Deep Brain Stimulation, Psychiatric Genetics, and iPS cell models of disease

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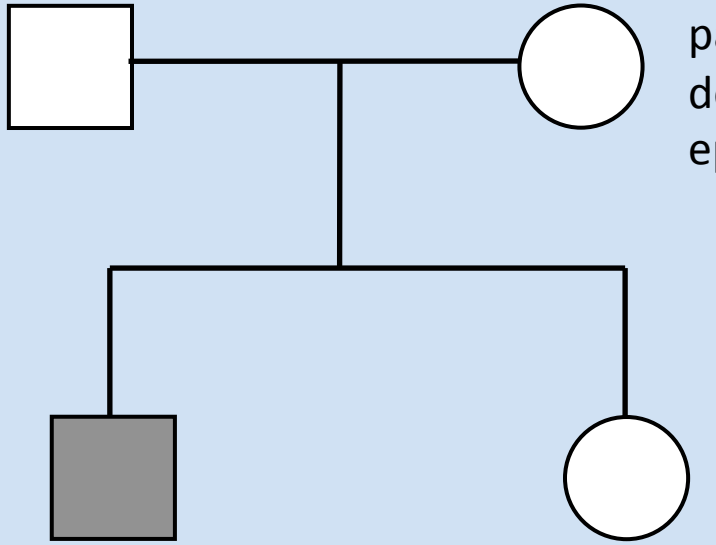
our study families



Mother with mild OCD and past history of bipolar with depression and one manic episode

Boy with Tourette Syndrome

Tourette's is diagnosed when multiple motor tics, and at least one phonic tic, are present for more than a year.

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Complex Tics and Complex Management in a Case of Severe Tourette's Disorder (TD) in an Adolescent

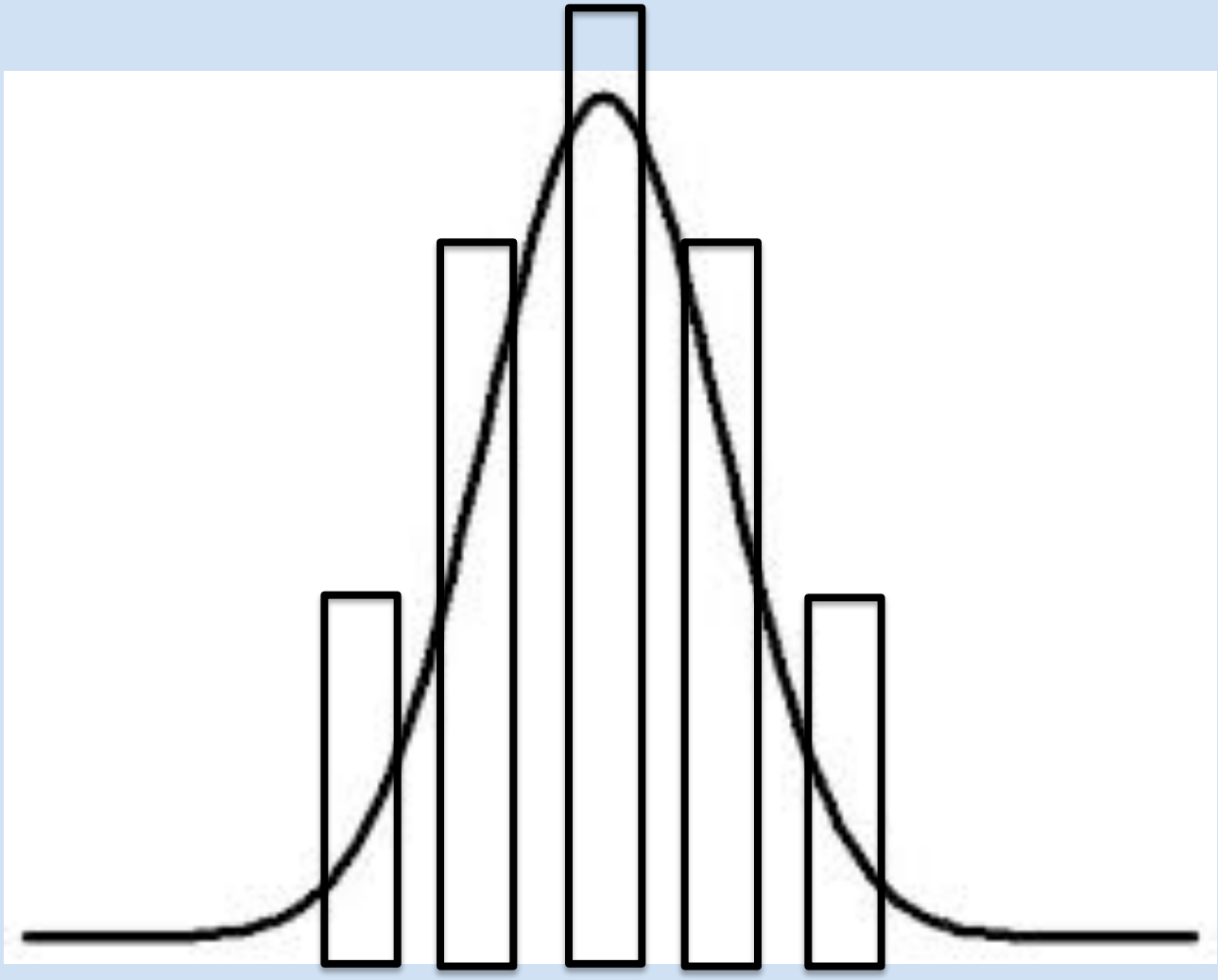
Presenter: Gholson J. Lyon, M.D., Ph.D.[1]
Discussant: Barbara J. Coffey, M.D., M.S.[2]

