiatric Registry. Schizophrenia-related diagnosis ("schizophrenia") was defined as a discharge diagnosis of [ICD-10] F20-F29. Cox proportional hazards models were used to estimate the relative risk (RR) of hospitalization for schizophrenia in offspring who had a first-degree relative hospitalized for schizophrenia.
Results: 806 offspring (0.94%) were hospitalized with schizophrenia. With both sexes combined, the RRs associated with an affected mother, father, 1+ brothers or 1+ sisters were; 4.7 (3.5-6.1); 3.3 (2.4-4.5); 3.7 (2.7-5.0) and 5.5 (4.0-7.6) respectively. Females with 1+ affected brothers were 2.7 (1.6-4.6) times as likely to be hospitalized with schizophrenia. Females with 1+ affected sisters showed a 10-fold increase in risk (6.5-15.6). Males with 1 + affected sister had an RR of 3.4 (2.1-5.4) and 4.4 (3.0-6.4) with 1+ affected brothers. In older fathers, the risk between sisters was three times the risk between brothers.
Conclusions: Our findings suggest an X-chromosome contribution to schizophrenia risk. The stronger association of schizophrenia between sisters than between brother and sister, imply involvement of a paternal rather than a maternal allele.
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854. SAT-1 T589C Polymorphism and Susceptibility to Psychosis

Concepción Vaquero Lorenzo[1], **Carlos Riaza Bermudo-Soriano**[2], Enrique Baca Garcia[3], Montserrat Diaz-Bernardez[4], Jeronimo Saiz-Ruiz[2], Jose Fernandez Piqueras[4], Negueruela Monica[3]

[1]Department of Genetics, Universidad Autonoma De Madrid, Madrid, Spain,[2]Psychiatry, Hospital Ramon Y Cajal, Madrid, Spain,[3]Psychiatry, Fundación Jiménez Díaz, Madrid, Spain,[4]Department of Genetics, Universidad Autonoma de Madrid, Madrid, Spain

Background: Psychotic patients show several disturbances on polyamine metabolism. There is a significant positive correlation between blood polyamine concentration and the severity of illness. The aim of the present study was to examine the association between dbSNP 7891589 (T/C) polymorphism of the main gene regulating polyamine catabolism (SAT-1) and the risk of developing psychotic disorders.
Methods: A case-control design was used in order to compare the genotypes for that dbSNP between psychotic patients (n=180), other non-psychotic psychiatric patients (n=413), and healthy controls (n=251). DSM-IV diagnosis for psychiatric patients was provided using MINI 4.4. Genomic DNA was

extracted from peripheral blood samples collected from participants. PCR amplification of a 298-bp fragment from the promoter region of SAT-1 gene (X cromosome), containing the PRE and nearby dbSNPs: 7891589, was carried out using the following primers: forward: 5′-GAAGGCCTTTTCCTCCTCTG-3′ and the reverse: 5′- GATAGGGCCTCACCATCTTG-3′, and subsequently digested with Msp I and visualized in ethidium bromide agarose gels.
Results: No significant association in the distribution of the two genotypes of the T589C polymorphism between psychotic patients, non-psychotic controls, and healthy controls, was found in males (T/C) (Linear-by-Linear association χ^2=1,278; df=1; P=0,258), or in females (T/T, T/C, and C/C) (Linear-by-Linear association χ^2=1,94; df=1; P=0,164).
Conclusions: This is the first study that analyses the role of polymorphic variants of genes involved in polyamine metabolism in psychosis. Though our study could not demonstrate a significant association between SAT-1-T589C polymorphism and the risk of suffering from psychosis, it opens a new field of research.
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855. A PRODH Haplotype which Increases Risk for Schizophrenia, is Associated with Deficient PPI in Healthy Males

Panos Roussos, Stella G. Giakoumaki, Panos Bitsios

Psychiatry and Behavioral Sciences, University of Crete, Heraklion, Crete, Greece

Background: Prepulse inhibition (PPI) of the startle reflex has been proposed as an endophenotype for schizophrenia. There is evidence supporting a role for the PRODH locus in this disorder[1] and knock out mice for PRODH have deficient PPI[2]. It is not known whether PRODH is a significant determinant of human PPI.
Methods: Three polymorphisms in the 3' region of the gene (1945A>G, 1766T>C and 1852G>A) were analyzed in 117 healthy males. PPI (75-dB and 85-dB prepulses at 30-, 60-, 120-ms intervals) was examined. Hardy-Weinberg equilibrium for PRODH markers was checked using Haploview version 4.0[3]. Data for each separate allele were analyzed with repeated measures ANOVA with prepulse and interval as the within- and polymorphisms as the between-subject factors. QTPHASE from the UNPHASED package was used for the association analysis of haplotype data[4].
Results: The ANOVA and the QTPHASE analyses revealed significant main effects of the PRODH alleles and haplotypes, respectively. The 1945G, 1766C and 1852A alleles, and the GCA haplotype, consisted of these alleles, were associated with deficient PPI.
Conclusions: Healthy human subjects carrying the PRODH GCA haplotype have deficient PPI. This haplotype has been previously associated with an increased risk for schizophrenia. This risk may be attributed, at least in part, to deficient sensorimotor gating conferred by the PRODH GCA haplotype.
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856. Hyperactivity and Hyperconnectivity of the Default Network in Schizophrenia and in First Degree Relatives of Persons with Schizophrenia

Susan Whitfield-Gabrieli[1], Heidi W. Thermenos[2,3], Snezana Milanovic[2,4], Ming T. Tsuang[5], Stephen V. Faraone[6], Robert W. McCarley[2,7], Martha E. Shenton[7,8], Alan I. Green[9], Peter LaViolette[4], Joanne Wojcik[2], John D. E. Gabrieli[1], **Larry J. Seidman**[2,3,4]

[1]Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Boston, MA,[2]Department of Psychiatry, Harvard Medical School/ Beth Israel Deaconess Medical Center, Boston, MA,[3]Massachusetts Institute of Technology/ Harvard Medical School and Massachusetts General Hospital, Martinos Center for Biomedical Imaging, Charlestown, MA,[4]Department of Psychiatry, Harvard Medical School/ Massachusetts General Hospital, Boston, MA,[5]Department of Psychiatry, Institute of Behavior Genomics, University of California, San Diego, La Jolla, CA,[6]SUNY Genetics Research Program/ Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY,[7]Department of Psychiatry, Harvard Medical School/ Brockton/West Roxbury VA Medical Center, Brockton, MA,[8]Department of Psychiatry, Harvard Medical School/ Brigham and Womenâ€™s Hospital, Boston, MA,[9]Departments of Psychiatry and of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH

Background: We examined the status of the neural network mediating the default mode of brain function, which typically exhibits greater activation during rest than during task, in patients in the early phase of schizophrenia and in young first-degree relatives of persons with schizophrenia.
Methods: During functional magnetic resonance imaging (fMRI), patients, relatives, and controls alternated between rest and performance of working memory tasks.
Results: As expected, controls exhibited task-related suppression of activation in the default network including medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC)/Precuneus, lateral parietal cortex, and hippocampus. Patients and relatives exhibited reduced task-related suppression in all those regions, except in the PCC for the relatives. Increased task-related suppression in the MPFC was correlated with better working memory performance and less psychopathology in all three groups. Patients and relatives exhibited abnormally high functional connectivity between default network regions during rest, with the degree of connectivity correlating with psychopathology in the patients.
Conclusions: Hyperactivation (reduced task-related suppression) of default regions and hyperconnectivity of the default network may contribute to disturbances of thought in schizophrenia and the risk for the illness.
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857. Effect of Sigma-1 Receptor Gene Polymorphism on Prefrontal Hemodynamic Response in Schizophrenia; a Multi-Channel NIRS Study

Ryu Takizawa[1], Mamoru Tochigi[1], Yuki Kawakubo[1], Kohei Marumo[1], Tsukasa Sasaki[2], Masato Fukuda[3], Kenji Hashimoto[4], Kiyoto Kasai[1]

[1]Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan,[2]Health Service Center, The University of Tokyo, Tokyo, Japan,[3]Department of Psychiatry and Human Behavior, Graduate School of Medicine, Gunma University, Maebashi, Japan,[4]Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, Chiba, Japan

Background: Several lines of evidence suggest that the sigma-1 receptor (Sig-1R) may contribute to the pathophysiology of schizophrenia and mechanisms of drug efficacy. A functional polymorphism (Gln2Pro) of Sig-1R that is

involved in endoplasmic reticulum retention signal is thought to be a candidate that affects brain function in schizophrenia. Spatiotemporal characteristics of prefrontal hemodynamic response and the association with Sig-1R genotype were investigated using a non-invasive neuroimaging technique, multi-channel near-infrared spectroscopy (NIRS).
Methods: Subjects included 40 right-handed patients with schizophrenia and 60 healthy controls, who gave written informed consent in accordance with the ethics committee of the University of Tokyo Hospital. The NIRS signals, monitored over the prefrontal cortex (PFC) from 52-channel NIRS (HITACHI ETG-4000) during verbal fluency task, were compared between two Sig1-R genotype subgroups (Gln/Gln individuals and Pro carriers) matched for age, gender, premorbid IQ and task-performance.
Results: Even after controlling for medication effect, schizophrenia patients with Gln/Gln genotype had greater task-associated increase in [oxy-Hb] in the PFC than those with Pro carriers after false discovery rate (FDR) correction for multiple comparisons (p < FDR .05), although clinical symptoms were not significantly different between the two Sig-1R genotypes. These differences were not found to be significant in healthy controls.
Conclusions: Our finding is the first functional imaging-genetics study that implicated the effect of Sig-1R genotype on prefrontal cortical function in schizophrenia. Prefrontal hemodynamic response assessed by non-invasive NIRS might be a useful intermediate phenotype for schizophrenia.

858. AKT1 Influences Human Prefrontal Cortical Structure and Dopaminergic Function

Hao-Yang Tan[1], Kristin K. Nicodemus[1], Qiang Chen[1], Zhen Li[1], Jennifer K. Brooke[1], Robyn Honea[1], Bhaskar S. Kolachana[1], Richard E. Straub[1], Yoshitasu Sei[1], Andreas Meyer-Lindenberg[1,2], Venkata S. Mattay[1], Joseph H. Callicott[1], Daniel R. Weinberger[1]

[1]Clinical Brain Disorders Branch, National Institute of Mental Health, Bethesda, MD,[2]Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany

Background: AKT1-dependent molecular pathways control diverse aspects of cellular development and adaptation, including novel interactions with neuronal dopaminergic signaling implicated in working memory and neuropsychiatric disease.
Methods: We examined AKT1 effects on cognition, lymphoblast protein expression, fMRI of working memory, MRI grey matter volume and risk for schizophrenia. Further, the hypothesized AKT1 coupling with cortical dopamine was examined in the context of a functional polymorphism (Val158Met) in COMT.
Results: A coding genetic variation in AKT1 rs1130233 (Glu242Glu; formerly rs2498799) influenced frontostriatal cognitive performance in healthy individuals (n=319, p<0.005), prefrontal physiology assayed in fMRI in two independent samples (n=46 and n=68; combined $p=9x10^{-7}$), frontostriatal gray matter volume (n=171, p<0.05 corrected), and AKT1 protein levels in human B lymphoblasts (n=32, p<0.05). Moreover, on prefrontal fMRI and MRI measures showing a main effect of AKT1 genotype, there was an epistatic interaction with COMT (fMRI: combined p=0.0008; MRI p=0.002). In a case-control dataset (n=358 probands and 370 controls), we found additional evidence for a genetic association of AKT1 rs1130233 with risk for schizophrenia (p=0.024).
Conclusions: These convergent data implicate AKT1 in modulating human prefrontal structure and function, and risk for psychosis, suggesting that the mechanism of this genetic effect involves, at least in part, dopaminergic signaling.
Supported by NIMH Intramural Research Program

859. Genetic Findings in Hispanic Schizophrenics

James Wilcox

Psychiatry - VAMC, University of Arizona, Tucson, AZ

Background: Many candidate genes have been described for schizophrenia. Although several ethnic groups have been examined in some detail, the Hispanic population is often ignored. There is presently a lack of information on this group. This poster is an attempt to include Hispanic populations into the genetic database.
Methods: Sets of triples were gathered from families of 56 Hispanic patients with schizophrenia. Similar sets of triples were gathered from Hsipanic families with no history of mental illness. Standardized laboratory methods were used to search for known genes of risk.
Results: No significance was found for the presence of Presenilin-1 or 2, Neuregulin-2 or D-4 loci in our study. Hispanic families of schizophrenics were more likely to carry positive COMT and Neuregulin-1 loci than controls.
Conclusions: We feel that it is possible that a grouping of genes related to the expression of COMT and Neuregulin-1 is important in the expression of psychosis in Hispanic individuals.

860. Effect of Dopamine Transporter VNTR Polymorphism on Prepulse Inhibition in Schizophrenia

Ikwunga Wonodi[1], L. Elliot Hong[1], O. Colin Stine[2], Jada Lewis[1], Ping-I Lin[1], Gunvant K. Thaker[1]

[1]Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD,[2]General Clinical Research Center (GCRC) Genomics Core Facility, University of Maryland School of Medicine, Baltimore, MD

Background: Prepulse inhibition (PPI) is a schizophrenia endophenotype commonly used in animal models of psychosis. Extensive pharmacological profiling suggests a complex role of dopamine in modulating PPI. The dopamine transporter gene (DAT1) VNTR polymorphism affects extracellular dopamine availability and associated neurocognitive functions. Since PPI has high cross-species homology, and DAT1 knockout mice display PPI deficits, we hypothesized that DAT1 variation might affect PPI in humans.
Methods: We examined the effect of DAT1 10/10 genotype, which results in increased synaptic dopamine, on PPI. Genotyping was performed in 457 individuals, including 240 schizophrenia patients and 217 healthy controls. PPI was tested in a subgroup of 275 subjects of which 93 cases and 71 controls were responders to startling stimulus.
Results: DAT1 10/10 genotype was not associated with schizophrenia (all p=0.40). Schizophrenia subjects had significantly reduced PPI compared to controls (p=0.046). There was no DAT1 genotype by diagnosis interaction on PPI (p=0.30). Analyses by ethnicity demonstrated a trend DAT1 by diagnosis interaction on PPI in Caucasian subjects (p=0.08), but not in African-American (AA) subjects (p=0.33). Separate analyses in cases and controls showed significant effect of DAT1 genotype on PPI in Caucasian controls (p=0.02), but not patients (p=0.80). In AA subjects, there was no effect in controls (p= 0.65) or cases (p=0.29).
Conclusions: Data supports a dopaminergic effect on PPI in controls, but not in schizophrenia patients. This DAT1 variant may interact with race and perhaps medication status and other etiological factors in a complex way to affect the PPI endophenotype in schizophrenia.
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861. The Gamma-Aminobutyric Acid Type A Receptor Gamma2 Subunit Gene is Associated with Schizophrenia

Clement C. Zai, Arun Tiwari, Vincenzo De Luca, Greg W. H. Wong, James L. Kennedy

Neurogenetics, Centre for Addiciton and Mental Health, Toronto, ON, Canada

Background: gamma-aminobutyric acid (GABA) is produced in areas of the brain implicated in schizophrenia, and several genes coding for $GABA_A$ subunits, including GABRG2 encoding the γ2 subunit, are clustered at 5q31-q35, a chromosomal region associated with schizophrenia in genome scan studies.
Methods: We tested five polymorphisms spanning GABRG2 for association with schizophrenia and also suicidal behaviour. The sample consisted of 109 small nuclear families and 229 schizophrenia cases paired with 229 healthy controls.
Results: rs183294 in the 5' region of GABRG2 was found associated with schizophrenia in both samples with C over-represented in schizophrenia cases and over-transmitted in schizophrenia families (combined p=3⊠10^{-3}).
Conclusions: Taken together, the results of the present study suggest GABRG2 may be involved in schizophrenia susceptibility, but further studies are required. We are currently genotyping additional polymorphisms spanning GABRG2.
Supported by MOP79525

862. Reduced Phase Locking to Auditory Stimulation in Schizophrenia; Influence of Reduced NMDA Receptor Signaling

Stephan Bickel, Peter Lakatos, Elisa Dias, Charles E. Schroeder, Daniel C. Javitt

Cognitive Neuroscience and Schizophrenia Program, Nathan Kline Institute of Psychiatric Research, Orangeburg, NY

Background: Patients with schizophrenia show alterations in early auditory information processing. For example, they show reduced amplitudes of the auditory evoked potentials P1 and N1 in the EEG. Patients also show alterations in electrophysiological measures of neural synchrony. We investigated if patients show changes in phase resetting of ongoing oscillatory activity by tones presented with different inter-stimulus intervals. Furthermore, we investigated the involvement of the NMDA receptor in this mechanism by means of intracortical recordings in the monkey.
Methods: The EEG of patients (N=33) and controls (N=18) was recorded while tones were delivered with different inter-stimulus intervals to investigate possible entrainment. We used the same paradigm to analyze the laminar response in the auditory cortex of the awake macaque monkey, prior and following systemic administration of the NMDA receptor antagonist phencyclidine (PCP).
Results: The controls showed significant inter-trial phase locking (IPL) between 2 to 14Hz in the P1-N1 window. IPL was significantly reduced in the patients. Similar alterations were observed in the monkey recordings following PCP administration. Furthermore, PCP induced remarkable increases of baseline activity in the gamma frequency range (>30Hz) in supra-granular layers.
Conclusions: In addition to well-documented deficits in early auditory evoked potentials, patients with schizophrenia also show deficits in phase resetting of ongoing oscillatory activity. Though, it is still unclear how these alterations are related. We suggest that reduced signaling through the NMDA receptor could underlie both deficits.
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863. The Difference of Superior Temporal Gyrus Volume between Drug Naïve Schizophrenia and Healthy Volunteers

Wei-Tseng Chen[1], Po See Chen[1], Kao-Ching Chen[1], Yen Kuang Yang[1], Ru Band Lu[1,2]

[1]Psychiatry, National Cheng Kung University Hospital, Tainan, Taiwan,[2]Institute of Behavioral Medicine, Hospital and College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background: The most consistent brain image studies of structural changes in schizophrenia were volume decreasing of superior temporal gyrus. However, it was hard to exclude the drug effects in those studies. The current study was designed to compare the volume of superior temporal gyrus between the drug naïve schizophrenia patients and healthy volunteers. Results may help to clarify the factors attributing to the volume change of superior temporal gyrus.
Methods: Magnetic resonance scans was obtained from drug-naïve subjects with schizophrenia (n = 12) or control subjects (n = 12). Magnetic resonance images provided quantitative measures of temporal lobe regions of interest. The volume of right and left superior temporal gyrus was measured respectively. Statistics analysis was performed by using the SPSS software.
Results: There were no significant differences in either total superior temporal volume or each hemisphere between schizophrenic group and control group after control the variance of sex and age.
Conclusions: Our study showed inconsistent results with previous studies. Results from the drug-naïve patients suggested that the volume changes of superior temporal gyrus may not be the consequence of the disease only. The current study was limited by the small sample sizes. Moreover, further study need take the illness duration into consideration.

864. Alternative Strategies for Testing Epistasis in Pharmacogenetic Studies: Analysis of Serotonin System and Antipsychotic Response

Vincenzo De Luca[1], R. de Souza[1], Jan Volavka[2], J. Lieberman[3], Herbert Meltzer[4], James L. Kennedy[1]

[1]Psychiatry, University of Toronto, Toronto, ON, Canada,[2]Psychiatry, Nathan Kline Institute, Orangeburg, NY,[3]Psychiatry, Columbia University, New York, NY,[4]Psychiatry, Vanderbilt University, Nashville, TN

Background: Serotonin receptors blockade is the major basis for the antipsychotic action of atypical antipsychotic drugs. Genetic factors affecting the density and/or function of serotonergic receptors, transporters and enzymes may therefore affect antipsychotic response. This exploratory study investigates the effect of ten polymorphisms from HTR1A, HTR1D, HTR2A, HTR3A, HTR3B, HTR4, HTR6, SLC6A4, TPH1, TPH2 genes on antipsychotic response in a sample of 289 patients with DSM-diagnosis of schizophrenia.
Methods: Clinical Response was assessed using Brief Psychiatric Rating Scale (BPRS). Response was determined as 20% reduction improvement of BPRS compared to baseline. Selection of the biological relevant interactions, regardless the phenotype was performed using different statistics strategies regardless the phenotype to investigate epistasis within the serotonin system.
Results: The test for relevant interaction selection showed that 5HT4 and 5HT6 can be in epistatic relationship. The single locus analysis of these two receptor polymorphisms showed no significant results and the logistic regression model incorporating both genes, the clinical and demographic variables was not significant.
Conclusions: Even though this result is not significant, this strategy aimed to investigate the epistatic effect among genes could be useful for finding relevant biological interaction among genetic variants.

865. Unbiased Stereologic Quantification of Layer 3 of the Primary Auditory Cortex in Subjects with Schizophrenia: Pyramidal Cell Number and Mean Volume Determination

Kristen M. Delevich[1], Michael J. Marcsisin[1], Karl-Anton Dorph-Petersen[2], Hans Jorgen G. Gundersen[3], Allan R. Sampson[4], David A. Lewis[1], Robert A. Sweet[1]

[1]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA,[2]Centre for Psychiatric Research, Aarhus University Hospital, Risskov, Denmark,[3]Stereological and Electron Microsopic Research Laboratory, Institute of Experimental Clinical Research, University of Aarhus, Denmark,[4]Department of Statistics, University of Pittsburgh, Pittsburgh, PA

Background: Subjects with schizophrenia demonstrate functional deficits in early auditory sensory processing localized to the primary auditory cortex. Studies have reported gray matter reductions mapped to the auditory cortex of the STG in schizophrenics. Our group previously reported significant reductions (10.4%) in mean somal volume of pyramidal cells in deep layer 3 of primary auditory cortex of subjects with schizophrenia, which may contribute regional gray matter volume reductions and to auditory processing deficits.
Methods: The current study utilized a novel stereologic method that provides unbiased estimation of cell volume and number within individual cortical layers and sublayers to assess the primary auditory cortex of 12 subjects with schizophrenia or schizoaffective disorder, each matched to a comparison subject for age, gender, and post-mortem interval.
Results: Data collection has been completed for all 24 subjects, yielding somal volume estimation for 11,882 layer 3 pyramidal cells. Diagnostic groups will be compared for mean pyramidal cell somal volumes and pyramidal cell numbers in deep layer 3 and contrasted with findings from superficial layer 3.
Conclusions: Whether reduced mean pyramidal cell somal volume in patients with schizophrenia results from a generalized decrease in pyramidal cell somal volume or an alteration in the number or distribution of cells by size is unknown. Interpretation of results within the context of prior findings of reductions in pyramidal cell somal volume, axon terminal density, and dendritic spine density in this region will help determine the source of mean pyramidal cell somal volume reductions and explain regional gray matter reductions.
Supported by USPHS grants MH 045156 and MH 071533 and by the VISN 4 Mental Illness Research, Education and Clinical Center (MIRECC), VA Pittsburgh Healthcare System

866. Patients with Early-and Late-Onset Schizophrenia Show Grey Matter Volume Reductions of Different Brain Regions

Kazuteru Egashira[1], Koji Matsuo[1], Toshinari Mihara[2], Shuichi Yamauchi[3], Naofumi Matsunaga[3], Yoshifumi Watanabe[1]

[1]Psychiatry, Yamaguchi University, Ube, Japan,[2]Psychiatry, Wakamatsu Hospital, Okinawa, Japan,[3]Radiology, Yamaguchi University, Ube, Japan

Background: Manfred Bleular (1943) described late-onset schizophrenia (LOS) where illness onset is after age 40y. The different clinical characteristics between early-onset schizophrenia (EOS) and LOS are well documented. However, there are few neuroimaging studies concerning the affected brain mechanism between the two types of patients. We hypothesized that LOS and EOS patients would show volume reductions of different brain regions.
Methods: Twenty-five LOS and 30 EOS patients and 40 age- and sex- matched healthy subjects were studied. The mean±sd PANSS and SANS scores were 19.6±2.9 and 7.2±7.8 for LOS patients and 20.7±3.5 and 14.5±16.9 for EOS patients, respectively. Images were processed using a voxel based morphometry protocol. We compared the grey (GM) and white matter volumes among the three groups.
Results: The LOS patients showed smaller posterior cingulate GM volumes, and the EOS patients showed smaller superior lateral frontal gyrus, thalamus and parahippocampus GM volumes compared to the healthy subjects.
Conclusions: The results suggest that LOS and EOS may have a different brain pathophysiology.

867. Progressive Decrease of Right Prefrontal Cortex Gray Matter Volume in First-Episode Schizophrenia: A Longitudinal Magnetic Resonance Imaging Study

Toshiro Kawashima[1,2], Margaret Niznikiewicz[1], Motoaki Nakamura[1,2], Charlie Davidson[2], Dean F. Salisbury[1,3], Martha E. Shenton[1,2], Robert W. McCarley[1]

[1]Clinical Neuroscience Division, Laboratory of Neuroscience, Department of Psychiatry, Boston Veterans Affairs Healthcare System, Brockton Division, Harvard Medical School, Brockton, MA,[2]Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA,[3]Cognitive Neuroscience Laboratory, Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA

Background: The frontal lobes, and more specifically the prefrontal regions, have long been suspected to play an important role in the pathogenesis of schizophrenia. However, the findings of progressive prefrontal MRI grey matter volume reduction in first-episode schizophrenia have been inconsistent, possibly due to lack of gyral parcellation and a consequent inability to specify particular subcomponent regions that changed or did not change.
Methods: 1.5T MRIs were acquired from 17 first-episode (=first hospitalization) patients with schizophrenia (FESZ), 17 first-episode affective psychosis patients (FEAFF; bipolar disorder N=14, major depressive disorder N=3), and 17 healthy control subjects (HC) matched for age, gender, handedness, education, and socioeconomic status. Scans were repeated 1.5y later. Volumetric measurements of the grey matter in prefrontal regions were performed using 1.5mm thick coronal series of contiguous SPGR images. Anatomical criteria reliably (Intraclass correlation coefficients >0.94) guided parcellation of the prefrontal regions into four subcomponents (frontal pole, superior, middle, and inferior frontal gyrus).
Results: FESZ showed significant decreases in grey matter volume over time in the right frontal pole ($p < 0.030$) (5.70%) and, at trend level ($p < 0.057$), in the right superior frontal gyrus (3.39%). In contrast, no time-related changes were observed in FEAFF and HC. At initial scan, no significant group differences in grey matter volume in the four prefrontal subcomponents were found.
Conclusions: These findings suggest a right-biased progressive volume reduction in the frontal pole and superior frontal gyrus grey matter in FESZ in contrast to FEAFF and HC.
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868. Neurodevelopment in Adolescence and Young Adulthood (NAYA): Emotion Processing Impairment in Youths At-Risk for Psychosis

Christian G. Kohler, Monica E. Calkins, Karin E. Borgmann-Winter, Jan Richard, Noah Sasson, Colleen Brensinger, Ruben C. Gur, Raquel E. Gur

Neuropsychiatry, Univ. of PA, PHL, PA

Background: Neurodevelopmental abnormalities affecting behavior are present in children at-risk of developing psychosis long before the onset of illness. Cognitive abilities, including neurocognition and social cognition,

are extensively implicated in schizophrenia and may represent â€¨candidate endophenotypes. Impaired endophenotype performance in adolescents deemed at-risk for schizophrenia is a characteristic reflecting the endophenotypeâ€™s ability to serve as a marker for early identification and treatment. The primary purpose of the NAYA program is to combine endophenotype and prodromal risk strategies to further facilitate early identification of individuals at-risk for psychosis.

Methods: Youths (ages 14-25) completed a comprehensive diagnostic assessment and the University of Pennsylvania Computerized Neurocognitive Battery, which includes tests of emotion identification (ER40) and emotion differentiation (EmoDiff), and other studies. Groups included individuals deemed at-risk for psychosis [Genetic risk (GR): family history of schizophrenia, n=40; Clinical Risk (CR): prodromal symptoms but no family history, n=5]; schizophrenia (SZP): n=82; and healthy controls (CNT), n=89.

Results: On ER40, youths with SZP and those at-risk compared to CNT showed impairments in overall (SZP:p<001, at risk:p<.010), happy (SZP:p=020), sad (SZP:p=021), anger (SZP:p=005, at risk:p=.008) and fear (SZP:p=016, at risk:p=.05) identification. On EmoDiff, youths with SZP compared to CNT showed impairments in happy (p<.001)and sad (p=.037) differentiation, while performance of at-risk youth was intermediate.

Conclusions: Tests of emotion processing revealed that at-risk youth showed decreased performance similar to young persons with schizophrenia. Processing of facial affect may represent an endophenotypic marker and reflect pathophysiological abnormalities involved in the development of schizophrenia.

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869. "What" Versus "Where" in Patients with Schizophrenia: An Electrophysiological Investigation of Explicit Tasks of Dorsal and Ventral Pathway Auditory Processing

Victoria M. Leavitt[1,2], Sophie Molholm[2], John Foxe[1,2,3]

[1]Neuropsychology, CUNY-Queens College, Flushing, NY,[2]Cognitive Neurophysiology Laboratory, Nathan Kline Institute, Orangeburg, NY,[3]Psychiatry, St. Vincent's Psychiatric Hospital, Dublin, Ireland

Background: There is now an abundance of evidence for functionally and anatomically distinct auditory pathways governing sound localization and sound object recognition- the dorsal and ventral pathways. A recent study from our group implicated the existence of distinct dorsal and ventral auditory processing networks underlying the "what" and "where" functions in healthy controls. We conducted the present investigation to determine whether they can likewise be identified in patients with schizophrenia.

Methods: 168-channel electrophysiological recordings were collected from 12 controls and 6 patients as they completed tasks that distinguished dorsal (where) from ventral (what) auditory path functions. The 'where' task was to identify the location (1 of 7 speakers arranged on a 180-degree arc) from which an animal call was delivered. The 'what' task was to identify a target animal from seven randomly delivered animal calls. Participants were required to make a response immediately after each stimulus. Group averaged event-related potentials (ERPs) were analyzed for each condition.

Results: In controls, the data suggest that there are distinct dorsal and ventral auditory processing networks underlying "what" and "where" functions. When ERPs across speakers were collapsed and averaged, substantial differences between conditions are seen as early as the onset of the N1. Patients show statistically significant, though less striking, differences emerging at the N1.

Conclusions: Functional integrity of the dorsal and ventral auditory pathways in patients with schizophrenia may be compromised.

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870. Glucose Uptake and Anisotropy in the Anterior Cingulate in Schizophrenics and Normal Controls

Douglas S. Lehrer[1], Meicheng Chiang[1], Cemil Kirbas[2], Bin Wang[2], Holly Short[3], Mehdi Adineh[2], Monte S. Buchsbaum[4]

[1]Psychiatry, Wright State University Boonshoft School of Medicine, Dayton, OH,[2]Imaging Lab, Wallace-Kettering Neuroscience Institute, Kettering, OH,[3]Neuroscience, Cell Biology, & Physiology, Wright State University Boonshoft School of Medicine, Dayton, OH,[4]Psychiatry, Mt. Sinai School of Medicine, New York, NY

Background: Anterior cingulate abnormalities are implicated in schizophrenia. We report ^{18}F-fluorodeoxyglucose (FDG) distribution and anisotropy in gray/white matter in anterior cingulate Brodmann areas (BA) 23, 24, and 25.

Methods: We acquired FDG PET images in 27 psychotic individuals (24 schizophrenic, 3 schizoaffective; 24 never-medicated, 3 previously treated and not exposed to medications for at least 30 days) and in 17 matched controls. MRI diffusion tensor images (DTI) were also acquired in 24 of 27 ill subjects, and in 15 of 17 controls. Images were coregistered to MRI; gray/white matter pixels in BA 23, 24, 25 were identified using FSL segmentation and the Perry Atlas. We conducted ANOVA using diagnosis by hemisphere by BA by tissue (gray-white).

Results: Metabolism: There was a significant hemisphere-by-BA-by-tissue-by-diagnosis interaction (Huynh-Feldt adjusted p = 0.039), particularly resulting from lower glucose uptake by schizophrenics in BA 24. Anisotropy: Contrary to expectations, schizophrenic subjects showed higher anisotropy in the anterior cingulate (p = 0.019). We observed a significant negative correlation between FDG and anisotropy in BA 23 & 24 gray and white matter in the left hemisphere in normal subjects. This was observed in the left hemisphere of ill subjects, but only reached significance in gray matter.

Conclusions: We replicated previous reports of anterior cingulate hypometabolism within a cohort of predominantly treatment naïve subjects. The finding of increased anisotropy along with negative anisotropy-metabolism correlations may indicate failure in proper fanning of white matter cingulum fibers, a state that may be associated with reduced metabolism.

871. The Continuum of Psychotic Symptoms in a Population Based Study in Brazil

Alexandre A. Loch, Laura H. Andrade, Luis F. F. Tofoli, Bruno M. Coelho, Yuan-Pang Wang

Epidemiology Department, Psychiatry Institute - University of Sao Paulo, São Paulo, Brazil

Background: Psychotic symptoms are frequent in community samples. The perspective of considering psychotic symptoms as a continuum favors a framework towards etiologic search of complex mechanism underlying psychosis. This study aims to investigate the continuum of psychotic phenomena in a community sample in Brazil.

Methods: Data are from the Sao Paulo Catchment Area Study, a cross-sectional household survey with 1,464 subjects. Psychopathology was assessed through CIDI-1.1 interview. Seventeen psychotic-like symptoms were evaluated and classified as clinically relevant (CR), non-clinically relevant (NCR), secondary symptoms (SS) and symptoms with plausible explanation (PS).

Results: Although 1.9% of the total sample had an ICD-10 lifetime non-affective psychosis, the presence of any lifetime psychotic symptom was observed in 38.1%, with 7.3% classified as CR. The prevalence of psychotic symptoms increased to 50.9% in the subsample with any lifetime psychiatric diagnosis other than non-affective psychosis, being 14.1% CR. Those without any lifetime diagnosis, 31.7% presented at least one psychotic symptom, being 3.9% CR. Individuals with any psychiatric diagnosis were nine times more

likely to present CR delusion (OR: 9.3; 95% CI: 4.9-17.5), and around 4 time to report CR hallucination (OR: 3.8; 95% CI: 2.3-6.4), compared to those without any lifetime psychiatric diagnosis.
Conclusions: This data clearly points us that psychotic symptoms are widely present in the general population and also spread among all other psychiatric diagnoses other than psychotic diagnosis. The existence of a symptomatic continuum between subjects from the general population and subjects with clinical psychosis support the dimensional model of psychosis.

872. Cognitive Functioning in Childhood and Early Onset Psychotic and Depressive Symptoms in the 1970 British Birth Cohort

Valentin Matei[1], Abraham Reichenberg[2], Anthony S. David[2]

[1]Psychiatry, Lotus Medica, Bucharest, Romania,[2]Psychological Medicine, Institute of Psychiatry, King's College London, London, United Kingdom

Background: It is well established that as a group, individuals destined to develop schizophrenia have persistent cognitive impairments which are already evident in childhood. Because there is a paucity of information about the relationship between childhood cognitive functioning and later psychotic and depressive symptoms, we examined the relationship between early childhood cognitive functioning and late adolescence psychotic and depressive symptomatology.
Methods: A prospective cohort study (based on the 1970 British Cohort Study) which includes data about childhood (age 5) cognitive functioning and about presence of psychotic and depressive symptoms at age 16. 5,832 cohort members were included in the analysis. 23 cohort members reported psychotic symptoms that were confirmed by informants and independent sources, and 136 had confirmed depressive symptoms.
Results: Male adolescents with psychotic or depressive symptoms had lower age 5 IQ, and visual-constructional abilities compared to controls (all p values <0.05). Females did not show significant cognitive impairments at age 5.
Conclusions: Developmental abnormalities are common across depressive and psychotic symptoms. The gender specificity suggests differences in etiological processes between males and females.
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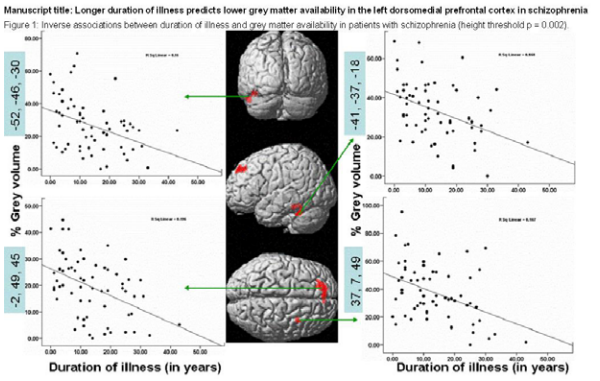
873. Longer Duration of Illness Predicts Lower Grey Matter Availability in the Left Dorsomedial Prefrontal Cortex in Schizophrenia

Preethi Premkumar[1], Dominic Fannon[2], Elizabeth Kuipers[1], Michael A. Cooke[1], Andrew Simmons[3,4], Veena Kumari[1]

[1]Psychology, Institute of Psychiatry, King's College London, London, United Kingdom,[2]Psychological Medicine, Institute of Psychiatry, King's College London, London, United Kingdom,[3]Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, London, United Kingdom,[4]South London and Maudsley Foundation NHS Trust, NIHR Biomedical Research Centre for Mental Health, London, United Kingdom

Background: The prefrontal cortex has an extended maturation period and may have a larger window of vulnerability to the long-term effects of schizophrenia. We tested this hypothesis by studying the relation between duration of illness and grey matter availability across the whole brain.
Methods: Sixty-four patients with schizophrenia and 33 healthy controls underwent structural MRI scanning. Participants also took part in a comprehensive neuropsychological and clinical assessment. Regression analyses were used to examine the relationship between duration of illness and grey matter availability across the whole brain. Correlational analyses examined the associations between duration of illness and neuropsychological performance and clinical symptoms.
Results: Longer duration of illness most strongly predicted lower grey matter availability in the left dorsomedial prefrontal cortex. Longer duration of illness also predicted lower grey matter availability in the right middle frontal gyrus, left fusiform gyrus and left cerebellum and was associated with poorer performance on both motor dexterity and sustained attention but not with symptoms.
Conclusions: Grey matter availability in the prefrontal cortex and cerebellum is associated with, and may be vulnerable to the persistence of schizophrenia illness.



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874. Cortical White Matter Diffusion Tensor Anisotropy in Schizophrenia

Jason S. Schneiderman[1], Joseph Friedman[1], Chelain R. Goodman[1], Randall E. Newmark[1], Yuliua Torosjan[1], Emily L. Camfield[1], Jonathan Enits[1], Karen Estefane[1], Vivian Mitropoulou[1], Cheuk Tang[2], Arash Hajianpour[2], Kenneth L. Davis[1], Jack Gorman[1], Monte S. Buchsbaum[1]

[1]Psychiatry, Mt Sinai School of Medicine, New York, NY,[2]Radiology, Mt Sinai School of Medicine, New York, NY

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.
Methods: 90 adults with schizophrenia and 103 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.
Results: Regions with low anisotropy in patients included Brodmann Areas 21, 22, 28 and 88 in the right temporal, and 21, 22, 27, 28, 41 and 42 in the left temporal. Regions with high anisotropy in patients included 4 in the right parietal, 32 in the right frontal, 37 in the right and left temporal, and 19 in the left occipital.
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.
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875. Premorbid Adjustment in First-Episode Schizophrenia Patients with and without Cannabis use Disorders

Serge Sevy[1], Delbert G. Robinson[1], Margaret G. Woerner[1], Barbara Napolitano[1], Raman C. Patel[2], Handan Gunduz-Bruce[3], Jose M. Soto-Perello[2], Alan Mendelowitz[1], Ali Khadivi[2], Rachel Miller[1], Joanne McCormack[1], Beth S. Lorell[2], Martin L. Lesser[4], Nina R. Schooler[5], John M. Kane[1]

[1]Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY,[2]Psychiatry, Bronx-Lebanon Hospital Center, Bronx, NY,[3]Psychiatry, Yale University School of Medicine, New Haven, CT,[4]Biostatistics, Feinstein Institute for Medical Research, Manhasset, NY,[5]Psychiatry, Georgetown University School of Medicine, Washington, DC

Background: Cannabis use disorders are common in first-episode schizophrenia patients and may be related to premorbid social, sexual, and scholastic adjustment factors. The purpose of this study is to assess these premorbid adjustment factors in first-episode patients with cannabis use disorders. Based on previous findings in multi-episode patients with schizophrenia and substance abuse, we hypothesized better premorbid social and sexual adjustments, but worse scholastic adjustment in first-episode patients with a lifetime history of cannabis use disorders compared to patients with no history of substance use disorders.

Methods: Forty-nine patients with first-episode schizophrenia and DSM-IV criteria for cannabis abuse or dependence were compared to 51 patients with first-episode schizophrenia and no substance use disorders for scores on the items of the Premorbid Adjustment Scale (Cannon-Spoor et al, 1982). Statistical significance was defined as $p<0.05$.

Results: Compared to patients without substance use disorders, patients with cannabis use disorders had better premorbid social adjustment in childhood and early adolescence, and better premorbid sexual adjustment in adolescence. In contrast, they had worse scholastic performance in early and late adolescence.

Conclusions: Compared to first-episode patients without substance use, first-episode patients with a lifetime history of cannabis use disorders had better premorbid social/sexual adjustments before the onset of cannabis use and psychotic symptoms. They had worse scholastic performance in adolescence, which may have been related to the onset of substance use during the same period. Multivariate analyses assessing the relationship between premorbid adjustment and cannabis use disorders will be explored.

Supported by NIMH60004; NIDA015541; N1MH41960; NCRR018535

876. Glutamate in the Medial Prefrontal Cortex of Chronic, Medicated Patients with Schizophrenia and Healthy Comparison Subjects Assessed with Proton MR Spectroscopy at 3 Tesla

Alexa J. Stern[1], Yan Zhang[2], Giacomo Salvadore[2], Antonina S. Savostyanova[1], Jose A. Apud[1], Jun Shen[2], Daniel R. Weinberger[1], Stefano Marenco[1]

[1]Clinical Brain DisordersBranch, GCAP, National Institute of Mental Health, Bethesda, MD,[2]Mood and Anxiety Disorders Program, National Institute of Mental Health, Bethesda, MD

Background: Emerging evidence suggests that glutamatergic dysfunction is implicated in the pathogenesis of schizophrenia. However, findings from magnetic resonance spectroscopic (^{1}H-MRS) studies are inconsistent and the majority of reports lack adequate spectral resolution to separate the glutamate (Glu) C4 proton signal from the overlapping glutamine, N-acetyl aspartate, glutathione and macromolecule signals. The present study was designed to measure Glu in the cortical gray matter and white matter of patients with schizophrenia and healthy adults. We hypothesized that, relative to healthy volunteers, patients would exhibit altered glutamate levels.

Methods: Single-voxel TE-averaged ^{1}H-MRS was performed on 15 medicated patients with schizophrenia and 27 age- and gender-matched healthy control subjects on a 3 Telsa General Electric scanner. Glu spectra were obtained in the medial prefrontal cortex (mPFC) and the right frontal (fWM) and/or parietal white matter (pWM) regions. Cre values were assessed independently with a separate PRESS sequence (TE=35 ms) in a subset of subjects.

Results: Glu/Cre was significantly reduced in the mPFC of patients with schizophrenia compared to healthy controls when including age as a covariate (ANCOVA, $p=0.027$). This difference was only marginally significant when both age and Cre were used as covariates in the model ($p=0.075$). No differences in Glu/Cre were observed in the fWM or pWM regions.

Conclusions: These preliminary findings are consistent with some literature reporting decreases in Glu in the cortical gray matter of chronic, medicated patients with schizophrenia, although larger sample sizes and possibly absolute quantification of metabolites will be necessary to interpret these data with confidence.

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877. Cortical Gray Matter Mapping during the Psychosis Prodrome

Daqiang Sun[1], Theo van Erp[1], Melita Daley[2], Carrie Bearden[1,2], Arsen Mkrtchyan[1], Molly Hardt[1], Alexandria Marino[1], Arthur Toga[3], Paul Thompson[3], Tyrone Cannon[1,2]

[1]Department of Psychology, UCLA, Los Angeles, CA,[2]Department of Psychiatry and Biobehavioral Sciences, UCLA, Los Angeles, CA,[3]Laboratory of Neuro Imaging and Department of Neurology, UCLA, Los Angeles, CA

Background: Deficits in brain structure volumes may predate the onset of schizophrenia and other psychotic disorders. Structural MRI studies have shown that patients who later converted to psychosis had smaller gray matter volumes during the prodromal phase of illness compared with those who did not develop psychosis, but a detailed mapping of cortical gray matter in these pre-onset individuals is still lacking.

Methods: High-resolution 3D brain MRI scans were acquired from 34 participants who were at ultra-high risk for psychosis, of whom 7 (5 males and 2 females, aged 18.5±4.7 years) later converted to psychosis, while the other 27 (19 males and 8 females, aged 17.2±3.0) did not, after 12 months of follow-up. We compared gray matter density (GMD) across the cerebral cortex, at baseline, in converters versus non-converters. A cortical pattern matching method was applied to the brain images, aligning brain surfaces based on manually traced major sulcal landmarks. Group averaged maps of cortical gray matter distribution were visualized on 3D cortical surface models.

Results: Compared to non-converters, converters showed significantly reduced gray matter in widespread cortical areas, including bilateral dorsal frontal and superior temporal regions. A weighted multi-voxel summation of GMD for the voxels that showed significant group differences was able to differentiate the majority of the converters from the non-converters.

Conclusions: Cortical gray matter deficits in brain regions critical for integrated cognitive activity therefore predates the onset of psychosis, suggesting that detailed cortical gray matter mapping may be useful in predicting the future onset of psychosis.