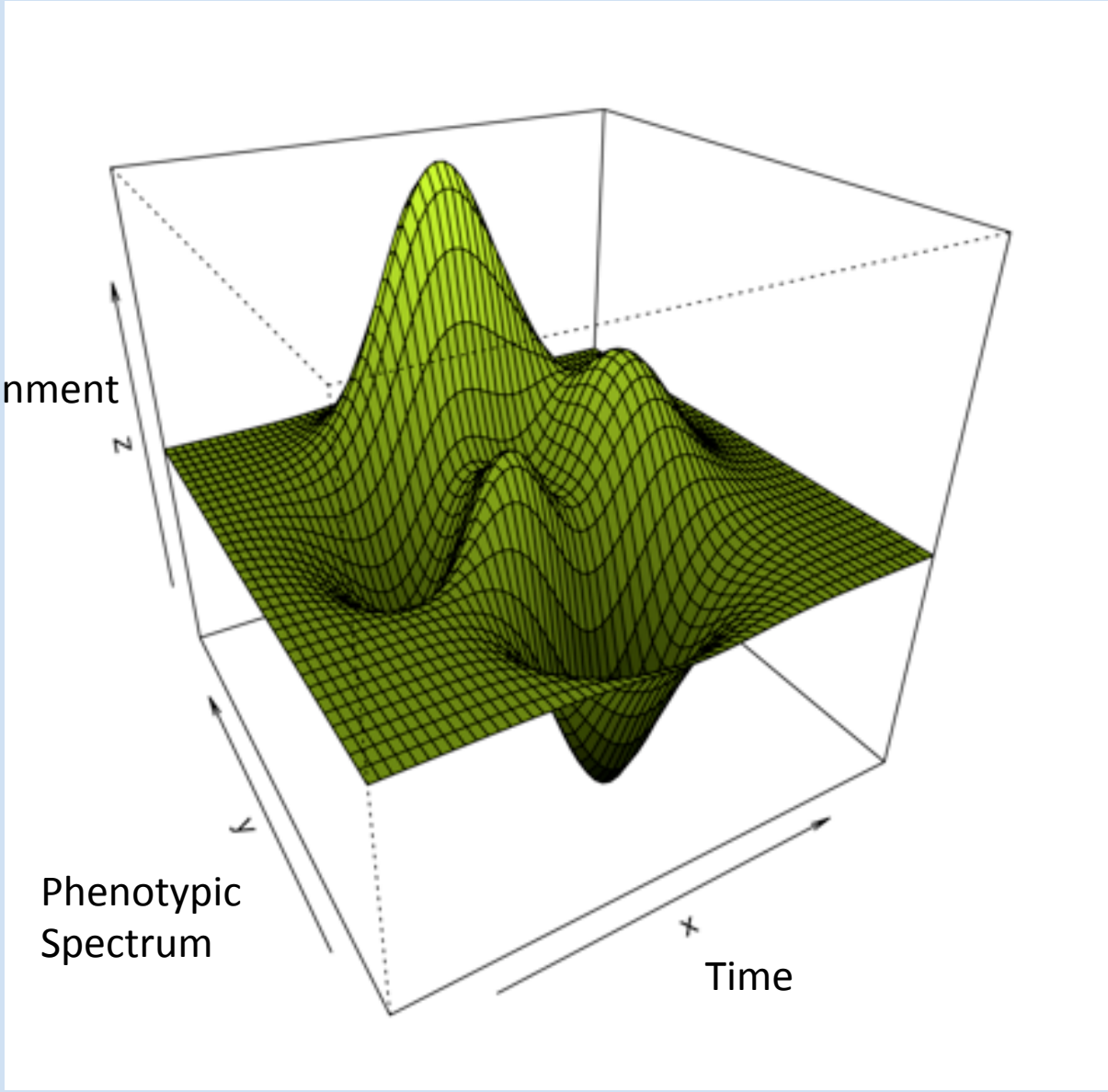
Multi-Axial Diagnoses

Axis I:	Tourette's Disorder, severe to marked. Obsessive-compulsive disorder, sub-threshold. Generalized anxiety disorder. Major depressive episode, secondary to risperidone and tetrabenazine, past.
Axis II:	Deferred.
Axis III:	Seizure disorder, not otherwise specified. Concussion twice within the past two years. Fractured arm, past.
Axis IV:	Level of psychosocial stressors: Severe: Hospitalized for tics and unable to attend the school in the past year.
Axis V:	Current Global Assessment of Functioning (GAF) Score: 40. Most severe lifetime GAF: 40.

In summary, S.'s tic symptom severity was profound, and his clinical course and follow-up illustrate some of the challenges of treatment of severe tics in an adolescent. While comprehensive biopsychosocial treatment approaches are aspired to in all cases, it is not always feasible to combine evidence-based treatments for each individual.

Categorical Thinking Misses Complexity





A conceptual model of genotype-phenotype correlations. The *y* plane represents a phenotypic spectrum, the *x* plane represents the canalized progression of development through time, and the *z* plane represents environmental fluctuations.

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Clinical genetics of neurodevelopmental disorders

Gholson J Lyon and Jason O'Rawe

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Schizophrenia Studies Find Genetic Risk Spread Across Shared Pathways
January 22, 2014
http://www.genomeweb.com/schizophrenia-studies-find-genetic-risk-spread-across-shared-pathways

> A co-author on both of the papers, called the findings "sobering but also revealing."
> "[I]t suggests that many genes underlie risk for schizophrenia and so any two patients are unlikely to share the same profile of risk genes," he said.

VIDEO

OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Articles

Lessons Learned from Open-label Deep Brain Stimulation for Tourette Syndrome: Eight Cases over 7 Years

Maria G. Motlagh[1*], Megan E. Smith[1], Angeli Landeros-Weisenberger[1], Andrew J. Kobets[2], Robert A. King[1], Joan Miravite[3], Alain C. J. de Lotbinière[4], Ron L. Alterman[5], Alon Y. Mogilner[6], Michael H. Pourfar[6], Michael S. Okun[7] & James F. Leckman[1]