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878. Psychotic Hyperactivity of the Prefrontal Cortex with Deficits in GABAergic Inhibition

Shoji Tanaka

Dept of Information and Communication Sciences, Sophia University, Tokyo, Japan

Background: Psychotic states are associated with hyperactivity of the prefrontal cortex (PFC) with hyperdopaminergic neurotransmission. GABAergic inhibition in the PFC has been reported to be reduced in schizophrenia.
Methods: A circuit model of the PFC is constructed, which describes dopaminergic modulation of neuronal activity in addition to glutamate and GABA neurotransmission. The GABAergic inhibition in the PFC has two different types in this model, which are chandelier cell-type inhibition with high activation threshold and general inhibition by other GABAergic interneurons.
Results: The PFC circuit has a bistable hyperactive mode (termed the 'H mode'). This hyperactivity is characterized by hyperdopaminergic neurotransmission. Transition to the H mode from a normal state occurs when GABAergic inhibition is reduced. The results of the computer simulation with the above model show that the roles of the two different types of GABAergic inhibition on PFC circuit dynamics are markedly different: The inhibition by the GABAergic interneurons other than chandelier cells effectively regulates the PFC activity with rather low or modest levels of dopaminergic transmission, which has an inverted-U shaped profile of dopaminergic modulation and is associated with normal cognitive functions. In contrast, chandelier cell-type inhibition regulates only the PFC activity with hyperdopaminergic neurotransmission.
Conclusions: Deficits in effective inhibition by chandelier cells in the PFC would produce the H mode, a "psychotic" hyperactive state with hyperdopaminergic neurotransmission. Weakening of other GABAergic interneurons would make the transition to the H mode more readily occur, thereby increasing the vulnerability to psychosis.
Supported by Sophia University Open Research Center

879. Gamma Band Abnormalities in Schizophrenia and Bipolar Disorder during an Auditory Oddball Task

Grantley Taylor[1], Dean Salisbury[2], Robert McCarley[3]

[1]Psychiatry, McLean Hospital; Harvard Med. School, Belmont, MA,[2]Cognitive Neuroscience Laboratory, McLean Hospital; Harvard Med. School, Belmont, MA,[3]Psychiatry, VA Boston Healthcare System, Brockton, MA

Background: EEG synchronization in the gamma frequency range may index local and distributed neural network activity and associated cognitive activity. Cognitive dysfunction in schizophrenia likely reflects impairments in the dynamic formation of neural ensembles. Abnormalities of gamma synchronization have been noted in several experiments. The auditory oddball task allows probing of sensory processing, selective attention, and working memory, all of which have been implicated in schizophrenia. Abnormalities in P300 ERPs have been described in both schizophrenia and bipolar disorder.
Methods: Twenty seven control subjects, twenty two patients with first episode bipolar disorder, and eighteen first episode schizophrenia patients matched for age, sex, parental SES, and WAIS-R information score performed an auditory oddball task (1 kHz, 85%, 1.2 kHz 15%, 50 msec, 75 dB). Wavelet analysis of 61 channel EEG allowed measurement of intertrial phase locking and evoked power in the gamma range (45-53Hz).
Results: Controls showed a greater PLV (phase locking value) in the 50-80 msec gamma band response (GBR) to standard tones compared to both patient groups. By contrast both controls and bipolar psychotic individuals showed greater evoked power 275-325 msec following targets in the gamma range than individuals with schizophrenia.
Conclusions: Both Schizophrenia and psychotic bipolar subjects showed reduced early PLV deficits in the local GBR. Schizophrenic individuals showed a different pattern of gamma band response compared to both controls and individuals with affective psychosis, especially in the 300 msec interval, likely indexing the working memory and selective attention components giving rise to P300.
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880. Quantitative Examination of a Novel Clustering Method using Magnetic Resonance Diffusion Tensor Tractography

Aristotle Voineskos[1,2], Lauren O'Donnell[3], Nancy Lobaugh[4], Doug Markant[2], Marc Niethammer[2], Benoit Mulsant[1], Bruce Pollock[1], Carl Frederik Westin[3], Martha Shenton[2]

[1]Psychiatry; Geriatric Mental Health Program, University of Toronto, Toronto, ON, Canada,[2]Psychiatry Neuroimaging Lab; Brigham and Women's Hospital, Harvard Medical School, Boston, MA,[3]Surgical Planning Lab; Brigham and Women's Hospital, Harvard Medical School, Boston, MA,[4]Neurology; Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada

Background: Magnetic resonance diffusion tensor imaging (DTI) is currently the only way to visualize the organization of white matter fiber tracts in vivo using DTI tractography. In this study, we examine scalar indices of the diffusion tensor with two different methods that use whole brain tractography: a novel clustering approach and a multiple region of interest (MROI) approach.
Methods: Twelve participants (schizophrenia: 58 ± 12 years, n=6; controls: 57 ± 21 years, n=6) were studied. DTI images were acquired on a 1.5 Tesla GE system with diffusion gradients applied in 23 non-collinear directions with 2.6 mm isotropic voxels with the acquisition repeated three times. Tractography and fiber tract creation was performed using 3D Slicer software. The uncinate and inferior occipito-frontal fasciculi, genu of corpus callosum, and cingulum bundle were compared.
Results: Fractional anisotropy (FA) and trace values were highly correlated between the clustering and MROI methods ($p<0.001$ all tracts). Additionally, an analysis using paired t tests showed no difference in measurements of FA or trace for any tract between each method (no $p<0.05$). There was good spatial agreement between the two methods measured using the k criterion of Landis and Koch (1977).
Conclusions: Overall there is a high level of agreement between our clustering method and the MROI method both quantitatively and spatially. The clustering method is less susceptible to user bias and is an efficient method for studies examining multiple tracts. Therefore, the clustering method is a viable alternative to the MROI method with advantages in specific circumstances.

881. A fMRI Study on the Effects of the Nicotine Patch on Brain Activation during Finger Tapping

Narin Wongngamnit[1], Laura F. Martin[1,2], Jason R. Tregellas[1,2], Jody L. Tanabe[1,3]

[1]Department of Psychiatry, University of Colorado Denver, Denver, CO,[2]Research Service, VA Eastern Healthcare System, Denver, CO,[3]Radiology, University of Colorado at Denver, Denver, CO

Background: Nicotine increases finger tapping (FT) rates in both healthy individuals and individuals with schizophrenia. The neurobiological effects of nicotine on cortical activity during FT have not been studied. We hypothesize that nicotine will not alter the sensorimotor cortex (SMC) activity patterns associated with finger tapping in healthy individuals when the behavioral rate of tapping is fixed.
Methods: This is a single-blind crossover trial of twelve non-smoking, right-handed subjects performing a paced FT task one hour after placement of a 7mg nicotine or placebo patch. FT consisted of pressing a response box with the right index finger in response to auditory cues at rates of 1 hz, 2hz and 4 hz during 20 second blocks. fMRI data were acquired using BOLD contrast technique in a 3T

MR scanner. Images were processed and analyzed using SPM2.
Results: The FT task elicited contralateral SMC and supplementary motor cortex activity. SMC activity increased with increasing FT rate. There were no effects of nicotine administration on SMC or SMA activation patterns. However, at a tapping rate of four Hz, nicotine was associated with greater temporal and reduced prefrontal cortical activity.
Conclusions: Our finding of increasing activity in SMC with increasing FT rate is consistent with prior work and is a potential confounding factor in pharmacological studies of FT. Nicotine did not affect SMC activity as we hypothesized; however, it did affect areas involved with the cognitive modulation of FT. Future studies will examine the effects of nicotine on FT in individuals with schizophrenia.
Supported by VA Research Service

882. Risperidone Long Acting Injection Treatment in Schizophrenia: 12-Month Results from the Electronic Schizophrenia Treatment Adherence Registry (E-STAR)

A. Alexandrov[1], Jose Olivares[2], Ivan Tuma[3], Jos Peuskens[4], Jan Pecenak[5], Lars Eriksson[6], B. Bork[7], Michael Povey[8], Annette Lam[9], Kostas Trakas[10], Zhongyun Zhao[10]

[1]De Zwolse Poort, Acute psychiatrie, Raalte, The Netherlands,[2]Hospital Meixoeiro Complejo, Hospitalario Universitario de Vigo, Vigo, Spain,[3]Medical School and Teaching Hospital Hradec Kralove, Charles University in Prague, Hradec Kralov, Czech Republic,[4]KU Leuven campus UC St. Jozef Kortenberg, Universitair Psychiatrisch Centrum, Kortenberg, Belgium,[5]Psychiatry, FNSP Bratislava, Bratislava, Slovakia,[6]Psychiatry, SU/Östra RPV, Hisings-Backa, Sweden,[7]Psychiatry, DP Tønder, Tønder, Denmark,[8]Statistics, SGS Life Science Services, Wavre, Belgium,[9]Health Economics, Johnson & Johnson Pharmaceutical Services, Toronto, ON, Canada,[10]Health Economics, Johnson & Johnson Pharmaceutical Services, Raritan, NJ

Background: To assess 12-month clinical and functioning outcomes of risperidone long-acting injection (RLAI) treatment in patients enrolled in the electronic-Schizophrenia Treatment Adherence Registry (e-STAR) from Belgium, Czech Republic, Denmark, Netherlands, Slovakia, Spain, Sweden.
Methods: e-STAR is an international, long-term, prospective, observational study of patients with schizophrenia who commence RLAI treatment. Data are collected retrospectively for 1 year and prospectively every 3 months for 2 years. Clinical outcomes measured by Clinical Global Impression-Severity (CGI-S) scale & patient functioning assessed by Global Assessment of Functioning (GAF) scale. Results are based on data from patients who have completed their 12-month follow-up visit.
Results: To date, 4,196 patients enrolled in e-STAR from the 7 European countries, 2,239 patients with at least 12-months of data available were included in this interim analysis. 61.8% were male with mean age of 38.7±12.0 years and mean time since diagnosis of 11.2±10.7 years. At 12 months, 89.7% of patients still continued on RLAI. Most frequent reasons for switching to RLAI were lack of compliance (36.4%) and lack of efficacy (28.9%) with previous therapy. Mean CGI-S score significantly decreased from 4.58±1.01 at baseline to 3.40±1.03 at 12 months ($p<0.001$). Percent patients with not ill/very mild/mild illness increased from 12.2% to 52.7% and with marked/severe/extremely severe decreased from 51.7% to 12.4% ($p<0.001$). Mean GAF score improved significantly from 47.8±14.9 at baseline to 63.8±15.7 at 12 months ($p<0.001$).
Conclusions: This 12-month interim data from seven European countries show that schizophrenia patients initiated on RLAI experienced significant improvements in disease severity and functioning.
Supported by Johnson & Johnson

883. Pooled Analysis Comparing Non-High Density Lipoprotein in Patients with Schizophrenia Randomized to Aripiprazole or Olanzapine (Studies CN138-002, -003, -047ext)

Jonathan M. Meyer[1], Trixia A. Camacho[2], **Ross A. Baker**[2], James Eudicone[2], Andrei Pikalov[3], Estelle Vester-Blokland[2], Robert D. McQuade[4], Gilbert J. L'Italien[5,6], John W. Newcomer[7]

[1]University of California, Department of Psychiatry, San Diego, CA,[2]Bristol-Myers Squibb, 777 Scudders Mill Rd, Plainsboro, NJ,[3]Otsuka America Pharmaceutical, Inc., 2440 Research Boulevard, Rockville, MD,[4]Otsuka Pharmaceutical Development & Commercialization, Inc., 100 Overlook Drive, Princeton, NJ,[5]Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT,[6]Yale University Medical School, 333 Cedar Street, New Haven, CT,[7]Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO

Background: CVD is the leading cause of death in patients with schizophrenia, partially related to underutilization of primary and secondary prevention.[1] Given the absence of non-HDL-C data in antipsychotic studies and the growing interest in CVD risk prevention in patients with mental illness, we quantified the change in non-HDL-C, a significant predictor of CVD,[2] in a pooled analysis of clinical trials assessing aripiprazole versus olanzapine.
Methods: Exploratory pooled post-hoc analysis of three trials compared olanzapine to aripiprazole in schizophrenia patients: one randomized, double-blind, 26-week (CN138-002), one randomized, double-blind, 52-week (CN138-003), and one 52-week, open-label trial (CN138-047ext). Non-HDL-C was calculated as Total Cholesterol minus HDL-C from data collected at weeks 6, 12, 26 and 52. Statistical comparisons were made using ANOVA with LOCF.
Results: Compared with baseline, there was a significant decrease in mean non-HDL-C at all time points ($p<0.001$) in aripiprazole patients, while olanzapine patients experienced a significant increase in mean non-HDL-C at all time points ($p<0.001$). The mean change in non-HDL-C in aripiprazole versus olanzapine patients was statistically significant as early as week 6 (-16.1 mg/dL and +10.4 mg/dL, respectively) and was maintained at weeks 12, 26, and 52 ($p<0.001$, all time points).
Conclusions: The early and sustained improvement in non-HDL-C for aripiprazole patients versus the relative worsening observed for olanzapine patients suggest that antipsychotic treatment can influence an important risk predictor for CVD. These results further support the need to understand long-term health implications when initiating or changing antipsychotic therapy.
[1]Newcomer. JAMA. 2007;298:1794-1796.
[2]Liu. AJC. 2006;98:1363-1368.
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884. A Comparison of Effects of Clozapine (CLZ) and Typical Neuroleptics (TYP) on Psychopathology, Tolerability and Functional Capacity in Neuroleptic-Responsive Schizophrenia (SCH) and Schizoaffective Disorder (SCHAD)

William V. Bobo, Herbert Y. Meltzer, Myung A. Lee, Philip Cola, Karuna Jayathilake

Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, TN

Background: Due to risk of agranulocytosis, clozapine has been restricted to treatment-resistant cases of SCH. However, considering other therapeutic advantages of clozapine (decreased suicidality, improvement in cognitive

function) it is of interest to assess clozapine's risks and benefits in neuroleptic-responsive SCH.
Methods: This was a randomized, masked trial of two years duration involving 85 early psychosis patients (CLZ n = 40; TYP n = 45) who met DSM-IV criteria for SCH or SCHAD and had a history of positive response to neuroleptic treatment. Assessments of psychopathology (using BPRS total and subscales, SAPS and SANS), quality of life (using the Quality of Life Scale [QOL]), and tolerability (BARS, AIMS) were obtained at baseline, 6 weeks, and 6, 12, and 24 months. Groups were also compared on relapse/rehsopitalization, study drop-out, and cost of treatment.
Results: Both treatments produced non-significantly different improvement in psychopathology, as assessed with the Brief Psychiatric Rating Scale (BPRS) and its subscales. However, more relapse/rehospitalization and drop-outs occurred in the typical neuroleptic-treated compared to the clozapine-treated patients. In addition, two patients treated with typical neuroleptics, but none treated with clozapine, became non-responsive to their treatment. The only difference in tolerability of the two treatments was significantly greater weight gain in the clozapine-treated group compared to the typical neuroleptic group.
Conclusions: Clozapine may not provide comparatively greater improvements in psychopathology than typical antipsychotics among patients with early SCH and a history of positive response to neuroleptic treatment, but may be more effective in preventing relapse during long term treatment.
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885. Structural Neural Markers of Short-Term Clinical Outcome in First Episode Psychosis: A Voxel-Based Morphometry Study

Michael Bodnar, Philippe-Olivier Harvey, Ashok Malla, Ridha Joober, Martin Lepage

Clinical Division, Douglas Mental Health University Institute, Verdun, QC, Canada

Background: Outcome from psychotic disorders is heterogeneous with poorer outcomes frequently identified too late to be influenced. Reduced putamen and temporal lobe volumes along with increased ventricular volumes have been related to poor long-term clinical outcome; however, no neural correlates for short-term clinical outcome have been reported.
Methods: Using optimised voxel-based morphometry (VBM) methods, we set out to identify specific neural correlates of poor response in first episode of psychosis (FEP) patients at the start of a specialised treatment program. The present study included 51 FEP patients, divided into two groups (29 non-responders, 22 responders) based on their therapeutic response (no or mild symptoms) six months after the initiation of treatment, along with 27 matched healthy controls.
Results: Non-responders had significantly smaller volumes in the bi-lateral superior frontal gyrii, bi-lateral inferior and middle temporal gyrii, and left occipital cortex compared to responders.
Conclusions: These findings suggest that specific neural correlates of not responding to treatment by six-months are present at the beginning of the treatment process in FEP patients. The affected areas may relate to visual and verbal processing deficits and to cognitive deficits of memory and executive functions that have been reported in psychotic disorders, which, in turn, negatively affect short-term outcome. The early identification of treatment non-response may encourage alternative treatments and/or the search for new medications in order to improve outcome.

Grey Matter Deficits in Non-Responders vs. Responders

Region	BA	Coordinates (x y z)			t-value	Cluster Size
Frontal						
L Superior Gyrus	10	15	66	-8	3.95	518
R Superior Gyrus	10	-13	68	-8	3.85	218
L Insula	13	-41	-16	0	3.68	264
Temporal						
R Inferior Gyrus	37	57	-56	-5	3.91	
R Middle Gyrus	21	66	-45	-6	3.55	1919
R Superior Gyrus	22	66	-42	6	3.62	
L Inferior Gyrus	37	-59	-51	-9	3.85	
L Middle Gyrus	21	-66	-44	-7	4.25	1066
L Fusiform Gyrus	20	-49	-32	-24	3.67	109
Occipital						
L Cuneus	17	-18	-91	3	4.62	
L Middle Gyrus	18	-18	-95	17	4.50	13932
	18	-29	-88	2	4.50	

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886. Remission in Schizophrenia and Patient-Relevant Outcomes: Findings from Three Studies

Cynthia Bossie, CV Damaraju, Young Zhu, John Verbanac, Wayne Macfadden

N/A, Ortho-McNeil Janssen Scientific Affairs, L.L.C., Titusville, NJ

Background: Remission criteria in schizophrenia include symptom severity (absent-mild ratings on core symptoms) and duration (≥6 consecutive months). We hypothesized that the duration component is required for improvement in patient-relevant outcomes.
Methods: Post-hoc analyses of three 1-year studies of schizophrenia patients assessed remission by the Positive and Negative Syndrome Scale. Mutually exclusive populations were defined: meeting symptom severity and duration criteria (≥6-month remitters); meeting symptom severity but not duration criteria (severity remitters); never meeting symptom severity criteria (nonremitters). Measures: Short-Form Health Survey (SF-36) functioning domains (study 1, N=633), Strauss Carpenter Levels of Functioning (LOF) and/or Personal and Social Performance (PSP) scale (study 2, N=316; study 3, N=235). ANCOVA assessed change scores.
Results: Study 1: ≥6-month remitters improved significantly more on SF-36 domains of social functioning, role-emotional and role-physical than severity remitters (mean[SE] difference in change scores: 13.3[2.4];16.6[3.9]; 9.8[3.7], respectively) and nonremitters (17.9[2.4];16.9[3.9];14.2[3.7], respectively) (all $P<0.01$). Severity remitters showed no significant improvement vs nonremitters on these domains.
Study 2: ≥6-month remitters, but not severity remitters, improved significantly more than nonremitters on LOF domains of quality and quantity of useful work (mean[SE] difference in change scores:1.3[0.6]), frequency and quality of social contacts (1.2[0.4]) and fullness of life (0.4[0.1]) (all $P<0.05$).
Studies 2 and 3: ≥6-month remitters and severity remitters improved significantly more than nonremitters on PSP total score ($P<0.05$). However, ≥6-month remitters improved significantly more than severity remitters ($P<0.05$).
Conclusions: Remission for ≥6 months is important for improvement in patient-relevant outcomes.
Supported by Ortho-McNeil Janssen Scientific Affairs, L.L.C.

887. A Double-Blind Placebo-Controlled Trial Comparing Paliperidone ER and Quetiapine in Patients with a Recent Acute Exacerbation of Schizophrenia

Carla Canuso[1], Jennifer Carothers[1], Bryan Dirks[2], Young Zhu[1], Colette Kosik-Gonzalez[1]

[1]Ortho-McNeil Janssen, Scientific Affairs, L.L.C., Titusville, NJ,[2]At the time of this analysis, was an employee of Ortho-McNeil Janssen Scientific Affairs, L.L.C., Titusville, NJ

Background: This analysis compared paliperidone extended-release (ER) and quetiapine monotherapy in schizophrenia patients with a recent acute exacerbation requiring hospitalization.
Methods: International, 6-week, double-blind study randomized recently and acutely exacerbated schizophrenia inpatients to paliperidone ER, quetiapine or placebo. A 2-week monotherapy was followed by a 4-week additive-therapy phase. Target doses: 9 or 12 mg/day paliperidone ER and 600 or 800 mg/day quetiapine. Outcomes: Positive and Negative Syndrome Scale (PANSS) and adverse events (AEs). Primary endpoint: PANSS total change score from baseline to monotherapy endpoint for paliperidone ER vs quetiapine.
Results: Preliminary data on 399 patients are presented; 78% on paliperidone ER, 67% on quetiapine and 64% on placebo completed. Significant improvement was observed with paliperidone ER vs quetiapine in mean[SE] PANSS total change score from day 5 (-11.4[1.1] vs -8.2[1.1]; P=0.011) through 2-week monotherapy endpoint (-23.4[1.8] vs -17.1[1.8]; P<0.001). Paliperidone ER, not quetiapine, showed significantly greater improvement vs placebo on PANSS total score. At 6-week study endpoint, paliperidone ER showed significant improvement vs quetiapine in mean[SE] PANSS total change score (-31.2[1.9] vs -26.6[1.9]; P=0.023). Most common AEs at monotherapy endpoint for paliperidone ER, quetiapine and placebo, respectively: tremor (14%, 5%, 8%), somnolence (9%, 12%, 1%), insomnia (10%, 9%, 11%) and headache (12%, 8%, 14%). Discontinuations due to AEs at 6-week study endpoint for paliperidone ER, quetiapine and placebo, respectively: 4%, 10%, 6%.
Conclusions: Paliperidone ER exhibited greater short-term efficacy than quetiapine for treating a recent acute schizophrenia exacerbation requiring hospitalization.
Supported by Ortho-McNeil Janssen Scientific Affairs, L.L.C.

888. Early Onset of Antipsychotic Action in Schizophrenia: A Clinical Marker Discriminating Active Drug from Placebo

Bruce J. Kinon[1], **Lei Chen**[1], Jennifer Sniadecki[1], Haya Ascher-Svanum[1], Virginia Stauffer[1], Sara Kollack-Walker[1], Shitij Kapur[2]

[1]Neuroscience, Eli Lilly and Company, Indianapolis, IN,[2]Institute of Psychiatry, King's College of London, London, United Kingdom

Background: The objectives of this analysis were to determine if: a) early non-response is predictive of subsequent non-response in patients treated with placebo, b) early non-response discriminates placebo from active drug, and c) the difference observed early in treatment is sustainable at subsequent timepoints.
Methods: A post-hoc, pooled analysis of 2 randomized, clinical trials was performed comparing patients treated with placebo or low dose olanzapine (1 mg/day) (placebo/low dose, PBO group, n=170) to patients treated with haloperidol (10-20 mg/day) or olanzapine (7.5-17.5 mg/day) (active drug, AD group, n=252). Psychopathology was assessed with Brief Psychiatric Rating Scale (BPRS). Early improvement at 2 weeks was defined as at least 25% reduction in BPRS total score (minimal improvement). Subsequent response at 6 weeks was defined as at least 40% improvement in BPRS total score.
Results: Based on 25% improvement in BPRS total score at 2 weeks, 71% of PBO patients were early non-responders while 48% of AD patients met criterion of early non-response. Early non-response was predictive of subsequent non-response in both the PBO (Negative Predictive Value, NPV=95%) and AD (NPV=84%) groups. At 2 weeks, the reduction in BPRS total score was significantly greater for AD group (LS mean=25.5%) compared to PBO group (LS mean=10.3%), and a significant between group difference was observed at every subsequent timepoint up to 6-weeks.
Conclusions: These findings suggest that early response/non-response may serve as a clinical marker of subsequent clinical improvement.
Supported by Eli Lilly and Company

889. Optimal Thresholds of Early Non-response to Atypical Antipsychotics: Application of Signal Detection Analysis

Lei Chen, Haya Ascher-Svanum, Virginia Stauffer, Bruce J. Kinon, Oladapo Tomori, Sara Kollack-Walker

Neuroscience, Eli Lilly and Company, Indianapolis, IN

Background: This study used signal detection methods to identify the optimal magnitude of early non-response to antipsychotic medication at various early time points that best predicts subsequent non-response at 8 weeks, using different criteria of subsequent non-response.
Methods: Data were pooled from 5 randomized, double-blind clinical trials of atypical antipsychotics in the treatment of patients with schizophrenia-related disorder, and included 1437 patients (n=1137 with at least moderate symptom severity; n=300 with lesser symptom severity). Signal detection methods were used to identify the optimal response threshold based on improvement from baseline on the Positive and Negative Syndrome Scale (PANSS) total score at different early time points (Week 1 to Week 4 of treatment) to predict subsequent non-response at 8 weeks, while controlling false positive rate at ≤30%.
Results: The optimal thresholds for patients with at least moderate symptom severity were 7-12% at Week 1, 14-23% at Week 2, 20-38% at Week 3, and 26-45% at Week 4. For patients with lesser symptom severity, the optimal thresholds were 3-4% at Week 1, 7-12% at Week 2, 6-14% at Week 3, and 15-20% at Week 4. Results were validated using data from another clinical trial.
Conclusions: For schizophrenia patients with at least moderate symptom severity, lack of at least 14-23% improvement on the PANSS total score at 2 weeks is an optimal predictor of subsequent non-response following 8 weeks of treatment. This early response threshold appears to be an important clinical marker of subsequent non-response to antipsychotic therapy.
Supported by Eli Lilly and Company

890. The Metabolic Profile of Iloperidone: Summary of Phase III Schizophrenia Trials

Andrew J. Cutler[1], John Feeney[2]

[1]Department of Psychiatry, University of Florida, Maitland, FL,[2]Clinical Affairs, Vanda Pharmaceuticals, Rockville, MD

Background: Many atypical antipsychotics are associated with adverse effects on metabolic parameters that may increase diabetes and cardiovascular risk. Iloperidone is a mixed D_2/5-HT_2 antagonist for the treatment of schizophrenia. Body weight, blood glucose, cholesterol, triglyceride, and prolactin level changes were assessed in a pooled analysis.
Methods: Four 4- to 6-week, phase III, double-blind, placebo-controlled trials of adults with schizophrenia were included in the analysis. Changes in weight and metabolic parameters were evaluated.
Results: A total of 2505 patients (iloperidone 4-24 mg/day, n=1344; haloperidol 5-20 mg/day, n=118; risperidone 4-8 mg/day, n=306; ziprasidone 160 mg/day,

n=150; placebo, n=587) were included. In iloperidone, haloperidol, risperidone, ziprasidone, and placebo (I/H/R/Z/P) groups, mean changes from baseline to endpoint in body weight were +2.0,-0.1,+1.5, +1.1, and -0.1 kg, respectively, and the rates of meaningful weight gain (defined as ≥7% increase) from baseline to endpoint were 13.5%, 5.1%, 11.9%, 5.4%, and 4.3%. In I/H/R/Z/P groups, respective mean changes at endpoint in blood glucose levels were +9.0, +14.4, +1.8, +9.0, and 0.0 mg/dL. In I/H/R/Z/P groups, mean changes at endpoint in total cholesterol were 0.0, +3.9, -3.9, +3.9, and -7.7 mg/dL, and mean changes at endpoint in triglycerides were -17.7, -8.8, -26.5, +8.8, and -26.5 mg/dL. In I/H/R/Z/P groups, respective mean changes at endpoint in prolactin levels were -19.2, +133.0, +203.5, +2.0, and -40.9 µg/L.
Conclusions: Pooled analysis results indicate that iloperidone has a favorable short-term metabolic profile, with values similar to or better than the comparator antipsychotics used in these clinical trials.
Supported by Vanda Pharmaceuticals

891. Exploring SNPs of the Neuropeptide Y and Acetyl-Coenzyme A Carboxylase α and ß Genes that may be Associated with the Direct Effects of some Antipsychotics on Lipid Levels

Jose de Leon[1], Alexander Meary[2], Maria J. Arranz[2], Francisco J. Diaz[3]

[1]Psychiatry, University of Kentucky, Lexington, KY,[2]Psychological Medicine, Institute of Psychiatry – King's College, London, United Kingdom,[3]Department of Statistics, Universidad Nacional, Medellin, Colombia

Background: Antipsychotics may cause hyperlipidemia (hypertriglyceridemia or hypercholesterolemia) through two possible mechanisms: (1) an indirect mechanism, associated with weight gain, that leads to obesity; and (2) a direct mechanism by which some antipsychotics (particularly clozapine, olanzapine, and phenothiazines) can directly cause hyperlipidemia. Mirtazapine may also increase lipids.
Methods: In a sample of 357 patients taking antipsychotics, the acetyl-coenzyme A carboxylase α, ACCα SNP (rs4072032) was significantly associated with a hypertriglyceridemia model. The neuropeptide Y, NPY (rs1468271) and ACCß, (rs2241220) were significant in the hypercholesterolemia model. The goal of this study was to further explore other SNPs in these genes that may be associated with direct effects of some antipsychotics on hyperlipidemia. From a published cross-sectional sample, 357 patients on antipsychotics were genotyped for the 8 additional ACCα SNPs (rs1266175; rs7208415; rs725038; rs9906543; rs4794750; rs12453407; rs4795194; and rs11650168), 7 additional ACCß SNPs (rs741402; rs2268391; rs2268387; rs2239608; rs3742026; rs7974040; and rs2268384); and 3 additional NPY SNPs (rs16145; rs16478; and rs16141). A total of 173 patients were taking olanzapine, quetiapine, chlorpromazine or mirtazapine which may directly cause hypertriglyceridemia or hypercholesterolemia. Another 184 patients taking other antipsychotics were controls.
Results: This extension of a prior analysis of these genes uses more systematic SNP assessments and haplotypes. These analyses reflect gene function better than prior analyses, which better establishes that these genetic variations may be associated with direct effects (not explained by obesity) of some antipsychotics on hyperlipidemia.
Conclusions: These SNPs and haplotypes need to be studied in other samples.
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892. Safety and Efficacy of Ziprasidone in Pediatric Bipolar Disorder

Melissa P. DelBello[1], Robert L. Findling[2], Paul P. Wang[3], Balarama Gundapaneni[3], Mark Versavel[3]

[1]Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati, OH,[2]Psychiatry, Case Western Reserve University, Cleveland, OH,[3]Global Research and Development, Pfizer Inc, Groton, CT

Background: We conducted this study to evaluate the efficacy and safety of oral ziprasidone in children and adolescents with bipolar I disorder.
Methods: A 4-week, double-blind, placebo-controlled multicenter study of ziprasidone in subjects aged 10 -17 years with bipolar I disorder (manic or mixed). Subjects were randomized in a 2:1 ratio to flexible-dose ziprasidone (80-160 mg/d) or placebo, titrated over 1 to 2 weeks; treatment duration was 4 weeks. The primary and key secondary outcome measures were the change from baseline to end point in YMRS total and CGI-S scores, respectively. Safety assessments included treatment-emergent AEs, vital signs, laboratory measures, ECGs, and movement disorder scales
Results: 150 subjects were randomized to ziprasidone and 88 to placebo. In the ITT population, the estimated least squares (LS) mean changes from baseline to end point in YMRS total score were -13.83 (ziprasidone) and -8.61 (placebo; p=0.0005); a significant difference was also confirmed in the per-protocol population (p=0.0004). The estimated LS mean changes from baseline to end point for CGI-S score in the ITT population were -1.43 (ziprasidone) and -0.74 (placebo; p=0.0001). The most commonly reported AEs in the ziprasidone group were sedation (22%), somnolence (25%), nausea (13%), fatigue (13%), and dizziness (11%). No changes in mean BMI z scores, lipids, liver enzymes, or glucose levels were observed. QT prolongation ≥460 msec was reported in 1 (0.7%) ziprasidone-treated subject.
Conclusions: These results suggest that ziprasidone is effective and generally well tolerated for the acute treatment of mania in children and adolescents with bipolar disorder.
Supported by Pfizer Inc.

893. Atypical Antipsychotic Drugs and Diabetes Mellitus in the US FDA Adverse Event Reporting System (AERS) Database in Pediatric and Adult Patients

P. Murali Doraiswamy[1], Ramin A. Arani[2], David Gan[2], Andrei Pikalov[3], Quynh-Van Tran[3], Raymond Mankoski[4], Ross A. Baker[4]

[1]Departments of Psychiatry and Medicine, Duke University Medical Center, Durham, NC,[2]Bristol-Myers Squibb, 311 Pennington-Rocky Hill Road, Hopewell, NJ,[3]Otsuka America Pharmaceutical, Inc., 2440 Research Boulevard, Rockville, MD,[4]Bristol-Myers Squibb, 777 Scudders Mill Rd, Plainsboro, NJ

Background: The risk of diabetes-related adverse events (DRAEs) is a substantial concern in younger patients receiving atypical antipsychotics, especially given recent and impending US FDA approvals for their use in the pediatric population.
Methods: Adjusted reporting ratios (Empiric Bayes Geometric Mean, EBGM) and 90% confidence intervals (EB05;EB95), were calculated to estimate the degree of association between 24 DRAEs and aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or haloperidol in patients stratified by age using a Multi-item Gamma Poisson Shrinker data-mining algorithm on the FDA AERS database (through December 2006). Drug-event combinations with EB05 ≥2 are considered potential drug-event associations.
Results: 258 cases of the 24 DRAEs were identified for patients <18 years of age; diabetes mellitus (DM, 58 cases) was among the most frequently reported. EBGM scores and EB05;EB95 CIs for DM were: aripiprazole 1.69 (0.83,

3.13), clozapine 4.10 (2.30, 7.50), olanzapine 3.83 (2.52, 5.67), quetiapine 2.42 (1.31, 4.17), risperidone 2.45 (1.62, 3.58), ziprasidone 1.31 (0.48, 3.04), and haloperidol 1.31 (0.55, 2.75) For adults (18 to 64), all drug-event combinations for DM had EB05 ≥2 except haloperidol 2.29 (1.96, 2.68) and aripiprazole 2.47 (1.97, 3.07).
Conclusions: The potential for an association between DM and haloperidol or aripiprazole was low in both pediatric and adult populations. In contrast, potential associations, as defined as EB05 ≥2, were observed between DM and olanzapine or clozapine in both populations. Potential associations were observed for risperidone, quetiapine, or ziprasidone only in adults. These results reinforce the importance of metabolic monitoring in both pediatric and adult patients.
Supported by Bristol-Myers Squibb and Otsuka

894. Differential Effects of Typical and Atypical Antipsychotic Drugs on Striatal Subregions in Patients with Schizophrenia: An FDG-PET and MRI Imaging Study

Nicola Dusi, Jonathan J. Entis, M. Mehmet Haznedar, Randall Newmark, Kingwai Chu, Erin A. Hazlett, Monte S. Buchsbaum

Psychiatry, Mount Sinai Hospital, New Yok, NY

Background: The dorsoventral gradient in D2 receptor density and anteroposterior organization for cognitive/motor function indicate the importance of examining the striatum in 3D.
Methods: We studied two samples: 1) 22 never-previously medicated psychotic adolescents (mean age 15.7, range 13-19) 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 2) 15 adult patients with schizophrenia (mean age 42.6, range 22-59) received an anatomical MRI and FDG-PET scan after 6 weeks of a randomized double-blind trial of either sertindole or haloperidol. Adult patients were then crossed to the other treatment and scanned again at week 12. The caudate and the putamen were traced on the anatomical MRI by a tracer blind to the diagnosis and applied to the FDG-PET
Results: Younger adolescents 13-15 treated with haloperidol had a significant increase in the relative metabolic rate of both the caudate and putamen at dorsal levels while treatment with olanzapine generally decreased metabolic rates. The difference between the two medications was most marked in the head of the putamen where only haloperidol showed a metabolic rate increase while any putamen increase with olanzapine was limited to small dorsolateral posterior regions. Similarly, in the adult sample we found that the metabolic rates of the caudate and the putamen were significantly higher with haloperidol than with sertindole.
Conclusions: These findings are consistent with the different D2 receptor occupancy of these drugs and consistent with striatal organization.
Supported by H. Lundbeck A/S and Eli Lilly and Company

895. Weight Gain and Hyperprolactinemia in Schizophrenic Patients Treated during Twelve Months with Long Acting Risperidone

Fabrice Duval, Frederico Duarte Garcia, Felix Gonzales Lopera, Marie-Claude Mokrani, Yann Hode, Said Fattah, Than Son Diep

Psychiatry, Centre Hospitalier, Rouffach, France

Background: Risperidone (RISP) may induce both elevated prolactin (PRL) levels and weight gain. The aim of this study was to evaluate body weight and mass index (BMI), and PRL modifications in schizophrenic patients treated for 1 year with long-acting risperidone (LAR).
Methods: Body weight and BMI (calculated as weight in kilograms divided by height in meter squared) were determined at baseline and at endpoint in 19 schizophrenic patients (9 men and 10 women; mean[SEM] age 33.4[2.9]years). PRL levels were determined at baseline, after oral risperidone treatment (mean length of treatment: 79[30] days; mean dose: 5.8[0.5] mg daily) and during a 12 month treatment with LAR (mean dose : 50[10] mg every 2 weeks ; PRL levels were measured before each injection).
Results: At endpoint, a significant weight gain (Δweight: 8,1[1,4] kg) and BMI (ΔBMI: 2,9[0,5] kg/m²) was observed (both $p<0.0002$). Compared with baseline, PRL levels were significantly increased ($p<0.0007$; mean ΔPRL: 33[8] ng/ml). There was an association between ΔBMI>1,5 kg/m² and ΔPRL>40 ng/ml ($p<0.04$). Moreover ΔBMI was linked to the length of treatment (rho=0.47; n=19; $p<0.05$).
Conclusions: Our results suggest a link between weight gain and long term hyperprolactinemia in patients treated with LAR. It has been hypothesized that PRL may have a role in the regulation of food intake by increasing leptin synthesis and secretion.

896. Withdrawn

897. FDG-PET and MRI Imaging of the Effects of Typical and Atypical Neuroleptics on the Medial Dorsal Nucleus of the Thalamus in Schizophrenia

Jonathan J. Entis, Nicola Dusi, William Byne, M. Mehmet Haznedar, Eileen Kemether, Randall Newmark, Kingwai Chu, Erin A. Hazlett, Ella B. Teague, Monte S. Buchsbaum

Psychiatry, Mount Sinai School of Medecine, New York, NY

Background: Schizophrenia is associated with sensory, cognitive, and motor impairments that have been linked to thalamic dysfunction. Typical and atypical neuroleptics have unique receptor binding and may differentially affect dopaminergic receptors in the thalamus.
Methods: Two samples were studied to assess thalamic activity after treatment with neuroleptics: 1) 22 never-medicated psychotic adolescents (mean age 16.2; range 13-20) received an MRI and FDG-PET scans at baseline and after 8-9 weeks of a randomized double-blind trial of either olanzapine or haloperidol and 2) 15 adult patients with schizophrenia (mean age 42.6, range 22-59) received an MRI and FDG-PET scan after 6 weeks of a randomized double-blind trial of sertindole or haloperidol. Patients were crossed to the other treatment and scanned again at week 12. In both samples, thalamic nuclei (MDN, PULV, and APN) were traced on the MRI and applied to the FDG-PET.
Results: In the adolescent sample, greater activity occurred after treatment with olanzapine in the mediodorsal nucleus ($p=0.02$) and anterior principle nucleus ($p=0.04$). Decreased activity in these nuclei occurred after treatment with haloperidol. In the adult sample, greater activity was found in the MDN ($p=0.02$) and the right APN ($p=0.02$) after treatment with sertindole than after treatment with haloperidol. Greater correlation between the metabolic rate change of the MDN and the prefrontal regions was found with olanzapine than with haloperidol. Sertindole/haloperidol patterns were similar.
Conclusions: These results suggest greater coordination between the MDN and prefrontal regions with atypical rather than typical neuroleptic treatment, possibly consistent with greater cognitive improvement.
Supported by H. Lundbeck A/S and Eli Lilly and Company

898. Effect of Ziprasidone Dose on Rates of Medication Discontinuation in Acute Schizophrenia or Schizoaffective Disorder

Leslie Citrome[1], Ruoyong Yang[2], James Harnett[2], **Paul Glue**[2], Onur Karayal[2]

[1]Psychiatry, New York University School of Medicine, New York, NY,[2]Pfizer Inc., Pfizer Inc., New York, NY

Background: Prior research suggests that higher ziprasidone doses may be related to better outcomes in patients with schizophrenia or schizoaffective disorder.
Methods: Data were analyzed for the first 28 days from 4 pivotal, randomized, double-blind, fixed-dose ziprasidone trials of patients with schizophrenia or schizoaffective disorder. Ziprasidone dose (40 mg/d, n = 186; 80 mg/d, n =154; 60mg/d, n = 125; 160 mg/d n = 104) and its relationship to all-cause, efficacy and adverse event related discontinuations, within 28 days relative to placebo were examined using Cox proportional hazard models to adjust for confounding factors.
Results: All-cause discontinuation for ziprasidone ranged from 26.9% for 160 mg/d to 40.9% for 40 mg/d compared with 49.5% for placebo. Doses of 120 - 160 mg/d were the only ziprasidone regimens associated with significantly lower all-cause discontinuation rates versus placebo ($p < 0.05$). Ziprasidone 160 mg/d was the only dose associated with a significantly lower all-cause discontinuation rate versus lower dose ziprasidone (40 mg/d and 80 mg/day, $p < 0.05$). Lack of efficacy and AEs accounted for 51% and 8.6% of all medication discontinuations for ziprasidone, compared with 62% and 4.4% for placebo, respectively. Overall discontinuation due to lack of efficacy findings are consistent with all-cause discontinuation.
Conclusions: Higher doses of ziprasidone (120-160 mg/d) are associated with significantly lower all-cause medication discontinuation than placebo and 160mg/d vs. lower dose ziprasidone (40-80 mg/d), primarily due to lower rates of discontinuation for lack of efficacy. These findings support other research associating higher doses of ziprasidone with improved treatment outcomes.
Supported by Pfizer Inc.

899. A 12 Weeks Open Label Trial of Quetiapine in Adolescents with Psychotic Disorders

Laurent Holzer[1], Ulrich Preuss[2], Stéphanie Clarke[3], Olivier Halfon[4], Pierre Baumann[5]

[1]Child and Adolescent Psychiatry, Department of Psychiatry, LAusanne, Switzerland,[2]Child and Adolescent Psychiatry, Universitäre Psychiatrische Dienst, Bern, Switzerland,[3]Service de Neuropsychologie, CHUV, Lausanne, Switzerland,[4]Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne, Switzerland,[5]UBPC, Department of Psychiatry, Lausanne, Switzerland

Background: Clinical effectiveness, tolerability and pharmacokinetics of quetiapine in adolescents with psychotic disorders have been established, but cognitive functions have not yet been examined specifically in this population.
Methods: 23 adolescents (13-18 years old) with psychotic disorders participated in a 12 weeks open label trial assessing clinical efficacy, tolerability and impact on cognitive functions of quetiapine (50 -750 mg daily).
Results: Adolescents were treated with lower doses compared to adults, a decrease in CGI and PANSS total score was observed while neuropsychological functioning remained stable after 12 weeks of quetiapine treatment.
Conclusions: Quetiapine is an effective and well tolerated treatment in adolescents with psychotic disorders, no improvement in cognitive functioning has been observed in this trial.
Supported by AstraZeneca

900. Safety and Tolerability of the Investigational Antipsychotic Paliperidone Palmitate Injected in the Deltoid or Gluteus Muscle in Patients with Schizophrenia

Srihari Gopal[1], Jean-Pierre Lindenmayer[2], **David Hough**[1], Rama Melkote[1], Pilar Lim[1], Mariëlle Eerdekens[3]

[1]CNS, J&J PRD, Titusville, NJ,[2]New York University, New York University, New York, NY,[3]Division of Janssen Pharmaceutica N.V, J&J PRD, Beerse, Belgium

Background: To assess safety and tolerability of initiating treatment with paliperidone palmitate via deltoid vs. gluteal injection given every 4 wks and of switching injection sites in adults with stable schizophrenia.
Methods: In this crossover trial, patients (N=252) were randomized 1:1:1 to 3 treatment groups (Paliperidone palmitate 50, 75, or 100 mg eq.) and 2 injection sequences during the double-blind phase (blinded to dose): deltoid muscle (period 1 [13 wks]) followed by gluteal muscle (period 2 [12 wks]) or the reverse.
Results: The ITT population had 249 patients: mean age= 43 (SD:12.8) yrs; men (57%); white (81%); baseline mean PANSS total score=56 (SD:11.5). The most common (≥5% overall) treatment-emergent adverse events (TEAEs) were: (period 1) insomnia, anxiety, headache, and agitation; and (period 2) insomnia, psychotic disorder, weight increase, and tachycardia. During treatment initiation (period 1), rates of systemic TEAEs were similar between the 2 injection sites across all dose levels (proportion of patients reporting TEAE for gluteus minus deltoid [90%CI]): -6.7% (-23.5, 10.7) for 50 mg eq.; -0.7% (-17.6, 16.5) for 75 mg eq.; and -3.4% (-20.4, 13.8) for 100 mg eq. The total difference between the rates (90% CI) across doses was -3.3% (-13.3, 6.7). A comparison of systemic TEAE rates during the last 8 wks of the 2 study periods did not reveal significant differences upon switching of injection sites.
Conclusions: The incidence of systemic TEAEs was similar when initiating treatment with either deltoid or gluteal injections. Switching between injection sites was also safe and well tolerated.
Supported by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

901. Paliperidone Palmitate, an Injectable Antipsychotic, in Prevention of Symptom Recurrence in Patients with Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study

David Hough[1], Srihari Gopal[1], Ujjwala Vijapurkar[1], Pilar Lim[1], Margarita Morozova[2], Mariëlle Eerdekens[3]

[1]CNS, Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ,[2]Mental Health Research Center, Mental Health Research Center, Moscow, Russian Federation,[3]Division of Janssen Pharmaceutica N.V, Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium

Background: We assessed efficacy and tolerability of an investigational, injectable antipsychotic, paliperidone palmitate (PP), in preventing symptom recurrence in adults with schizophrenia.
Methods: Eligible patients (PANSS total scores <120) were transitioned to gluteal injections of PP during a 9-week (wk) open-label flexible-dose phase. The first 2 injections of 50 mg eq. were given 1 wk apart. Subsequent injections, which could be adjusted (25, 50, or 100mg eq.), occurred every 4 weeks. Patients with total PANSS <75 at wk 9 continued into the 24-wk maintenance phase. Patients clinically stable on a fixed dose for the last 12 wks were randomized 1:1 to continue on their PP dose or start placebo in the double-blind phase of variable duration.
Results: The preplanned interim analysis at 68 recurrence events included 312 patients: mean age=40 yrs, 55% men, 66% white, baseline PANSS (SD): placebo, 69.5 (16.89); PP, 69.3 (17.39). Time-to-first-recurrence (primary measure) favored PP ($p<0.0001$, log-rank test): median time-to-first-recurrence was 163 days for

placebo and not estimable for PP. Based on the significant efficacy results, the study was stopped early. Treatment-emergent AE rates during double-blind phase (final analysis: N=408) were: 38% PP, 44% placebo. Weight increase and gastroenteritis (viral) occurred more frequently with PP (difference ≥2% vs. placebo). Local injection-site tolerability was good. For PP treated patients (n=205), the investigators reported injection-site pain as usually absent (81%) or mild (18%) at double-blind endpoint, similar to placebo-treatment.
Conclusions: Paliperidone palmitate treatment significantly delayed time-to-first recurrence and was generally well-tolerated, locally and systemically, in patients with schizophrenia.
Supported by Johnson & Johnson Pharmaceutical Research & Development

902. The Safety and Effectiveness of High Dose D-Serine in the Treatment of Schizophrenia

Joshua T. Kantrowitz[1], Rachel T. Ziwich[1], Barbara A. Cornblatt[2,3,4], Anil K. Malhotra[2,3,4], Gail Silipo[1], Scott W. Woods[5], Daniel C. Javitt[1,6]

[1]Life Sciences, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY,[2]Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY,[3]Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY,[4]Early-Phase Schizophrenia Center, The Feinstein Institute for Medical Research, Manhasset, NY,[5]Department of Psychiatry, Yale University, New Haven, CT,[6]Department of Psychiatry, New York University School of Medicine, New York, NY

Background: D-serine is a potential novel medication for treatment of schizophrenia working via the allosteric modulatory site of the NMDA receptor complex. Randomized clinical trials of D-serine have been done with doses of 30 mg/kg/day (approximately 2 g/day), but no formal dose escalation or PK/PD studies have been performed. This study describes effects of D-serine administered at a dose of 60 mg/kg/day (approximately 4 g/day) open label for 4 weeks.
Methods: 20 antipsychotic-stabilized patients with schizophrenia or schizoaffective disorder participated. Safety labs (SMA20, CBC, UA) were obtained weekly and clinical measures (PANSS, SANS) were obtained biweekly. Neuropsychological (MATRICS) and event-related potential measures (MMN, visual P1, auditory 40 Hz response) pre and post treatment.
Results: 19 patients completed. No clinically significant changes in any of the renal function, microscopic urinalysis, CBC, EKG, or liver function tests were noted. No statistical changes in extrapyramidal symptoms occurred. Mean peak concentration was 272.3±13.9 nmol/ml at two hours after dose administration, well below levels associated with preclinical nephrotoxicity.
Significant improvements were noted in the total PANSS (p=0.05;d=0.49), Hopkins Verbal Learning Test-Revised (p=0.009;d=0.67), Category Fluency (p=0.05;d=0.49), Continuous Performance Test (p=0.05;d=0.49) and nearly significant in negative symptoms (p=0.068;d=0.44). No significant improvements occurred in the SANS. Apparent improvements were noted in several ERP measures, including auditory MMN. In our earlier, 2 g/day trial, no significant neuropsychological improvements occurred.
Conclusions: This novel study of d-serine 60 mg/kg/day demonstrates safety and produces moderate effect size changes in multiple clinical and cognitive measures, calling for double-blind, placebo controlled investigations.
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903. Effectiveness of Risperidone Long Acting Injection in the Treatment of Recently Versus Longer Diagnosed Patients with Schizophrenia

Tim Lambert[1], Jose Olivares[2], Ivan Tuma[3], Jos Peuskens[4], Jan Pecenak[5], H. bij de Weg[6], Lars Eriksson[7], B. Bork[8], Michael Povey[9], Annette Lam[10], Kostas Trakas[11], Zhongyun Zhao[11]

[1]Central Medical School, University of Sydney, Sydney, Australia,[2]Servicio de Psiquiatria, Hospitalario Universitario de Vigo, Vigo, Spain,[3]Medical School and Teaching Hospital Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic,[4]KU Leuven campus UC St. Jozef Kortenberg, Universitair Psychiatrisch Centrum, Leuven, Belgium,[5]Psychiatry, FNSP Bratislava, Bratislava, Slovakia,[6]Psychiatry, GGZ Friesland locatie Dammelaan, Leeuwarden, The Netherlands,[7]Psychiatry, SU/Östra RPV, Hisings-Backa, Sweden,[8]Psychiatry, DP Tønder, Tønder, Denmark,[9]Statistics, SGS Life Science Services, Wavre, Belgium,[10]Health Economics, Johnson & Johnson Pharmaceutical Services, Toronto, ON, Canada,[11]Health Economics, Johnson & Johnson Pharmaceutical Services, Raritan, NJ

Background: To evaluate treatment effectiveness of risperidone long-acting injection (RLAI) in recently diagnosed schizophrenia patients versus those diagnosed for a longer period.
Methods: The electronic-Schizophrenia Treatment Adherence Registry (e-STAR) is an international, long-term, prospective, observational study of patients with schizophrenia who start RLAI. Data are collected retrospectively for 1 year and prospectively every 3 months for 2 years. Effectiveness was measured by the Clinical Global Impression-Severity (CGI-S) and the Global Assessment of Functioning (GAF) scale. Recency of diagnosis was dichotomized into those diagnosed recently (<5 years) versus patients who have been diagnosed longer (≥5 years). This interim report is based on pooled data from Australia, Belgium, Czech Republic, Denmark, Netherlands, Slovakia, Spain, and Sweden.
Results: Among 4,252 patients enrolled in e-STAR, to date, 2,239 patients have been followed for at least 12-months with 44%classified as recently diagnosed. Compared to recently diagnosed patients, those diagnosed longer were older (42.5 vs. 31.4 years, p<0.001) and had longer disease duration (16.2 vs. 2.2 years, p<0.001). The proportion of patients still on RLAI at 12 months was similar in both groups (diagnosed <5 years=85.2%, diagnosed ≥5 years=85.6%). Both groups experienced significant improvements in CGI-S and GAF scores. However, the recently diagnosis group experienced greater improvements in CGI-S and GAF (CGI-S, -1.28 vs. -0.99, p<0.0001; GAF, +17.1 vs. +14.1, p=0.0002).
Conclusions: This 12-month interim data show that long-acting risperidone treatment significantly improves illness severity and patient functioning in patients with schizophrenia, those who were recently diagnosed experienced greater improvement compared to those diagnosed longer.
Supported by Johnson & Johnson

904. The Monitor of Serum Prolactin Level and Related Clinical Observations among Individuals with Schizophrenia Spectrum Illnesses in a 12 weeks Aripiprazole Treatment

Tsuo-Hung Lan[1,2,3], Hsien-Jane Chiu[1,2], Yu-Chuan Wu[1], Yun-Ru Liu[3,4], Bo-Jian Wu[1], Tsung-Ming Hu[1], El-Wui Loh[3], Keh-Ming Lin[3]

[1]Psychiatry, Yu-Li Hospital, DOH, Hualien, Taiwan,[2]Psychiatry, National Yang-Ming University, Taipei, Taiwan,[3]Division of Mental Health Research, National Health Research Institutes, Taipei, Taiwan,[4]Pathology, National Taiwan Univeristy, Taipei, Taiwan

Background: Aripiprazole as a partial dopaminergic agonist reduces prolactin level in most users. We present a clinical study to follow up serum prolactin level in patients treated with aripiprazole.
Methods: This is randomized open-label trial on serum prolactin monitoring in schizophrenic subjects. We enrolled 48 inpatients (29 Males, 19 Females) meeting DSM-IV criteria for schizophrenia from one Taiwan psychiatric hospital. After consent form fulfilled, participants were randomly assigned to three different treatment arms (dosage per day): (1) A - 10~15 mg aripiprazole ; (2) B - 20~30mg aripiprazole; (3) C - 10 mg aripiprazole combined with 1 mg risperidone. All subjects were evaluated by using PANSS scale and serum prolactin level at baseline, 4th week, 8th week, and 12th week. Other demographic data were also collected.
Results: The mean prolactin level reduced from 54.1± 40.9 (baseline) to 12.0± 24.8 (12th week) with a p-value < 0.00001. The comparison of prolactin level between three arms of aripiprazole intervention shows no significant difference, although the reduction trend of Arm C was more than the other two Arms. The maximal prolactin level reduction was observed in the third week of aripiprazole, after adjusted for sex and previously prescribed antipsychotics.
Conclusions: It is suggested that prolactin level returns to normal after 3 weeks of aripiprazole treatment progressively and remains until the 12th week. The prolactin level is not observed elevated by 1mg risperidone in Arm C. This may be explained by the high affinity to dopaminergic receptors in aripiprazole.
Supported by YLH-IRB-9602

905. Positron Emission Tomography (PET) Study with RGH-188 in Healthy Volunteers

Istvan Laszlovszky[1], Gyorgy Nemeth[1], Gabriella Pasztor Meszaros[2], Margit Kapas[2], David J. Brooks[3], Nicola Pavese[4], Zsolt Szombathelyi[2]

[1]Medical Division, Gedeon Richter Plc., Budapest, Hungary,[2]Pharmacological and Drug Safety Research, Gedeon Richter Plc., Budapest, Hungary,[3]Hammersmith Imanet Ltd., Hammersmith Hospital, London, United Kingdom,[4]Imperial College, MRC Clinical Sciences Centre, London, United Kingdom

Background: RGH-188 is a potent dopamine D_3/D_2 receptor antagonist/ partial agonist atypical antipsychotic. The aim of present PET study was to investigate the striatal dopamine D_2/D_3-receptor occupancy in healthy male subjects after single and multiple oral doses of RGH-188 and to investigate the associated plasma concentrations.
Methods: In an open-label study striatal D_2/D_3 receptor occupancy was measured by PET using 11C-raclopride. Two subjects received a single dose of 0.5 mg RGH-188, while three subjects received 0.5 mg/day RGH-188 on Days 1-2 and 1.0 mg/day on Days 3-14. PET scans were performed at baseline and 4 h after the last dose. Pharmacokinetic plasma samples were analyzed for RGH-188 and its two metabolites by HPLC-MS-MS.
Results: RGH-188 blocked specific binding in the investigated brain regions (caudate, putamen, ventral striatum). Across these regions, D_2/D_3 receptor occupancy was reduced by up to 12 % following single dose and 63 % to 79 % following multiple dosing. Low plasma RGH-188 concentrations after single dose administration were associated with low D_2/D_3 receptor occupancy, whilst higher plasma concentrations were associated with higher occupancy in the multiple dose group. Similar patterns were observed for the two metabolites.
Conclusions: Multiple administration of 1.0 mg RGH-188 resulted in over 70% D_2/D_3 receptor occupancy in healthy male subjects and the displacement showed correlation with RGH-188 and metabolites levels.
Supported by Gedeon Richter Plc.

906. An Open-Label Study Changing Generic Clozapine Formulation to FazaClo® (clozapine, USP) Orally Disintegrating Tablets in Stable Patients with Schizophrenia or Schizoaffective Disorder

Jean-Pierre Lindenmayer[1,2,3], Sashank Kaushik[2,3], Anzalee Khan[2,3], Saurabh Kaushik[2,3]

[1]Psychiatry, New York University School of Medicine, New York, NY,[2]Psychopharmacology Research Program, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY,[3]Psychopharmacology Research, Manhattan Psychiatric Center, Wards Island, NY

Background: FazaClo, an orally disintegrating clozapine formulation has been shown to be bioequivalent to Clozaril® tablets, but similar data on conversion of generic clozapine to Fazaclo is not available.
Methods: 16 treatment-refractory schizophrenia or schizoaffective inpatients enrolled in a 17 day open label study (mean total PANSS = 72.81 (5.49)). Patients were on stable b.i.d dosage of generic clozapine and on concomitant psychotropics for at least 28 days. Trough concentrations for clozapine and desmethyl-clozapine were obtained on Days 1, 3, 4, 10 and 17; patients were switched to Fazaclo on Day 4.
Results: 15 patients completed the study and 1 patient withdrew consent on Day 10. Clozapine and desmethyl-clozapine plasma levels at Days 1, 3 and 4 did not show significant differences with Days 10 and 17. There was a significant difference in the clozapine/desmethyl-clozapine plasma ratio at Day 10 compared to Days 1-4. Patients with ≥ 71 PANSS total (n = 9) showed a significant increase in plasma level at Days 10 and 17 compared to patients with ≤ 70 total PANSS. Results also indicated patients with higher psychopathology measured by the PANSS have a clozapine/desmethyl-clozapine ratio of 2.45 while those with PANSS scores ≤ 70 had a ratio of 1.97. No study drug side effects were observed.
Conclusions: FazaClo is bioequivalent to generic clozapine, and both FazaClo and generic clozapine were tolerated similarly. FazaClo may be substituted for generic clozapine on a mg-for-mg basis. Further investigation is underway with a larger sample (current effect size = .348).
Supported by Azur Pharmaceuticals

907. Cardiovascular and Metabolic Status in Neuroleptic-Treated Schizophrenia Patients Screening for Clinical Trials: Comparison to NHANES Controls

Robert E. Litman[1,2], Megan B. Shanahan[1], Camelia M. Graham[3]

[1]Psychiatry, CBH Health, LLC, Rockville, MD,[2]Psychiatry, Georgetown University Medical Center, Washington, DC,[3]Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

Background: People with schizophrenia are at risk for the development of co-morbid metabolic and cardiovascular illness. Atypical antipsychotic therapy may be a contributing factor.

Methods: Metabolic and cardiovascular data from 357 chronically ill (38.3 + 10.05 years old, 251 Male, 70.4% African-American) schizophrenia patients who were screened for participation in clinical trials from 1998-2007 (80.2% on atypical antipsychotics, 12.3% on typical antipsychotics, 7.5% untreated) were compared to a sample of 2,531 non-schizophrenic age-matched controls from the 2003-2004 Center for Disease Control and Prevention's **National Health and Nutrition Examination Survey** (NHANES) on measures including fasting blood sugars and lipids, BMI, and blood pressure.
Results: 29.1% of patients were overweight (BMI>25) and 37.8% were obese (BMI>30). Fasting lipids, cholesterol and triglycerides were elevated in 39.3% and 40.5% of patients respectively. Elevations in fasting blood sugar (FBS >110mg/dl) were found in 16.7% of patients with 7.6% having diabetes (FBS >126mg/dl). 15.5% were hypertensive (diastolic BP >85mmHg), and 54.5% had abnormal ECGs. 34% had metabolic syndrome (n=189). There were no differences across variables when compared to the age-matched NHANES controls. No association with either typical or atypical neuroleptic treatment was found based on χ^2 tests of differences.
Conclusions: Lack of differences with recent NHANES control data and lack of association with neuroleptic therapy suggests that other factors besides neuroleptic treatment (eg. diet, lifestyle) play a role in metabolic and cardiovascular abnormalities found in schizophrenia patients.

908. Efficacy and Tolerability of Paliperidone Palmitate: 9-week, Placebo-Controlled Study in Schizophrenia Patients

Michelle Kramer[1], **Robert E. Litman**[2], Rosanne Lane[1], Pilar Lim[1], David Hough[1], Marielle Eerdekens[3]

[1]Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ,[2]CBH Health, LLC, Rockville, MD,[3]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium

Background: This study evaluated the efficacy and safety of paliperidone palmitate, a long-acting injectable agent, in the treatment of schizophrenia patients.
Methods: A 9-week, double-blind, placebo-controlled study randomized patients to placebo or paliperidone palmitate 50 or 100 mg eq. on Days 1, 8 and 36 (without oral supplementation). Efficacy and tolerability were evaluated via changes in mean Positive and Negative Syndrome Scale (PANSS) total scores and adverse event (AE) reporting, respectively.
Results: The intention-to-treat population included 197 patients (male=62%, mean±standard deviation [SD] age=39.3±10.3y; placebo N=66; paliperidone palmitate 50 mg eq. N=63; paliperidone palmitate 100 mg eq. N=68). Mean±SD PANSS total scores significantly improved (p≤0.001) from baseline (87.0±12.5) to end point for paliperidone palmitate 50 mg eq. (–5.2±21.5) and 100 mg eq. (–7.8±19.4) versus placebo (+6.2±18.3), with significant improvements observed from Day 8. Responder rates (≥30% improvement in PANSS total score at end point) were significantly greater in both paliperidone palmitate groups versus placebo (p≤0.007). AEs occurring ≥3% more in either paliperidone palmitate group versus placebo (safety population, N=247) were insomnia, schizophrenia, restlessness, sedation, extrapyramidal disorder, hypertonia, attention disturbance, electrocardiogram abnormal, constipation, myalgia, asthenia and vertigo. Extrapyramidal symptoms–AE rates were comparable for paliperidone palmitate and placebo, with the exception of parkinsonism (7% and 1%, respectively). Serious AEs in ≥1 patient (any group) were schizophrenia and psychotic disorder. Injections were generally well tolerated. No deaths occurred.
Conclusions: Paliperidone palmitate (50 and 100 mg eq. doses) is effective and well tolerated in acute symptomatic schizophrenia.
Supported by Johnson & Johnson Pharmaceutical Services, LLC., and Johnson & Johnson Pharmaceutical Research & Development

909. Pharmacokinetics (PK) of Multiple Doses of Olanzapine Long Acting Injection (OLAI), an Intramuscular (IM) Depot Formulation of Olanzapine (OLZ), in Stabilized Patients with Schizophrenia

Darcie Kurtz, Richard Bergstrom, **David P. McDonnell**, Malcolm Mitchell

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN

Background: Olanzapine pamoate is a long-acting depot formulation of OLZ that is an effective treatment for patients who benefit from the advantages of a depot. It has not yet been approved.
Methods: Schizophrenic patients stabilized on daily oral OLZ received multiple OLAI injections at doses of 100, 150, 160, 200, and 300 mg/2 weeks and 200, 255, 300, and 405 mg/4 weeks for 24 weeks. After each injection, serial plasma OLZ concentration samples were collected. PK were characterized using non-compartmental methods.
Results: The injections were well tolerated overall. Absorption-limited PK were observed. Plasma OLZ concentrations were sustained throughout both the 2- and 4-week injection intervals. On average, OLZ concentrations accumulate 2- to 3-fold upon multiple dosing and reach steady-state conditions after about 3 months of dosing. Peak-to-trough fluctuation in OLZ concentrations averages 51% for the 2-week injection interval and 75% for the 4-week interval. Maximum concentration and area under the concentration versus time curve for OLZ were proportionate to OLAI dose. Relative to oral OLZ (t_{max} = 6 hr, $t_{1/2}$ = 29 hr), the time of peak concentration following OLAI was 4 days and the half-life was approximately 26 days. The average steady-state concentrations sustained by OLAI correspond to those maintained by daily OLZ in the dosage range of 5-20 mg/day.
Conclusions: IM administration of OLAI is well tolerated and provides steady-state concentrations that are sustained over 4 weeks and are comparable to oral treatment.
Supported by Eli Lilly and Company

910. Relapse Prevention: Risperidone Long-Acting Injectable Vs Quetiapine or Aripiprazole

Rossella Medori

Medical Affairs, Janssen-Cilag, Beerse, Belgium

Background: To investigate if risperidone long-acting injectable (RLAI) provides better efficacy maintenance over 2 years, as measured by the time to relapse, in comparison to the oral atypical antipsychotic quetiapine or aripiprazole.
Methods: Open-label, active-controlled, multicenter, randomized, 2-year trial of RLAI versus oral quetiapine or aripiprazole in 731 patients with schizophrenia currently treated with oral risperidone, olanzapine or conventional neuroleptics. Symptomatically stable patients on a stable dose of an antipsychotic for ≥4 weeks were enrolled. Primary efficacy evaluation was time to relapse. Secondary efficacy evaluations included: Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), Montgomery-Asberg Depression Rating Scale (MADRS) and Social and Occupational Functioning Assessment Scale (SOFAS). Safety evaluations included adverse events monitoring, Extrapyramidal Symptom Rating Scale (ESRS), clinical laboratory tests and vital signs.
Results: 808 subjects were screened and 731 (58.3% male, mean age 41.5 [SD:12.8] years) were randomised to treatment. Mean time since first onset was 13.9 (SD:11.2) years; mean time since first treatment was 12.5 (SD:10.7) years. At baseline 34.4% of subjects fulfilled the remission severity criteria. Reasons for switching (>1 allowed) included: insufficient efficacy; negative (29.8%), positive (14.1%), and general symptoms (21.1%) and adverse events (18.9%). Baseline scores were: PANSS: 73.0 (SD:21.8), CGI-S: 3.7 (SD:1.0),

MADRS: 13.1 (SD:7.6), SOFAS: 56.9 (SD:14.2) and ESRS: 4.3 (SD:7.0). Treatment outcome data will be presented.
Conclusions: This study shows that the subjects enrolled in this relapse prevention trial are representative of the present treatment habits, as well as identifies the unmet needs and dissatisfaction in current treatment options.
Supported by Jansen-Cilag EMEA

911. A 28-Week, Randomized, Double-Blind Study of Olanzapine versus Aripiprazole in the Treatment of Schizophrenia

John M. Kane[1], **Olawale Osuntokun**[2], Ludmila A. Kryzhanovskaya[2], Wen Xu[2], Virginia Stauffer[2], Susan B. Watson[2]

[1]Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY,[2]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN

Background: The current study evaluated the effectiveness of olanzapine (OLZ) versus aripiprazole (APZ) in patients with schizophrenia.
Methods: Patients 18 to 65 with schizophrenia were randomized to either OLZ (n=281) or APZ (n=285) for 28 weeks of double-blind treatment. The primary outcome was time to all-cause discontinuation. Symptom efficacy was measured by Positive and Negative Syndrome Scale (PANSS) total change from baseline (LOCF). Time-to-event data were analyzed via the Kaplan Meier method and log-rank test.
Results: Treatment groups did not differ significantly in time to all-cause discontinuation (p=.067) or discontinuation rates (OLZ 42.7%, APZ 50.2%, p=.053). OLZ patients had a significantly greater LS mean decrease in the PANSS (-30.2) than APZ patients (-25.9, p=.014). Mean weight change (kg) was +3.4 for OLZ and +0.3 for APZ (p<.001). Fasting mean glucose change (mg/dL) was +4.9 for OLZ and +0.9 for APZ (p=.045). Percent of patients with baseline glucose <100 and glucose ≥126 at any time was 1.7% for OLZ and 0.6% for APZ (p=.623). Fasting mean total cholesterol change (mg/dL) was +4.1 for OLZ and -9.8 for APZ (p<.001). Percent of patients with baseline total cholesterol <200 and cholesterol ≥240 at any time was 9.2% for OLZ and 1.5% for APZ (p=.008).
Conclusions: OLZ and APZ groups did not differ significantly on the primary outcome. OLZ patients had significantly greater improvement in symptom efficacy. Significantly greater increases in weight, glucose, and total cholesterol were observed in OLZ-treated patients. Results are generally consistent with previous clinical trials comparing the 2 therapies.
Supported by Eli Lilly and Company

912. Long-Term Symptomatic Remission of Schizophrenia with Once-Daily Extended Release Quetiapine Fumarate

Joseph Peuskens[1], Jitendra K. Trivedi[2], Martin Brecher[3], Ola Svensson[4], Frank Miller[4], Didier Meulien[4]

[1]Psychiatrisch Centrum, Universitair Psychiatrisch Centrum KU Leuven, Kortenberg, Belgium,[2]Psychiatry, King George Medical University, Lucknow, India,[3]Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Wilmington, DE,[4]Pharmaceuticals, AstraZeneca R&D, Södertälje, Sweden

Background: Relapse prevention with once-daily extended release quetiapine fumarate (quetiapine XR) was evaluated in a randomized, double-blind, placebo-controlled study (D1444C00004) in schizophrenia.
Methods: Patients (n=327) were treated with open-label, flexible-dose, once-daily quetiapine XR (400, 600 or 800 mg/day) for a 16-week stabilization period. Following this, clinically stable patients were randomized to either continue (double-blinded) flexible-dose quetiapine XR or placebo. The primary endpoint was time from randomization to first schizophrenia relapse up to 1 year. Interim analyses were planned after 45 and 60 relapse events. Remission rates (as defined by Andreasen et al, Am J Psychiatry 2005:162:441-9, ie PANSS ≤3 for items P1, G9, P3, P2, G5, N1, N4 and N6 for ≥6 months) and time to non-remission were evaluated post hoc for patients who were in remission during the stabilization period. Time from randomization to relapse and non-remission were analyzed using the Cox proportional hazards model.
Results: The study was terminated early after the first interim analysis, as quetiapine XR (mean dose 669 mg/day; mean randomized-treatment period 4 months) was significantly superior to placebo for time to relapse: HR 0.16 (95% CI 0.08, 0.34; p<0.001). Using the time to non-remission analysis, the estimated remission rates 6 months after randomization were 76% for quetiapine XR and 52% for placebo. Time to non-remission was significantly shorter with placebo compared with quetiapine XR: HR 0.39 (95% CI 0.19, 0.81; p=0.009).
Conclusions: Once-daily quetiapine XR (400-800 mg/day) prevents relapse and is associated with sustained remission in patients with clinically stable schizophrenia.
Supported by AstraZeneca Pharmaceuticals LP

913. Asenapine in Schizophrenia: An Overview of Clinical Trials in the Olympia Program

Steven Potkin[1], John M. Kane[2], Robin A. Emsley[3], Dieter Naber[4], John Panagides[5]

[1]Department of Psychiatry, University of California, Irvine, Orange, CA,[2]Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY,[3]Department of Psychiatry, University of Stellenbosch, Cape Town, South Africa,[4]Department of Psychiatry and Psychotherapy, University of Hamburg-Eppendorf, Hamburg, Germany,[5]Clinical Development, Organon, a part of Schering-Plough Corporation, Roseland, NJ

Background: Asenapine is a novel psychopharmacologic agent being developed for treatment of schizophrenia and mania associated with bipolar 1 disorder.
Methods: We reviewed completed schizophrenia studies in the 3000+ patient Olympia clinical trial program: 4 acute studies (Hera) and 1 long-term safety study (ACTAMESA). Results from long-term studies such as Aphrodite (481 patients), which focuses on prominent persistent negative symptoms, will be available soon.
Results: In 2 of the 4 randomized short-term Hera studies, a high placebo effect was observed: difference on the PANSS total score (asenapine-placebo) did not reach statistical significance. However, in 2 randomized controlled 6-week trials (622 patients), asenapine produced 19- to 21-point reductions in PANSS total score (significantly superior to placebo using mixed-model for repeated measures analysis). Asenapine also showed benefit in reducing negative symptoms, a finding under further study in the aforementioned long-term Aphrodite study. Asenapine was associated with mild effects on weight (0.5–0.7 kg vs –0.4 to 0.2 kg with placebo) and prolactin levels (–15 to –2 µg/L vs –19 to –4 µg/L with placebo). In the year-long randomized ACTAMESA study (1219 patients treated with flexibly dosed asenapine or olanzapine), overall adverse event (AE) rates were similar for asenapine and olanzapine (drug-related AEs, 60% and 61%, respectively; withdrawals due to AEs, 6.3% and 6.8%). Extrapyramidal symptoms were more common with asenapine (18% vs 8% with olanzapine), clinically significant weight gain was more common with olanzapine (36% vs 15% with asenapine).
Conclusions: Asenapine is effective and well tolerated in the treatment of schizophrenia.
Supported by Organon, a part of Schering-Plough

914. Obsessive-Compulsive Symptoms or Obsessive-Compulsive Disorder in Patients with Schizophrenia Treated with Clozapine or Haloperidol

Antonio R. Sa, Ana G. Hounie, Aline S. Sampaio, Euripedes C. Miguel, Helio Elkis

Department & Institute of Psychiatry, Clinical Hospital, School of Medicine, University of São Paulo., São Paulo, Brazil

Background: We conducted a cross-sectional study to compare the prevalence and the severity of OCS and OCD in patients with schizophrenia treated with clozapine or haloperidol.
Methods: SCID-I/P was used for the diagnoses of schizophrenia and OCD. All subjects (n= 60) completed the Y-BOCS, PANSS and CGI. Best Estimate Diagnoses were assigned by the first author and two psychiatrists to assure reliability. Chi-square test with Yates correction, Mann-Whitney U test and Kruskal-Wallis test were used for the statistical analyses.
Results: Among the 60 schizophrenia patients evaluated, 10 (16.7 %) met DSM-IV criteria for both schizophrenia and OCD; 13 (21.7 %) had OCS but not OCD and 37 (61.6 %) had neither OCD nor OCS. The prevalence of OCD or OCS was similar in patients taking clozapine or haloperidol (40% vs 35% respectively). Patients using clozapine showed higher severity of OCS than patients using haloperidol (P= 0.027). Patients with schizophrenia and OCD also showed higher severity of schizophrenic symptoms when compared to patients with schizophrenia without OCS (P= 0.002).
Conclusions: Although the presence of OCS or OCD was similar in the groups taking clozapine or haloperidol, patients using clozapine showed higher scores on the YBOCS. These results may support an association between the exacerbation of obsessive-compulsive phenomena and the use of clozapine.

915. Correlating Functional Domains and Symptom Clusters in Schizophrenia

Bruce Simonson, Wayne Macfadden, Tom Haskins, Cynthia Bossie, Young Zhu, Larry Alphs

Ortho-McNeil Janssen Scientific Affairs, L.L.C., Titusville, NJ

Background: Meaningful measures of functioning are important in determining treatment effectiveness for schizophrenia patients. The Personal and Social Performance (PSP) scale is a validated clinician-rated measure of patient functioning; how its domains correlate to other clinical measures has not been established. This analysis explored the relationship between PSP domains, measures of symptomatology and demographics in schizophrenia patients.
Methods: Post-hoc analysis evaluated baseline data from an open-label, rater-blinded, multicenter study of patients randomized to risperidone long-acting injectable or aripiprazole for up to 2 years. Correlational and categorical analyses compared PSP total score and its four domain scores (socially useful activities, personal & social relationships, self-care, disturbing & aggressive behaviors) to the Positive and Negative Syndrome Scale (PANSS) factor scores, onset of illness and demographics.
Results: 355 evaluable subjects were included in this baseline analysis. Data did not suggest a significant relationship between PSP domain scores and age, gender or onset of illness. Each PSP domain score correlated with several PANSS factors, as follows: socially useful activities with positive (0.323; P<0.0001), negative (0.405; P<0.0001) and disorganized thoughts (0.489; P<0.0001); personal & social relations with negative (0.501; P<0.0001) and disorganized thoughts (0.454; P<0.0001); self-care with negative (0.344; P<0.0001) and disorganized thoughts (0.450; P<0.0001); and disturbing & aggressive behavior with positive (0.300; P<0.0001), disorganized thoughts (0.309; P<0.0001) and uncontrolled hostility/excitement (0.598; P<0.0001).
Conclusions: For the first time, functioning domains of the PSP have been shown to correlate with clinical measures of symptomatology used for treating schizophrenia.
Supported by Ortho-McNeil Janssen Scientific Affairs, L.L.C.

916. Naturalistic Treatment of Functional Deficits in the Schizophrenia Prodrome

Christopher W. Smith, Andrea Auther, Christoph Correll, Lauren Baskir, Danielle McLaughlin, Barbara Cornblatt

Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY

Background: Research on the schizophrenia prodrome has focused largely on determining rates and predictors of conversion to psychosis. However, social and role functioning are increasingly studied in the prodrome, both for prediction of conversion and as outcomes. The Recognition and Prevention Program previously found that functional deficits precede psychosis and are stable over time. However, examining group means can mask subgroup differences. This study will explore whether differences in naturalistic pharmacological treatment affect social and role functioning.
Methods: Study subjects (n=35) were considered prodromal based on attenuated positive symptoms assessed with SIPS/SOPS. Subjects were evaluated at baseline and ~12 months. Functioning was assessed using Global Functioning: Social and Role scales. Psychopharmacological treatment was prescribed by physician's choice and included primary treatment with antipsychotics (AP; n=24) or antidepressants (ADP; n=11). Separate RMANOVAs were performed on social and role domains, with medication-group as the between-subjects factor.
Results: For social functioning, neither the main effect (p=.46), nor the interaction with medication-group (p=.86) were significant. For Role functioning, both the main effect of time (p=.01) and the interaction with medication-group (p<.0005) were significant, with ADP improving. No baseline symptom or functional differences between medication groups (p>.18) were observed.
Conclusions: Findings suggest that antipsychotics may not be useful for improving social or role functioning in the prodrome, but antidepressants may improve role functioning. Non-randomized medication assignment is a limitation. However, no obvious baseline differences exist between medication groups. Results indicate that social (moreso than role) deficits are core, treatment-resistant aspects of the vulnerability for schizophrenia.
Supported by RO1MH61523: Cornblatt, PI, Characterization of Prodromal Schizophrenia; P30MH74543: Kane, PI, Early Phase Schizophrenia: Optimizing Outcomes

917. Extrapyramidal Symptom and Akathisia Profile of Iloperidone in Phase III Schizophrenia Clinical Trials

Peter J. Weiden[1], Rosarelis Torres[2]

[1]Center for Cognitive Medicine, Univeristy of Illinois at Chicago, Chicago, IL,[2]Clinical Affairs, Vanda Pharmaceuticals Inc., Rockville, MD

Background: Antipsychotic-induced extrapyramidal symptoms (EPS) and akathisia can influence functioning, quality of life, and treatment adherence. Iloperidone, a mixed D_2/5-HT_2 antagonist being developed for the treatment of schizophrenia, is under review by the FDA. Currently available atypical antipsychotics still show a range of liability to cause EPS or akathisia, so these adverse events are important aspects of any developing antipsychotic agent.
Methods: EPS and akathisia were assessed in a pooled analysis of iloperidone data from 4 short-term, Phase III, double-blind, placebo-controlled clinical trials of adult patients with acute schizophrenia. Outcomes include rates of treatment-emergent adverse events (TEAEs), changes from baseline in Extrapyramidal Symptoms Rating Scale (ESRS) and Barnes Akathisia Scale (BAS), and rates of concurrent anticholinergic use.

Results: A total of 2505 patients (iloperidone [ILO] 4-24 mg/day, n=1344; haloperidol [HAL] 5-20 mg/day, n=118; risperidone [RIS] 4-8 mg/day, n=306; ziprasidone [ZIP] 160 mg/day, n=150; placebo [PBO], n=587) were included. EPS was reported as a TEAE in 4.6% (ILO), 20.3% (HAL), 9.5% (RIS), 9.3% (ZIP), and 4.1% (PBO) of patients. Mean changes in overall ESRS from baseline to endpoint were -0.3 ILO, 1.8 HAL, -0.3 RIS, 0.2 ZIP, and -0.3 PBO. Akathisia was reported as a TEAE in 2.5% (ILO), 13.6% (HAL), 6.9% (RIS), 7.3% (ZIP), and 2.7% (PBO) of patients, and worsening of akathisia (BAS scores) was reported in 7.8% (ILO), 15.5% (RIS), 15.6% (ZIP), and 11.4% (PBO) of patients.
Conclusions: Iloperidone may have a lower propensity to cause EPS or akathisia than haloperidol, risperidone, or ziprasidone.
Supported by Vanda Pharmaceuticals funded this analysis

918. Suicide Attempts among Women during Hypoestrogenic Phases

Enrique Baca-Garcia[1,2,3], Carmen Diaz-Sastre[4], Antonio Ceverino[5], M. Mercedes Perez-Rodriguez[4], Jeronimo Saiz-Ruiz[4,6], Jose de Leon[7], Maria A. Oquendo[1]

[1]Department of Neurosciences, Columbia University Medical Center, New York, NY,[2]Psychiatry, Fundacion Jimenez Diaz Hospital, Madrid, Spain,[3]Psychiatry, Autonoma University, Madrid, Spain,[4]Department of Psychiatry, Ramon y Cajal Hospital, Madrid, Spain,[5]Department of Psychiatry, Fundacion Jimenez Diaz Hospital, Madrid, Spain,[6]Psychiatry, Alcala University, Madrid, Spain,[7]Mental Health Research Center (MHRC), Eastern State Hospital,, Lexington, KY

Background: To determine whether perimenstrual phases in fertile women are associated with acute risk for suicide attempt, to explore whether risk is elevated during all hypoestrogenic periods, and to examine the characteristics of suicide attempts during hypoestrogenic periods.
Methods: Women (N=431) recruited within 24 hours of a suicide attempt were assessed for psychopathology, suicidal behavior and LH, FSH, estradiol and progesterone blood levels.
Results: Women who attempted suicide during hypoestrogenic periods (menstrual phase, amenorrhea and menopause) reported more severe suicide intent than those whose attempts occurred during other phases.
Conclusions: Suicide attempts among women when estrogen levels are low are associated with greater severity. Low estrogen levels may constitute a key factor in the neurobiological basis of suicidal behavior among women, suggesting a novel, testable hypothesis regarding the underpinnings of suicidal acts.
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919. Differences in Suicidal Behavior may help to Differentiate between Narcissistic and Antisocial Personality Disorder

Hilario Blasco-Fontecilla[1], Kanita Dervic[2], José de León[3], Maria Oquendo[4], Enrique Baca-García[5]

[1]Department of Psychiatry, DR. R. Lafora Hospital, Madrid, Spain,[2]Department of Child and Adolescent Neuropsychiatry, University Hospital, Medical University of Vienna, Vienna, Austria,[3]Department of Psychiatry, University of Kentucky Mental Health Research Center at Eastern State Hospital, Lexington, KY,[4]Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY,[5]Department of Psychiatry, Fundación Jiménez Diaz, Madrid, Spain

Background: Narcissistic personality disorder (NPD) and antisocial PD (APD) are not always easily differentiated disorders. Though both PDs are grouped into DSM-IV cluster B, subjects diagnosed with NPD might exert a better impulse control. Impulsivity and lethality seem to be inversely associated during suicide attempts. Our main objective was to test whether suicide attempts are different in terms of impulsivity/lethality in suicide attempters (SA) diagnosed with NPD and APD.
Methods: We assessed 446 SA admitted to the emergency room at two general Hospitals in Spain between 1999 to 2003. The diagnosis of PDs was made by using the DSM-IV version of the International Personality Disorder Questionnaire-Screening Questionnaire (IPDE-SQ). An adjusted cut-off point was used in order to increasing specificity. The following scales were used in order to measure impulsivity/lethality of suicide attempts: The Lethality Rating Scale (LRS), the Risk-Rescue Rating Scale, the Suicide Intent Scale (SIS), and the Barratt Impulsiveness Scale (BIS).
Results: subjects diagnosed with NPD had suicide attempts characterized by an increased expected lethality (SIS factor 1) (T= -4.244, gl= 439, p< 0.000), while in those diagnosed with APD were characterized by a higher impulsivity (BIS) (T= -3.961, gl= 442, p= 0.000).
Conclusions: Suicide attempts in subjects diagnosed with NPD are not characterized, in contrast to APD, by a higher impulsivity. The characteristics of a suicide attempts might help in differentiating between both PDs. Targeted therapies aimed to decreasing suicidal risk may be different depending on specified PD diagnosis.
Supported by NARSAD, FIS, CIBER

920. Lower CSF MHPG Predicts Short-Term Risk for Suicide Attempt

Hanga Galfalvy

Psychiatry, Columbia University, New York, NY

Background: Low cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) predicts suicide in mood disorders in prospective studies. Our goal was to study the association between other CSF monoamine metabolite levels and future suicide attempts.
Methods: 184 subjects presented for treatment within the context of a Major Depressive Episode. CSF levels of 5-HIAA, homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) were assayed. 159 subjects returned for follow-up interviews 3 months and/or 1 year later. Survival analysis was used to examine the association between monoamines and suicide attempts during follow-up.
Results: Low MHPG predicted future suicide attempt (HR=2.6, p=.023) and correlated with higher medical seriousness of attempts (r= -0.4, p = 0.038). HVA was inversely associated with the medical seriousness, but not the likelihood, of past or future suicide attempts. Low ratio of HVA to 5-HIAA levels was associated with the likelihood of past and future medically serious attempts (OR=1.9, p=.029; HR=2.5, p=.042). MHPG and HVA were significantly associated with history of drug or alcohol abuse/dependence and with current smoking, a predictor of future suicide attempts (HR=2.6, p=.015) but were not associated with severity of other psychopathology or childhood adversity.
Conclusions: We have identified a relationship between MHPG and both probability and lethality of future suicide attempts in major depression. In addition we confirmed previous studies showing that a low HVA/5-HIAA ratio is associated with a greater likelihood of and more serious future suicide attempts in depressed patients. Both HVA and MHPG are linked to tobacco use, another known predictor of future suicide attempts.
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921. Risk Factors for Adolescent Suicidality in Offspring with and without Borderline Personality Disorder

Marianne Goodman[1,2], Joseph Triebwasser[1,2], Uday Patil[1], Antonia New[1,2], Elizabeth Diamond[1], Larry Siever[1,2]

[1]Psychiatry, Mount Sinai School of Medicine, New York, NY,[2]Psychiatry, James J Peters VA Medical Center, Bronx, NY

Background: Suicide is the third leading cause of death in Americans aged 15-24; each year, 1,600 U.S. teenagers commit suicide (Gould et al., 2003). Borderline personality disorder (BPD) is an important cause of attempted and completed suicide in adults (Soloff et al., 2002). We present data about developmental antecedents of adolescent suicidality in a sample enriched for BPD.
Methods: We have gathered data on suicide attempts and suicidal ideation, via surveys of parents who have at least one adolescent and/or adult child with BPD. We have developed a questionnaire concerning both BPD and non-BPD offspring, with over 100 questions covering infancy through young adulthood, targeting the development of psychopathology and assessing suicide-related and deliberate self-harm variables in detail.
Results: To date over 800 surveys have been completed, with approximately 500 having usable data. We report on 496 offspring, 170 with strictly defined BPD, 206 psychiatrically ill but without BPD, and 120 healthy controls. Significant predictors of adolescent suicidality, derived from binary logistic regression, included 1) childhood factors of few friends and picky eating 2) adolescent factors of delusions, homicidality, teenage romantic relationships, rape and pregnancy variables, property destruction, and impulsivity. Being a perpetrator of bullying was a protective factor.
Conclusions: Suicidality is frequent in adolescents with BPD and Axis I disorders. Adolescents at increased risk for suicidal behavior exhibit impulsivity, homicidality and delusions and experience interpersonal problems since childhood, and precocious sexual involvement in adolescence. Suicidal behavior appears to be distinct from outward expressions of aggression.

922. CSF 5-HIAA and DST Non-Suppression - Orthogonal Biologic Risk Factors for Suicide in Male Mood Disorder Inpatients

Jussi Jokinen, Anna-Lena Nordström, Peter Nordström

Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Background: Two biomarkers of suicide risk; nonsuppression in the dexamethasone suppression test (DST) and low 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) have evidence for predictive power for suicide in mood disorders. The interrelation of the two systems seems to be different in suicide attempters compared to depressed inpatients without suicide attempt, indicating that two biomarkers may be seen as independent. This investigation determined the interrelation of low CSF 5-HIAA and the DST nonsuppression in suicide victims with mood disorder.
Methods: Fifty-eight mood disorder inpatients not receiving any treatment with antidepressants underwent lumbar puncture and the DST. Plasma cortisol levels at 8:00 a.m., 4:00 p.m. and 11:00 p.m. were analyzed in relation to CSF 5-HIAA. All patients were followed up for causes of death and suicides were verified with death certificates.
Results: During follow-up (mean 21 years), 11 (19 %) patients had committed suicide. In male suicide victims (n=6), the serum cortisol level at 4:00 p.m. showed a significant positive correlation with CSF 5-HIAA. Low CSF 5-HIAA predicted all early suicides (within one year), whereas all males who committed suicide after one year were DST nonsuppressors. In female suicide victims (n=5), the postDST serum cortisol did not correlate with CSF 5-HIAA.
Conclusions: Low CSF 5-HIAA and DST nonsuppression are orthogonal biologic risk factors for suicide in male mood disorder inpatients. CSF 5-HIAA is associated with short-term suicide risk; HPA axis dysregulation seems to be a long-term suicide predictor.

923. Characterization of Decision-Making Impairment in Suicide Attempters and the Influence of Attention to Wins on Suicidal Intent and Repetition

Fabrice Jollant[1], Sébastien Guillaume[1], Isabelle Jaussent[2], Didier Castelnau[3], Alain Malafosse[4], Philippe Courtet[1]

[1]CHU Montpellier, Department of Psychological Medicine and Psychiatry, Université Montpellier 1 & Inserm U888, Montpellier, France,[2]Department of Biostatistics, Université Montpellier & Inserm U888, Montpellier, France,[3]Department of Psychological Medicine and Psychiatry, CHU Montpellier, Montpellier, France,[4]Département de médecine génétique et Laboratoires, Hôpitaux Universitaires de Genève, Geneva, Switzerland

Background: Impaired decision-making may represent a cognitive factor of vulnerability to suicidal behavior. Recent development in the analysis of decision-making performance measured by the Iowa Gambling Task (expectancy-valence model) enables to distinguish 3 modes of decision-making: decisions guided by attention to losses vs. to wins, decisions guided by past vs. recent outcomes and consistent vs. erractic choices.
Methods: We compared these 3 modes of decision-making in 143 healthy subjects, 125 patients with a past history of affective disorders but no history of suicidal acts (affective controls) and 179 patients with a past history of both affective disorders and suicidal acts (suicide attempters). All patients were normothymic at the time of assessment.
Results: In comparison to both control groups and after adjustment for age and gender, suicide attempters make decisions significantly more often on the basis of a higher attention to wins (p=0.03) and in an erractic way (p=0.03). Control groups were not different from each other. Moreover, a higher attention to gain was associated with higher suicidal intent of the most severe suicidal act (p=0.008) and with more than 3 past suicidal acts (p=0.02).
Conclusions: Different processes may underlie decision-making impairment in suicide attempters. Potential mechanisms and implications for understanding the cognitive aspects of vulnerability to suicidal behavior will be discussed.
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924. fMRI Markers of Early-Onset Suicide Attempt--Evidence of Decreased Activation in the Medial Prefrontal Cortex

Lisa Pan, Stefanie Hassel, Sharon Nau, David Brent, Mary Phillips

Western Psychiatric, University of Pittsburgh Med Ctr, Pittsburgh, PA

Background: Clinical and epidemiological studies consistently describe difficulties in emotion regulation and impulsivity in suicide attempters. However, these domains have rarely been assessed using standard performance tasks, which in turn are linked to neural function. The primary objective of this research project is to examine the neural circuitry underlying trait dependent abnormalities in adolescents with early onset suicidal behavior by focusing on emotional processing. We therefore aimed to employ fMRI to examine corresponding activity in neural regions implicated during performance of these tasks in suicide attempters versus control groups.
Methods: Three groups of adolescents, those with: (1) lifetime history of attempt and remitted MDD (attempters, SA); (2) history of remitted MDD, but

no attempt (affective controls, AC), and (3) healthy controls (HC) participated in the study. All participants performed standardized happy and fearful facial expression gender labeling tasks. Neural activity during performance of these tasks was compared in SA versus AC and HC.
Results: Preliminary data show reduced activity to angry faces in the medial pre-frontal cortex (PFC, BA 10/32) in SA (n=5), versus AC (n=3). Exposure to happy faces elicits no group differences in PFC activity. We are currently analyzing data in larger numbers of participants.
Conclusions: Brodmann Area 10/32, is involved in the exercise of restraint, and has been implicated in risky decision making in adults. Our findings in adolescent SA are consistent with previous studies that demonstrate a difficulty with regulation of negative emotion, beyond depression, related to the etiology of suicidal behavior.
Supported by Klingenstein Third Generation Foundation and American Foundation for Suicide Prevention

925. Hallucinations, Pseudohallucinations- Severity of Suicidal Ideations among Emergency Psychiatry Patients: A Pilot Study

Praveen Penagaluri[1], Kristen L. Walker[2], Rif S. El-Mallakh[1]

[1]Psychiatry, University of Louisville School of Medicine, Louisville, KY,[2]Psychology, University of Louisville School of Medicine, Louisville, KY

Background: Prediction of suicide is a difficult but essential task in nearly all clinical psychiatric evaluations. A multitude of suicide risk factors have been identified that include symptoms such as psychosis and command hallucinations. Yet, despite knowledge of these factors, prediction of suicidal behavior remains suboptimal. Hallucinations, in particular command hallucinations, are significant risk factors. This study investigated relative relationships between auditory hallucinations and non psychotic hallucinations (pseudohallucinations) and suicidal risk.
Methods: A sample of 206 consecutive patients seen in an emergency psychiatric service were evaluated for the presence and intensity of hallucinatory experiences (assessed by the hallucination item of the Positive and Negative Symptoms Scale [PaNSS]), suicidal intensity (assessed by the suicide item of the Montgomery Asberg Depression Rating Scale [MADRS]), and cumulative suicide risk (determined by the total number of risk factors).
Results: Individuals with pseudohallucinations appeared to experience greater intensity of acute suicidal ideation compared with either subjects with no hallucinatory experiences (P = 0.006) or subjects with psychotic hallucinations (P = 0.003). There are no differences in the intensity of the hallucinatory experience, the number of risk factors for completed suicide in patients with pseudohallucinosis compared with patients with psychotic hallucinations or no hallucinatory.
Conclusions: Subjects with pseudohallucinosis experience more intense suicidality when they are ill than those with psychotic hallucinations or no hallucinatory experience. Suicidal evaluation can be improved if a determination is made as to the psychotic or nonpsychotic nature of hallucinatory experiences.

926. Suicidal Ideation, Violent Behavior, and Self-Injury in Schizophrenia Patients Treated with Long Acting Risperidone: 12-Month Results from E-Star

Jos Peuskens[1], Alex Rodriguez[2], Ivan Tuma[3], Jan Pecenak[4], M. van Kooten[5], Lars Eriksson[6], B. Bork[7], Michael Povey[8], Annette Lam[9], Zhongyun Zhao[10]

[1]KU Leuven campus UC St. Jozef Kortenberg, Universitair Psychiatrisch Centrum, Leuven, Belgium,[2]Psychiatry, Centro Forum de Barcelona, Barcelona, Spain,[3]Medical School and Teaching Hospital Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic,[4]Psychiatry, FNSP Bratislava, Bratislava, Slovakia,[5]De Geestgronden-Buitenamstel, Ambulant ACT,, Binnenweg 3 te Hoofddorp, The Netherlands,[6]Psychiatry, SU/Östra RPV, Hisings-Backa, Sweden,[7]Psychiatry, DP Tønder, Tønder, Denmark,[8]Statistics, SGS Life Science Services, Wavre, Belgium,[9]Health Economics, Johnson & Johnson Pharmaceutical Services, Toronto, ON, Canada,[10]Health Economics, Johnson & Johnson Pharmaceutical Services, Raritan, NJ

Background: To examine the incidence of suicidal ideation, violent behavior, and deliberate self-harm in patients with schizophrenia treated with risperidone long-acting injection (RLAI) enrolled in the electronic-Schizophrenia Treatment Adherence Registry (e-STAR) from seven European countries (Belgium, Czech Republic, Denmark, Netherlands, Slovakia, Spain, Sweden).
Methods: e-STAR is an international, long-term, prospective, observational study of patients with schizophrenia who commence RLAI treatment. Data are collected both retrospectively for 1 year and prospectively every 3 months for 2 years. The treating physician evaluated whether there was a presence of suicidal ideation, violent behavior, and self-injury at baseline and prospectively at 3 monthly intervals. Pooled results presented are based on data from patients who have completed their 12-month follow-up visit.
Results: To date, among 4,196 patients enrolled in e-STAR from the seven European countries, 2,239 patients who have been followed for at least 12 months (89.7 % were still on RLAI) were included in this interim analysis. Most were male (61.8%) with mean age of 38.7±12.0 years and mean time since diagnosis of 11.2±10.7 years. Compared to baseline, significant reductions were observed in the occurrence of suicidal ideation (12.2% to 1.0%, p<0.001), violent behavior (11.9% to 0.5%, p<0.001), and self-injury (4.6% to 0.4%, p<0.001).
Conclusions: Results from this pooled interim analysis showed that the incidence of suicidal ideation, violent behavior, and self-injury decreased in patients with schizophrenia treated with RLAI for 12 months.
Supported by Johnson & Johnson

927. Gene Expression Alterations Implicated in Suicide in Mood Disorder Subjects

P. Adolfo Sequeira[1], Marquis Vawter[1], Ling Morgan[1], Jun Li[2], Simon Evans[3], Brandi Rollins[1], Prabhakara Choudary[4], David M. Walsh[1], Richard M. Myers[2], Stanley J. Watson[3], Huda Akil[3], Edward G. Jones[4], William E. Bunney[1]

[1]Psychiatry and Human Behaviour, University of California, Irvine, Irvine, CA,[2]Stanford Human Genome Center, Stanford University, Palo Alto, CA,[3]Mental Health Research Institute, University of Michigan, Ann Arbor, MI,[4]Center for Neuroscience, University of California, Davis, Davis, CA

Background: Several lines of evidence point to an implication of mood disorders in suicide. Mood disorders patients often present suicidal behaviors and are at high risk to complete suicide. However, the majority of mood disorder patients never commit suicide. The purpose of this study was to investigate gene

expression changes in the dorsolateral prefrontal cortex (DLPFC) associated with suicide in mood disorder patients.
Methods: We used Affymetrix HG-U133 Plus 2.0 arrays to investigate gene expression changes and analysis of covariance to correct for age, pH, gender and RNA degradation. Confirmation was performed by RT-PCR with SYBRGreen and the DeltaDeltaCt method.
Results: A total of 121 genes were differentially expressed at the P<0.005 level between suicides and non-suicides. Ingenuity pathway analysis and gene ontology analysis both converged to point out to signaling and serotonin receptor signaling as particularly altered in suicide victims. Confirmation of these results was performed for a group of differentially expressed genes in the DLPFC with satisfactory agreement. The most significant gene, the 5-HT2A serotonergic receptor, also showed expression levels that were dependent on the -1438A/G promoter polymorphism genotype, suggesting a genetic and a functional interaction of this gene with suicide.
Conclusions: In conclusion, molecular alterations specifically associated with suicide in major depression and bipolar disorder subjects were observed in the DLPFC pointing out to possible molecular markers or therapeutic targets for suicide in mood disorders.
Supported by Pritzker Neuropsychiatric Disorders Research Fund L.L.C.

928. Treatment-Resistant Depression Registry: Lifetime Profile of Pharmacotherapy at Baseline

Michael J. Burke[1], Dana Soetaert[1], Ingela Danielsson[2]

[1]Psychiatry, University of Kansas School of Medicine, Wichita, KS,[2]Clinical and Medical Affairs, Cyberonics, Inc., Houston, TX

Background: The Treatment-Resistant Depression (TRD) Registry was established in 2005 by the manufacturer of the vagus nerve stimulation system. This presentation introduces lifetime profiles of pharmacotherapy for Registry patients.
Methods: Enrollment required that patients be in a major depressive episode, chronic (≥2 years) or recurrent (≥3episodes), AND had not responded to 4 or more adequate antidepressant treatments. This report is from baseline screening forms of 202 patients enrolled at the June 30, 2007, data lock.
Results: Of 202 patients, 136 (67.3%) were female, age 49.8/51 years (mean/median) at enrollment. Initial age at depression onset was 20.5/16 years with initial diagnosis at 29.7/30 years. Lifetime depressive episodes numbered 16.5/5 (range, 1-200). Lifetime psychiatric hospitalizations numbered 3.1/1(range, 0-62). During their lifetime, 60% had been hospitalized, 48% had attempted suicide. At baseline, pharmacotherapy courses averaged (mean, SD): 9.1 (3.3) (n=202); 70% reported monotherapy trials: 4.0 (2.5); 87% reported combination therapies: 5.0 (3.4); 49% reported augmentation therapies: 4.0 (3.1). Regarding treatment response, 49.6% of medication courses elicited partial responses (n=158); 19.6% of treatment course were not tolerated (n=63). Medication courses included selective serotonin reuptake inhibitors (SSRI) 3/1-6 (median, range) (n=190); tricyclic antidepressants1/1-5 (n=103); other antidepressants 3/1-6(n=193); lithium 1/1-2(n=92); anticonvulsants 1/1-5(n=152); atypical antipsychotic drugs 1/1-2(n=98); and stimulants 1/1-5(n=92).
Conclusions: Pharmacotherapy for these TRD patients was characterized by multiple SSRI, monotherapy, and combination therapy trials with relatively little use of monoamine oxidase inhibitors and lithium. Presentation will feature detailed analysis of pharmacologic treatments including additional enrolled patients from the December 2007 data lock.
Supported by Cyberonics, Inc.

929. Clinical Significance of Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Depression

Mark Andrew Demitrack[1], Michael E. Thase[2]

[1]Medical, Neuronetics, Inc., Malvern, PA,[2]Psychiatry, University of Pennsylvania, Philadelphia, PA

Background: To explore the relationship between prior treatment resistance and clinical outcome in a recently completed multisite RCT of TMS for pharmacoresistant depression.
Methods: Clinical outcomes from a recently completed RCT of TMS in depression (O'Reardon, 2007) and an open-label extension study of treatment non-responders in that RCT (Avery, submitted) were stratified for the level of prior treatment resistance determined by the Antidepressant Treatment History Form (ATHF).
Results: Approximately half of the original study population (164/301; 54.5%) had failed to benefit from only one ATHF adequate antidepressant trial in current episode (median treatment exposures = 4, range 1 to 23). The primary outcome, MADRS total score change from baseline, was statistically significant in favor of active TMS (mean diff: -5.0, 95%CI [-7.8, -2.2], P, 0.0006) and was larger than the outcome observed in the remainder of the study population (ES = 0.94 ATHF 1 vs -0.01 ATHF >2). Seventy-nine patients (48.2%) failed to benefit from the blinded, randomized treatment and were enrolled in the open-label extension study. In the open-label study, a similarly greater benefit was observed in the ATHF 1 population in sham non-responders from the RCT compared to the remainder of the study population (MADRS mean change from baseline: -20.8, 95%CI [-16.9, -24.7] ATHF 1 vs -13.3, 95%CI [-9.0, -17.5] ATHF >2).
Conclusions: Prior treatment resistance has a negative influence on subsequent treatment outcome. These data confirm the clinical significance of TMS in the treatment of patients with depression who have failed to benefit from prior pharmacotherapy.
Supported by Neuronetics, Inc.

930. Feasibility Study of an Implantable Cortical Stimulation System for Patients with Major Depressive Disorder

Darin D. Dougherty[1], Michael E. Thase[2], Robert H. Howland[3], Karleyton C. Evans[1], Harold Harsch[4], Douglas Kondziolka[5], Emad Eskandar[6], Alvaro Pascual-Leone[7]

[1]Psychiatry, Massachusetts General Hospital, Charlestown, MA,[2]Psychiatry, University of Pennsylvania, Philadelphia, PA,[3]Psychiatry, University of Pittsburgh, Pittsburgh, PA,[4]Psychiatry, Medical College of Wisconsin, Milwaukee, WI,[5]Neurosurgery, University of Pittsburgh, Pittsburgh, PA,[6]Neurosurgery, Massachusetts General Hospital, Boston, MA,[7]Neurology, Beth Israel-Deaconess Medical Center, Boston, MA

Background: Repetitive transcranial magnetic stimulation has short-lived antidepressant effects when applied to the left DLPFC. These findings prompted study of an investigational implantable cortical stimulation (CS) system targeting the left DLPFC.
Methods: After an observation phase (≥8 weeks) with stable medication, 12 refractory MDD patients were implanted with an epidural CS system (Renova™ DT, Northstar Neuroscience, Seattle, WA). Patients were randomized to single blind active or sham stimulation for 8 weeks (primary endpoint), then active stimulation. Medications were not changed unless indicated. Efficacy: Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Global Assessment Function (GAF).
Results: Patients: 6 female, 6 male (48±6 years); MDD for 27±10 years; current

episode duration 6.9±8.1 years; failed 9.8±1.7 antidepressant treatments. Ten received ECT (16.2±23.2 treatments). At baseline: mean HDRS=35.3±5.8; MADRS=32.7±4.6; GAF=42.3±5.8. One patient was excluded from further analysis (protocol deviation). Week 8: HDRS decreased by 22±20% (active stimulation; n=6) vs 3±17% (sham; n=5); MADRS decreased 22±21% (active) vs 8±15% (sham); GAF increased 23±32% (active) vs 12±9% (sham). Weeks 8 to 16 (active stimulation; n=11): mean change scores improved: 21% to 26% (HDRS), 22% to 32% (MADRS), 25% to 46% (GAF). No device-related serious adverse events. PET imaging results will be discussed relative to patient outcomes.
Conclusions: This study describes the first use of a CS system targeting the DLPFC. Preliminary results suggest that CS has a therapeutic effect that increases over time. A larger study is needed to confirm these findings.
Funding: Northstar Neuroscience.
Supported by Northstar Neuroscience

931. The Antidepressant Effect of Transcranial Magnetic Stimulation is Strongly Correlated with the Distance of the Coil from the Midline

Gary Hasey[1], Mark H. C. Shew[1], Jackie Heaslip[1], Duncan MacCrimmon[1], Gabby Abraham[2], Roumen Milev[2], Alvaro Pascual-Leone[3], Russell Joffe[4]

[1]Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada,[2]Psychiatry, Queen's University, Kingston, ON, Canada,[3]Neurology, Harvard Medical School, Boston, MA,[4]Psychiatry, New Jersey Medical School, Newark, NJ

Background: The inconsistent results of studies of the antidepressant effect of transcranial magnetic stimulation (TMS) may be related to differences in the site of stimulation. In this study we examine response in relation to the location of the treatment site (TS).
Methods: After a 10 day drug washout, 65 depressed subjects with Major Depressive Disorder or Bipolar Disorder were treated with SSRI antidepressants and either true or sham TMS at 90-110% motor threshold over 10 days to the left dorsolateral pre-frontal cortex (DLPFC) (10 Hz X 8 seconds/train X 20 trains / day), the right DLPFC (1 Hz X 60 seconds/train X 2 trains /day) or both. The TS was marked on a spandex swim hat landmarked to the nasion, inion, vertex and auditory meati. TS was arbitrarily determined to be 5 cm forward, in a parasagittal plane, from the motor site. The distance of the TS from the anterior to posterior midline (DFM), variable across subjects, was measured. For subjects receiving bilateral TMS, DFM was defined as the mean of both sides.
Results: The % change of the Hamilton depression rating scale from baseline was positively correlated with DFM in subjects getting true TMS (N=43, R2= .184, p=0.004) but not in subjects getting sham TMS (N=22, R2= .016, p=0.571).
Conclusions: The magnitude of the antidepressant effect of TMS is strongly related to the positioning of the coil from the midline. More lateral coil placement is associated with superior efficacy. Further studies to determine optimal coil positioning are required.
Supported by Canadian Psychiatric Research Foundation, Ontario Mental Health Foundation, Stanley Research Foundation

932. TMS for Depression using an Optimized Prefrontal Coil Positioning

Kevin A. Johnson[1], Qiwen Mu[1], Ziad Nahas[1], Multisite OPT-TMS Study Group[2]

[1]Psychiatry, Medical University of South Carolina, Charleston, SC,[2]Psychiatry, Columbia University, Emory University, Medical University of South Carolina, Washington University, Charleston, SC

Background: The antidepressant response to rTMS appears to be dose and target dependent. An ongoing NIMH funded study uses TMS parameters to maximize the stimulation duration and intensity. It also seeks to ensure that TMS is optimally positioned over the prefrontal (and not pre-motor) cortex following a visual inspection method (VIM).
Methods: All enrolled subjects receive an entry MRI scan, while wearing a swim cap with fiducials marking the motor thumb scalp position and the location of the presumed prefrontal target, 5 cm more anterior. A single researcher examines scans from all 4 sites and determines the clinical target site in reference to the anterior pole of temporal lobes. He then instructs investigators if they should move their coil placement by 1 cm to increase the probability of reaching the prefrontal cortex on either hemisphere.
Results: To date, VIM resulted in 50/123 recommendations to move the coil 1 cm forward (left hemisphere) and 52/116 (right hemisphere) with 7 scans missing right fiducials. A repeated analysis identified 16/123 cases where fiducials sat at the border of pre-motor and prefrontal cortex. Percentages of nudging forward for the left hemisphere across 4 sites were 52%, 52%, 46% and 15%. Ongoing analysis using an automated system will provide complementary information on specific Brodmann areas and the validity of the VIM.
Conclusions: Using a conservative VIM algorithm, 40% of subjects have benefited from a stimulation site anterior to the standard 5 cm rule. Future analyses will link such targeting methods with treatment outcomes.
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933. Gamma Ventral Capsulotomy for Obsessive Compulsive-Disorder: Preliminary Results of a Randomized Controlled Trial

Antonio C. Lopes[1], Anita Taub[1], Carina C. D'Alcante[1], Maria E. de Mathis[1], Marcelo Q. Hoexter[2], Fernando S. Gouvêa[1], Janaína P. Cecconi[1], Marcelo Batistuzzo[1], Benjamin D. Greenberg[3], Georg Norén[4], Steven A. Rasmussen[3], Miguel M. Canteras[5], Fábio Duran[1], Daniel Fuentes[1], Cláudio C. Castro[6], Cláudia Leite[7], Geraldo Busatto Filho[1], Eurípedes C. Miguel[1]

[1]Department of Psychiatry, Faculty of Medicine - University of São Paulo, São Paulo, Brazil,[2]Department of Psychiatry, Federal University of São Paulo, São Paulo, Brazil,[3]Department of Psychiatry and Human Behavior, Brown University, Providence, RI,[4]Department of Clinical Neurosciences - Neurosurgery, Brown University, Providence, RI,[5]Institute of Neurological Radiosurgery, Hospital Santa Paula, São Paulo, Brazil,[6]Heart Institute (INCOR), Faculty of Medicine - University of São Paulo, São Paulo, Brazil,[7]Department of Radiology, Faculty of Medicine - University of São Paulo, São Paulo, Brazil

Background: Up to 40 % of Obsessive Compulsive Disorder (OCD) patients do not respond to medications or psychotherapy. For this subgroup, an improved, stereotactic radiosurgery (Gamma ventral capsulotomy - GVC) is a treatment option which has been recently developed. We report the preliminary results from a pilot study with this new technique, as well as from a double-blind, randomized controlled trial (DB RCT).
Methods: Fifteen refractory DSM-IV OCD patients were selected. The first

five patients were included in a pilot study. The other ten subjects were randomly assigned to receive active (5 patients) or "sham" radiosurgery (5 patients), as a DB RCT. Periodical pre and post-operative follow-up assessments were provided, including psychopathological, global status, neuropsychological and personality scales, and magnetic resonance imaging scans with voxel-based morphometry (VBM).
Results: Three patients from the pilot study and three patients from the RCT active group became responders. As a whole, six out of ten (60 %) patients who had received active radiosurgery responded, 12 months or more after surgery. For the sham group, none responded for 12 months of follow-up; one patient became responder only after an active procedure was conducted. Hypomanic/manic episodes, delirium, episodic headaches, dizziness, nausea were few times observed. Improved simple visual attention (p=0.04), logical memory (p=0.04), and verbal/full IQs (p=0.04) were observed in the pilot patients.Pre and post-operative VBM analysis is under way and will soon be available.
Conclusions: Preliminary findings indicate that GVC for OCD shows some efficacy, with relatively few adverse effects.
Supported by CAPES, Brazil (Dr Lopes). FAPESP (process n. 99/12205-7) and CNPQ (process n. 521369/96-7), Brazil (Dr Miguel)

934. Clinical Outcome of Ultrabrief ECT in Patients with Major Depression and Comorbid Personality Disorder

Angela Merkl, Jana Mertin, Arnim Quante, Eva-Lotta Brakemeier, Ion Anghelescu, Malek Bajbouj

Psychiatry, Charité, Berlin, Germany

Background: Previous research suggests that the comorbidity of major depression (MDE) with personality disorder is associated with poorer response to electroconvulsive therapy (ECT). We compared acute outcome of ECT in depressed patients with/without personality disorder (PD).
Methods: 55 patients with MDE who participated in a study on short-term and continuation right unilateral ECT were administered 28-item Hamilton depression rating scale (HAMDRS-28) at two time points: before starting ECT (T0) and after completing the acute course of ECT (T1), which was defined as the time after that response/remission of depressive symptoms had occurred or not. Patients were included with scores of at least 20 on HAMDRS-28. The SCID-II was conducted after completion of ECT. Due to small sample size PD group was not splitted into subgroups.
Results: Compared to patients without PD (N=33), patients with PD (N=22) showed no significant differences at T0 pre-treatment HAMDRS-28 scores (P=0.212). There were no differences in T1 post-ECT HAMDRS-28 scores (P=0.378). Patients with and without PD responded as well to ECT comparing response rate after completing the acute course (P= 0.659).
Conclusions: Comparing depressive patients with/without PD our results show no difference in response status to ECT. This is in line with one study on outcome of ECT in patients with comorbid PD. However, this might implicate that it is important to differentiate between different PD subgroups to explain poorer response in other PD groups, i.e. borderline personality disorder.

935. Modeling Antidepressant Properties of Vagus Nerve Stimulation (VNS Therapy) in the Context of a 12 Month Long Placebo Controlled Study

Ziad Nahas[1], Annie S. Simpson[2], Kit N. Simpson[3]

[1]Psychiatry and Neurosciences, Medical University of South Carolina, Charleston, SC,[2]Biometry and Epidemiology, Medical University of South Carolina, Charleston, SC,[3]Heath Administration and Policy, Medical University of South Carolina, Charleston, SC

Background: Conducting year long placebo controlled studies in treatment refractory depressed (TRD) subjects is critical to the field yet very problematic. Such studies are associated with ethical concerns of withholding effective treatments and prohibitive costs. VNS Therapy provides continued treatment delivery with good tolerability and clinical benefits in treatment-resistant depressed patients. Unfortunately, the open nature of these longterm follow-ups greatly limits their interpretations.
Methods: We employed a Markov strategy to model antidepressant properties of VNS Therapy under 12-month double blind placebo controlled conditions where pharmacological treatment is held constant. We defined 5 possible Markov health states that were mutually exclusive and jointly exhaustive based on the Inventory of Depressive Symptoms Self Report (IDS-SR). We classified each patient observation at the beginning of each 3-month period. We constructed two "progression" transition matrices for both active and placebo conditions. To simulate blinded conditions, the 'active' matrix was weighed by the relative risks of failures (RRF) extracted from the open label and controlled VNS data in their first quarters. In the placebo-VNS model, we used the observed placebo transitions for the first quarter. For the following 3 quarters we adjusted for the RRF derived from published pharmacological maintenance placebo controlled trials.
Results: At 12-month, 29.5% of VNS treated patients had no or mild depressive symptoms compared 5.0 % of placebo-VNS.
Conclusions: This model can compare expected longterm outcomes under strict conditions not otherwise feasible in clinical trials. It may prove useful in implantable brain stimulation devices and TRD clinical research.
Supported by Cyberonics Inc.

936. Patients with Psychosis Receiving Pharmaco- and Continuous ECT Treatment Show Different Slow Wave Activitis of Ictal EEG during Acute ECT

Masayuki Nakano, Koji Matuo, Noriko Abe, Fumihiko Higuchi, Kazuteru Egashira, Masatomo Suetsugi, Yoshifumi Watanabe

Division of Neuropsychiatry,Department of Neuroscience, Yamaguchi University Graduate School of Medicine, Ube, Japan

Background: Electroconvulsive therapy (ECT) is useful for treating patients with acute psychosis including severe major depressive disorder (MDD) and schizophrenia (Scz). However, there is little evidence suggesting which maintenance treatment should be preferred after acute ECT, pharmacotherapy or continuous ECT. Based on the evidence that high slow wave activity and postictral suppression of ictal electroencephalogram (EEG) during acute ECT are associated with therapeutic efficacy, we retrospectively studied the difference of ictal EEG findings during acute ECT between patients receiving continuous ECT and pharmacotherapy.
Methods: Twenty four MDD and Scz patients who recovered after acute ECT were studied. Twelve patients received continuous ECT (C-ECT) (6 MDD and 4 Scz, age 47.9±19.1y, female 80%) and the others took some psychiatric medications without continuous ECT (PHAR) (6 MDD and 4 Scz, age 60.0±19.4y, female 60%). EEG was measured on the left frontal region during acute ECT. The Clinical Global Impression scale was used to assess clinical

improvement after acute ECT.
Results: Analysis of covariance with age and sex as covariates revealed that the PHAR patients showed higher slow wave amplitude (F=9.79, p<0.05) and more stable regularity (F=5.35, P<0.05) compared to the C-ECT patients. The C-ECT patients recovered more fully than the PHAR patients.
Conclusions: The results suggest that the slow wave findings of EEG during acute ECT may provide some help in choosing maintenance treatments after recovery following acute ECT.

937. Efficacy and Tolerability of Extended Release Quetiapine Fumarate (Quetiapine XR) Monotherapy in Major Depressive Disorder: A Randomized, Placebo-Controlled Clinical Trial (Study 003)

Nizar El-Khalili[1], Michael Banov[2], Brian Bortnick[3], David Adson[4], Catherine Datto[5], Shane Raines[5], Willie Earley[5], Martin Brecher[5]

[1]East Office, Alpine Clinic, Lafayette, IN,[2]Behavioral Medicine, Northwest Behavioral Reserach Center, Marietta, GA,[3]CNS: Atlanta, Comprehensive Neuroscience, Atlanta, GA,[4]Department of Psychiatry, University of Minnesota, Minneapolis, MN,[5]Neuroscience, AstraZeneca, Wilmington, DE

Background: To evaluate the efficacy and tolerability of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy for patients with MDD.
Methods: Multicenter, double-blind, randomized, parallel-group, placebo-controlled study (D1448C00003) of quetiapine XR monotherapy. Eligible patients (HAM-D total score ≥22, item 1 score ≥2) received quetiapine XR 150mg/day for 8 weeks; in patients with an inadequate response (failure to achieve ≥20% improvement in MADRS) at Week 2 the dose was adjusted to 300mg/day for final 6 weeks.
Primary endpoint: change from randomization to Week 8 in MADRS total score. Secondary endpoints included: MADRS response (≥50% reduction in total score from randomization); changes from randomization to Week 8 in HAM-D and CGI-S. Adverse events (AEs) were recorded throughout the study.
Results: 310 patients were randomized to double-blind treatment: 154 quetiapine XR, 156 placebo. At Week 8, quetiapine XR significantly reduced mean MADRS score versus placebo (-16.49 vs -13.10, respectively; p<0.01). At Week 1 (Day 8) mean MADRS score was significantly reduced by quetiapine XR versus placebo (p<0.05). MADRS response rates were significantly greater at Week 8 for quetiapine XR versus placebo (61.9% versus 48.0%, respectively; p<0.05). Change in HAM-D total score at Week 8 was -14.75 quetiapine XR versus -12.35 placebo (p<0.05). Change in CGI-S score at Week 8 was -1.64 quetiapine XR versus -1.24 placebo (p<0.01). Most common AEs (>10% any group) were dry mouth, sedation, somnolence and headache.
Conclusions: In patients with MDD, quetiapine XR monotherapy is effective and generally well tolerated with symptom improvement seen as early as Week 1.
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938. Predictive Factors of Psychiatric Research Subjects' Willingness to Participate in Studies

Aarti Sharma[1], Cherise Rosen[2]

[1]College of Medicine, University of Illinois at Chicago, Chicago, IL,[2]Psychiatry, University of Illinois at Chicago, Chicago, IL

Background: Few studies exist that assess predictive factors of psychiatric patients' willingness to participate in studies. When asked, psychiatric patients expressed clear views on biomedical research regarding attitudes affecting motivation to participate, autonomy, inclusion of vulnerable populations, and influences on participation decisions. These findings supported autonomous decision-making by psychiatric patients who viewed participation as a way of helping society and expressed increased hope associated with involvement.
Methods: We studied 313 psychiatric patients admitted to an inpatient research unit. At the time of discharge, each participant completed a structured questionnaire designed to assess the experience of research participation and willingness to participate in future studies. Six variables were hypothesized to be associated with willingness to participate, including overall satisfaction as well as satisfaction with the following: information received in research psychoeducation group, the degree to which they were educated or informed about participation; protocol specific information, including details of the protocol, potential risks/benefits, alternatives, confidentiality, and rights; the level of perceived safety; and symptom evaluation.
Results: In all cases where a significant relationship occurred, individuals who were more satisfied expressed willingness to participate in future research (p<.001). This relationship was obtained for their satisfaction with general and protocol-specific research education (p<.001), safety (p<.01), and symptom ratings procedures (p<.01).
Conclusions: Overall the data suggests that psychiatric patients are more willing to participate in research studies if they are provided education regarding overall principles of research, ongoing education pertaining to specific research protocols, and the degree of perceived safety during procedures.

939. Serotonin Transporter Promoter Polymorphism and Antidepressant Efficacy: Systematic Review and Meta-Analysis

Matthew J. Taylor[1], Srijan Sen[2], Zubin Bhagwagar[2]

[1]Department of Psychiatry, University of Oxford, Oxford, United Kingdom,[2]Department of Psychiatry, Yale University, New Haven, CT

Background: The 5HTTLPR is a polymorphism in the serotonin transporter promotor region. The short 'S' variant is associated with reduced transporter expression. Early reports suggested that this polymorphism was associated with poorer response to antidepressant treatment, however results from subsequent studies have been mixed.
Methods: A systematic review and meta-analysis was performed of trials in which response to antidepressant treatment of major depression was reported along with 5HTTLPR genotype. Conventional pooled estimates of differences in treatment outcome were calculated for models with either 'S' or 'L' alleles functionally dominant and expressed as relative risks (RR).
Results: Rates of response to antidepressant treatment did not significantly differ with genotype in either model (SS versus SL/LL, RR 0.97, 95% Confidence Interval (CI) 0.83 to 1.14; SS/SL versus LL, RR 0.83, 95% CI 0.67 to 1.03). This finding remained in sensitivity analyses removing the single largest trial (STAR*D) or restricting studies to those using selective serotonin reuptake inhibitors alone. However, rates of remission, reported in fewer studies, did appear to be affected by presence of the 'L' allele (SS versus SL/LL, RR 0.81, 95% CI 0.67 to 0.97; SS/SL versus LL, RR 0.9, 95% CI 0.79 to 1.03).
Conclusions: The 5HTTLPR polymorphism does not appear to be associated with overall differences in rates of response to antidepressant treatment. Presence of increased transporter function with the 'L' allele may increase rates of remission with treatment. This contrast warrants further investigation.
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940. Differences in Peripheral Blood Gene-Expression as Predictors of Response to Treatment with Lithium in Subjects with Bipolar Depression

Robert D. Beech[1], Janine L. Leffert[1], Mary M. Taylor[1], Sheila Westman[2], Aiping Lin[3], Ji Young Lee[3], Anjana Muralidharan[1], Boris Lorberg[1], Hongyu Zhao[4], Samuel S. Newton[1], Shrikant Mane[2], C. Neill Epperson[1], Hilary Blumberg[1], Zubin Bhagwagar[1]

[1]Psychiatry, Yale University, New Haven, CT,[2]W.M. Keck Biotechnology Resource, Yale University, New Haven, CT,[3]W.M. Keck Biostatistics Resource, Yale University, New Haven, CT,[4]Epidemiology and Public Health, Yale University, New Haven, CT

Background: Lithium is considered first line treatment for mania, acute bipolar depression, and maintenance treatment. However, the response to lithium is extremely heterogeneous, and there are currently no established predictors of response to treatment with lithium.
Methods: Microarrays were used to measure levels of gene-expression in whole blood of subjects with Bipolar Disorder (BPD, n=20) at baseline and every two weeks during 8-weeks of open label treatment with lithium. Gene-expression changes were also measured in 15 untreated healthy controls sampled on two occasions at least two weeks apart to determine the level of random variation.
Results: BPD subjects were divided into treatment-responders (n=10) and non-responders (n=10) based on changes in mood-ratings. ANOVA analysis of the microarray data was used to identify a set of 127 genes with significant group x time interaction. Cluster analysis detected four distinct temporal patterns of change among these genes. Supervised learning algorithms (random forests and support vector machines) were used to identify 10 genes with the greatest predictive power in distinguishing lithium responders from non-responders among the BPD subjects. Baseline differences in the expression of a set of 8 of these genes were confirmed by RT-PCR.
Conclusions: Differences in clinical response to lithium were correlated with differences in gene-expression between lithium-responders and non-responders. These results support the hypothesis that differences in peripheral blood gene-expression can be used to predict response to lithium prior to initiation of treatment.
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941. Altered Expression of Cortical GABA-A Receptor α1 Subunit in Schizophrenia

Monica Beneyto[1], Takanori Hashimoto[2], Holly Bazmi[1], Dominique Arion[1], David A. Lewis[3]

[1]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA,[2]Department of Psychiatry, University of Kanazawa, Kanazawa, Japan,[3]Departments of Psychiatry and Neuroscience, University of Pittsburgh, Pittsburgh, PA

Background: Disturbances in the regulation of cognition in schizophrenia reflect functional abnormalities in the intrinsic circuitry of the dorsolateral prefrontal cortex (DLPFC). Working memory is associated with the gamma oscillations that are dependent upon fast inhibitory neurotransmission mediated by α1-containing GABA-A receptors. Considering the electrophysiological differences that α_1 (fast kinetics) and α_2 (slower decay time) subunits confer to GABA-A receptors, reduced expression of α_1-containing GABA-A receptors, and/or an altered ratio of α_1/α_2 subunits could contribute to the altered gamma oscillations in the DLPFC in schizophrenia.
Methods: We used in situ hybridization to compare the expression of α1 and α2 subunit mRNAs in the DLPFC of 23 subjects with schizophrenia, each individually matched with a control subject for age, sex, and postmortem interval (PMI). To further evaluate the change in expression of α1 mRNA, we are analyzing protein levels by western blot. Studies in monkey DLPFC with artificially created PMIs indicated that α1 protein was well-preserved with PMIs up to 24hrs.
Results: GABA-A α1 subunit mRNA expression was significantly reduced by 17 % in layers 3-6 of the DLPFC in schizophrenia, whereas α2 subunit mRNA showed a trend increase in layers 2-3. Blinded assessment of actin-corrected α1 protein levels in a subset of the subject pairs (all PMI < 20hrs) used for the mRNA analysis is in progress.
Conclusions: These findings indicate a decrease in the ratio of α1 to α2 subunits in GABA-A receptors in schizophrenia, which could impair the synchronized neuronal activity required for gamma oscillations.
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942. Expression Profiling of Post-Mortem Prefrontal Cortex from Persons with Major Depression versus Controls

Jomo Claiborne[1], Richard C. Shelton[1], Philip Ebert[1], Hal Manier[1], David A. Lewis[2], Karoly Mirnics[1]

[1]Psychiatry, Vanderbilt University, Nashville, TN,[2]Psychiatry, University of Pittsburgh, Pittsburgh, PA

Background: Major depression (MDD) is a condition that involves the dysregulation of the stress response axis (e.g., corticotrophin releasing hormone, adrenocorticotrophic hormone, and cortisol) and inflammatory factors. However, post-mortem tissue analysis has produced inconsistent results. The purpose of this study was to examine gene expression profiles of post-mortem brain (PMB) tissue samples from persons with MDD versus controls, using highly sensitive exon microarrays.
Methods: PMB samples from prefrontal cortex (Area 10) were obtained from the University of Pittsburgh CCNMD, and included persons with a lifetime history of MDD and matched controls (n=20 per group). Persons with MDD were not on psychotropics at the time of death. Premortem diagnosis was made via next-of-kin interview. mRNA expression was determined using Affymetrix 133 plus 2 exon arrays.
Results: Samples from persons with MDD showed abnormal expression of a variety of mRNAs. Pathway analysis discovered altered regulation of a cytokine/inflammatory pathway that included: interleukin 1A (IL1A), IL2, IL3, IL4, IL5, IL6, IL8, IL9, IL10, IL12A, IL12B, IL15, IL16, IL18, interferon gamma (INFγ), tumor necrosis factor α (TNFα), and TNFβ. The groupwise analysis showed marked between-groups separation.
Conclusions: These results suggest significantly altered regulation of the expression of a variety of mRNAs, but most particularly inflammatory factors include interleukins, tumor necrosis factors, and interferon.
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943. Altered Serotonin 2C Receptor RNA Splicing in Suicide: Association with Editing

Stella Dracheva[1,2], Benjamin Chin[1], Vahram Haroutunian[1,2]

[1]Psychiatry Research, Bronx VA Medical Center, Bronx, NY,[2]Psychiatry, Mount Sinai School of Medicine, New York, NY

Background: In our previous study we showed increases in the serotonin 2C receptor (5-HT_{2C}R) pre-mRNA editing in prefrontal cortex (PFC) that were specific to suicide victims irrespective of associated psychiatric diagnoses (bipolar disorder (BPD) or schizophrenia (SZ)). In this study we have tested the association between editing and splicing by investigating whether the differences in the 5-HT_{2C}R editing in suicide subjects affect the splicing of their 5-HT_{2C}R transcripts.

Methods: Using quantitative real time PCR, we have examined the expression of the 5-HT_{2C}R splice variants in the same brain specimens that were employed in our previous editing study. The study cohort consisted of subjects with BPD or SZ, and normal controls (NC) (Ns=35); fifteen of BPD and 7 of SZ subjects committed suicide.
Results: The results demonstrated that the ratio between two major 5-HT_{2C}R splice variants was significantly increased in suicide, but did not differ among the diagnoses (BPD, SZ, NC). The association analysis between this ratio and mRNA editing parameters revealed: 1) positive association with editing efficiencies; 2) negative association with the non-edited mRNA variant (NONE); and 3) positive association with the most prevalent variant in PFC (ABCD).
Conclusions: This report provides further evidence that variation in posttranscriptional modification of 5-HT_{2C}R mRNA by both editing and splicing may represent one of the risk factors for suicide that is distinct from those associated with the comorbid psychiatric disorders. The reported data also suggest that, consistent with previous in vitro findings, 5-HT_{2C}R pre-mRNA splicing is modulated by editing in human brain.
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944. Chronic Life Stress Experience and Polymorphic Variations of MAOA-VNTR and the Intron 2-VNTR of the 5-HTT Genes Modulates Endocrine Stress Response

Mbemba Jabbi[1], Ido P. Kema[2], Jacob Korf[3], Johan Ormel[3], Johan A. den Boer[3]

[1]Section on Integrative Neuroimaging, Cognitive Brain Disorders Branch, NIH/NIMH, Bethesda, MD,[2]Department of Pathology and Laboratory Medicine, University Medical Center Groningen (UMCG), Groningen, The Netherlands,[3]Department of Psychiatry, UMCG, Groningen, The Netherlands

Background: Highly prevalent stress-related disorders like major depression (MD) are characterized by a dysregulation of the neuroendocrine system. Although heritability for these disorders is high, the role of genes in the underlying pathophysiology remains elusive.
Methods: Sixty-nine adolescents/young adults (20.1yrs M; ranging from 15-32yrs, varying in degree of susceptibility to MD) who completed life event questionnaires, were exposed to acute psychological stress. Their MAOA-VNTR and the intron 2-VNTR of their 5-HTT gene were assayed to test the hypothesis that exposure to severe life events as well as polymorphic variations of monoaminergic and serotonergic genes may convergently or additively affect endocrine stress response.
Results: We showed that polymorphic variations of the intron 2-VNTR of the serotonin transporter (5-HTT) and monoamine oxidase A (MAOA) influences hypothalamic-pituitary-adrenal (HPA)-axis response to acute psychological stress. Additionally, we found a significant effect of the degree of experienced life stress prior to the laboratory challenge, which did not interact with genotype, on individual's glucocorticoid stress response.
Conclusions: Collectively, these results indicate a complex relationship between multiple monoaminergic genes and environmental factors regarding endocrine stress regulation. These findings point towards a complex underlying gene-environment interplay in the pathogenesis of stress-related disorders like MD. In this process, the functional influence of monoaminergic and serotonergic genes may become additive risk factors for such disorders in an adverse environment. If replicated, these findings may provide insights into strategies for clinically relevant gene targeting.
Supported by NWO

945. Serum Cytokine and Growth Factor Levels in Neuropsychiatric Disorders

Maureen V. Martin[1], Brandi Rollins[2], William E. Bunney[2], Marquis P. Vawter[2]

[1]Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA,[2]Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA

Background: The neurochemical responses to peripheral cytokines may contribute to the endocrine and behavioral responses in psychiatric disorders. Cytokine elevations have been observed in serum from subjects with psychiatric disorders.
Methods: We compared the levels of a panel of 20 cytokines in serum samples from subjects with schizophrenia, bipolar disorder and major depressive disorder that had received different medications to a control group. Serum samples were collected from adult subjects rapidly after death and a total of 25 µl of serum was assayed per sample in duplicate. The Panomics' Procarta Cytokine Assay system was used to simultaneously quantify protein levels of 20 cytokines. Protein concentrations were measured using a Bradford assay, and data were analyzed by t-test after normalizing for total protein concentration.
Results: There was a significant increase ($p < 0.05$) in serum levels of IFNγ in schizophrenia and bipolar disorder. There were trends towards increased IL-6 and TNF-alpha in bipolar disorder and increased FGF2 in schizophrenia and major depressive disorder compared to controls.
Conclusions: These results are consistent with previous literature reports of cytokine alterations in serum in psychiatric disorders and the results support the use of multiplex protein assays for identification of potential peripheral biomarkers for psychiatric disorders. The disease-specific profiles of cytokines suggest immune system activation may play a role in the pathogenesis of the disorders. More samples are being assayed in brain and blood and a replication in a larger, drug-naïve sample is needed as previous work suggests psychiatric drugs influence cytokine levels.
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946. Protein Kinase Protein and mRNA Expression in Post-Mortem Tissue from Prefrontal Cortex in MDD

Richard C. Shelton[1], Philip J. Ebert[1], Hal Manier[1], Karoly Mirnics[1], David A. Lewis[2]

[1]Psychiatry, Vanderbilt University, Nashville, TN,[2]Psychiatry, University of Pittsburgh, Pittsburgh, PA

Background: Protein kinases play key roles in cell function, including the expression of genes such as brain derived neurotrophic factor (BDNF), tyrosine kinase receptor B (TrkB), CREB, and glucocorticoid receptors (GR). Reduced levels of protein kinases A (PKA) and C (PKC) have been demonstrated in peripheral tissues and post-mortem brain (PMB) samples from persons with major depression (MDD) versus controls. This study assessed all PKA and PKC isoform proteins and mRNA levels.
Methods: PMB samples of prefrontal cortex (Area 10) were obtained from persons with a lifetime history of MDD (psychotropic free) and matched controls (n=20 per group). Premortem diagnosis was made via interview with next-of-kin. Protein levels were determined via Western blot and mRNA expression levels via Affymetrix 133 plus 2 exon arrays.
Results: Significant reductions were found in the following proteins in MDD samples: PKA regulatory Iα (PKARIα), PKCβ2, and PKCε; and the following at a trend level: PKARIβ, PKARIIβ, PKCα, and PKCβ1 ($p<0.10$). mRNA expression was significantly reduced for: PKACα, PKARIIα, PKCα ($p<05$); and at a trend level for PKARIα, PKCβ1 ($p<0.10$). Expression of a variety of regulatory factors, including phosphodiesterases and phosphatases were not different. BDNF, GR, and CREB1 expression levels were not altered, but the expression of TrkB was significantly reduced.

Conclusions: These data confirm the reduction in specific PKA and PKC subunits. The patterns of protein and mRNA expression levels do not suggest that the reductions are related to altered expression of mRNAs or proteins or changes in regulatory factors.
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947. Decreased GABA Concentrations in Patients with Treatment Resistant Depression: A Proton Magnetic Resonance Spectroscopy Study

Rebecca B. Price[1,2], Sanjay J. Mathew[1], Xiangling Mao[3], Paul Nestadt[1], Chris Kelly[1], Kate A. Collins[1], James Murrough[1], Dikoma C. Shungu[3]

[1]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY,[2]Department of Psychology, Rutgers University, Piscataway, NJ,[3]Department of Radiology, Weill Medical College of Cornell University, New York, NY

Background: Previous research using proton magnetic resonance spectroscopy (H-MRS) has documented alterations in amino acid neurotransmitter concentrations in patients with severe, melancholic major depressive disorder (MDD). We tested for similar alterations in a group of treatment-resistant depression (TRD) patients who failed to respond to at least 2 adequate antidepressant trials. TRD patients might possess a distinct neurobiology (e.g., impaired glial function leading to abnormal glutamate/glutamine/GABA cycling) which could contribute to persistent mood symptoms.
Methods: H-MRS scans were performed on 24 healthy volunteers (HVs), 20 non-TRD MDD patients, and 13 TRD patients (all psychotropic-free) to assess regional concentrations of glutamate/glutamine (GLX) and GABA, expressed as ratios relative to the unsuppressed voxel tissue water signal (W), in 2 regions of interest: bilateral occipital lobe (OCC) and anterior cingulate cortex (ACC). A 3.0 T GE 'EXCITE' MR system was used to record from 3x3x2 cm3 voxels using the J-editing technique (TE/TR 68/1500 ms).
Results: OCC GABA/W concentrations were decreased in TRD patients in comparison to both HVs and MDDs (20.4% mean reduction; p<.001). All 13 TRD patients exhibited OCC GABA/W concentrations below the group mean for non-TRD MDDs. No other group differences reached the threshold for significance (p's > .05).
Conclusions: Our findings corroborate previous reports of decreased occipital GABA in severely depressed patients, and provide preliminary evidence for a distinct neuronal amino acid profile in TRD patients, in comparison to non-TRD participants. These findings have possible implications for the treatment of TRD with agents that selectively target amino acid neurotransmitter function.
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948. Functional Abnormalities during Motor Control in Adults with ADHD

Eve M. Valera[1], Joseph Biederman[2], Thomas Zeffiro[3], Ainat Rogel[3], Megha Patel[4], Rebecca Spencer[5], Nikos Makris[6], Thomas Spencer[2], Stephen V. Faraone[7], Bruce Rosen[8], Larry Seidman[9]

[1]Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Psychiatry, Harvard Medical School/Massachusetts General Hospital, Charlestown, MA,[2]Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Psychiatry, Harvard Medical School/Massachusetts General Hospital, Boston, MA,[3]Psychiatry, Massachusetts General Hospital, Charlestown, MA,[4]Psychology, Brandeis University, Waltham, MA,[5]Psychology, University of California at Berkeley, Berkeley, CA,[6]Neurology and Radiology, Harvard Medical School/Massachusetts General Hospital, Charlestown, MA,[7]Psychiatry and Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY,[8]Athinoula A. Martinos Center for Biomedical Imaging, Radiology, Harvard Medical School/Massachusetts General Hospital, Charlestown, MA,[9]Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Psychiatry, Harvard Medical School/Beth Israel Deaconess Medical Center, Boston, MA

Background: Attention deficit hyperactivity disorder (ADHD) in both children and adults is associated with impairments spanning multiple life domains including academic, employment, and interpersonal areas. Interestingly, a large number of ADHD individuals have been found to have motor abnormalities in both fine and gross motor tasks such as tapping and skills requiring manual dexterity. Previous functional imaging studies of motor control have shown abnormal activation in several brain regions in ADHD children, but no studies have yet examined adults. We sought to examine the neural underpinnings of motor abnormalities in ADHD adults by using a tapping task with functional magnetic resonance imaging (fMRI).
Methods: A sample of adults with ADHD (N = 21) and controls (N = 19) recruited from ongoing studies of adult ADHD, performed a finger tapping task paced to a tone every 500 ms during fMRI. The blood oxygenation level dependent (BOLD) fMRI response was used as a measure of neural activity.
Results: Behavioral data showed no differences between groups in mean tapping rate but a trend toward greater intrasubject variability for tap-to-tap intervals for ADHD adults relative to the controls. Preliminary analyses using Statistical Parametric Mapping demonstrated that, relative to controls, ADHD adults showed significantly decreased activity in frontal, parietal, insular and cerebellar regions.
Conclusions: These data demonstrate that functional abnormalities associated with motor control in ADHD persist into adulthood. Data will be discussed in the context of understanding motor abnormalities in ADHD.
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949. Effects of Brain-Derived Neurotrophic Factor on Sodium-Induced Apoptosis in Human Olfactory Neuroepithelial Progenitor Cells

Lindsey Willett[1], YongLin Gao[2], Zhenmin Lei[3], Chengling Lu[4], Fred Roisen[5], Welby I. Winstead[6], Rif S. El-Mallakh[2]

[1]Undergraduate Research Program, Centre College, Danville, KY, [2]Psychiatry, University of Louisville, Louisville, KY, [3]Obstetrics and Gynecology, University of Louisville, Louisville, KY, [4]Anatomical Sciences and Neurobiology, University of Loiusville, Louisville, KY, [5]Anatomical Sciences and Neurobiology, University of Louisville, Louisville, KY, [6]Surgery, University of Louisville, Louisville, KY

Background: Low levels of brain-derived neurotrophic factor (BDNF) peptide are linked to the pathophysiology of mood disorders. Several single nucleotide polymorphisms (SNPs) across the BDNF gene (BDNF) have been associated with bipolar illness. Since both elevated intracellular sodium and apoptosis are believed to contribute to cellular dysfunction in bipolar disorder, it is important to determine the effect of BDNF on apoptosis induced by the high levels of intracellular sodium seen in ill bipolar patients.
Methods: Human olfactory neuroepithelial progenitor cells were treated with monensin, a sodium ionophore that increases intracellular sodium and leads to apoptosis. Apoptosis was quantified with enzyme-linked immunosorbent assay (ELISA) for mono- and oligonucleosomes.
Results: Monensin induced apoptosis. BDNF 100 ng/mL pre-treatment or co-treatment attenuated the monensin-induced apoptosis. Pretreatment with

BDNF reduced monensin-induced apoptosis by 93%. Co-treatment of BDNF and monensin reduced apoptosis by 66%.
Conclusions: Monensin models a process that is believed to occur during ill phases of bipolar illness. Treatment with BDNF greatly attenuates or prevents monensin-induced apoptosis. The functional consequences of BDNF SNPs known to be associated with bipolar illness, need to be examined.
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