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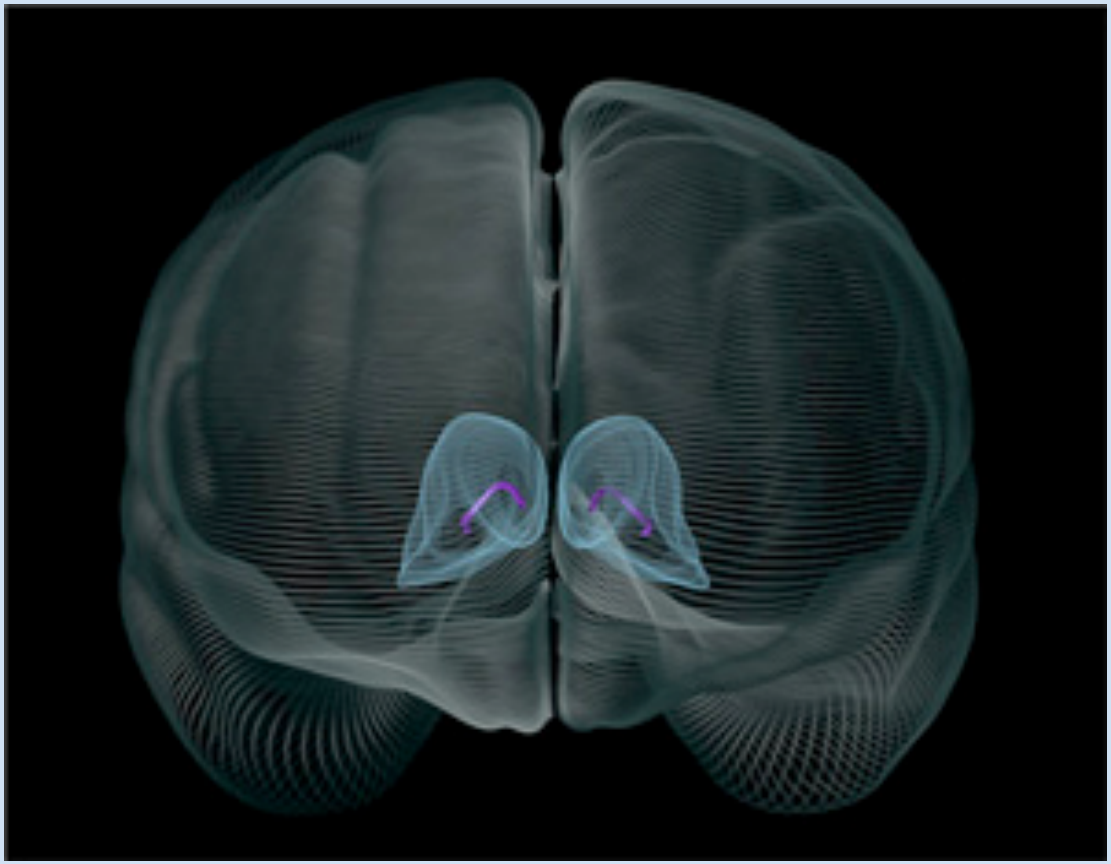
8	Thalamus X (mm lateral AC-PC)=5 Y (mm posterior AC-PC)=4 Z (mm beneath AC-PC)=0	Leksell frame, MRI/CT fusion, procedure performed under general anesthesia with propofol and remifentanil	R C+1-, 2.1 V, 90 μs, 130 Hz L C+1-, 1.9 V, 90 μs, 130 Hz

Subject	Sex	Age (Years)	Disease Duration (Years)	Tic Symptoms	Typical Waxing and Waning Course	Self-Injury	Comorbid Disorders	Family History	Living and Work Situation	Medication Before Surgery	Current Medication
8	M	17	13	Atypical long bouts of severe tics (20 minutes to 1 hour) interspaced with long tic-free periods, tics include opening mouth wide, arm and shoulder movements, head and neck jerks, rapidly shaking head from side to side, gyrating head, arching back, flexion and extension of arms one side at a time	No	Yes, pounding of chest, punching forehead	OCD, mild depression, some symptoms of general anxiety disorder	Yes for OCD	Unmarried, student	Pimozide, risperidone, ziprasidone, aripiprazole, fluphenazine, clonidine, guanfacine, fluoxetine, clonazepam, topiramate	None

Subject 8 underwent bilateral midline thalamic (VOI) implantation under general anesthesia due to the intensity of his tics. He experienced a dramatic micro-lesion effect with almost complete resolution of his tics in the immediate post-operative period. His tics remained dramatically improved at the time of initial programming.

Similar to our TS DBS subject #6, he also reported a sensation with the greatest ventral contact but generally had good tolerability with PW 90 and frequency of 130. Initial settings were set low given the near absence of tics (Left and Right IPGs: C+1- 1.0/90/130) and were subsequently mildly increased over the next six months following a mild return of his tics. At last programming, six months post-operatively, voltages had been increased to 2.1 on the left and 1.9 on the right with good tolerability.



Location of the thalamus in the brain, anterior view. The thalamus is the main part of the diencephalon, and is involved in integrating information from prethalamic inputs to the cerebral cortex. Purple lines denote the thalamus midline.

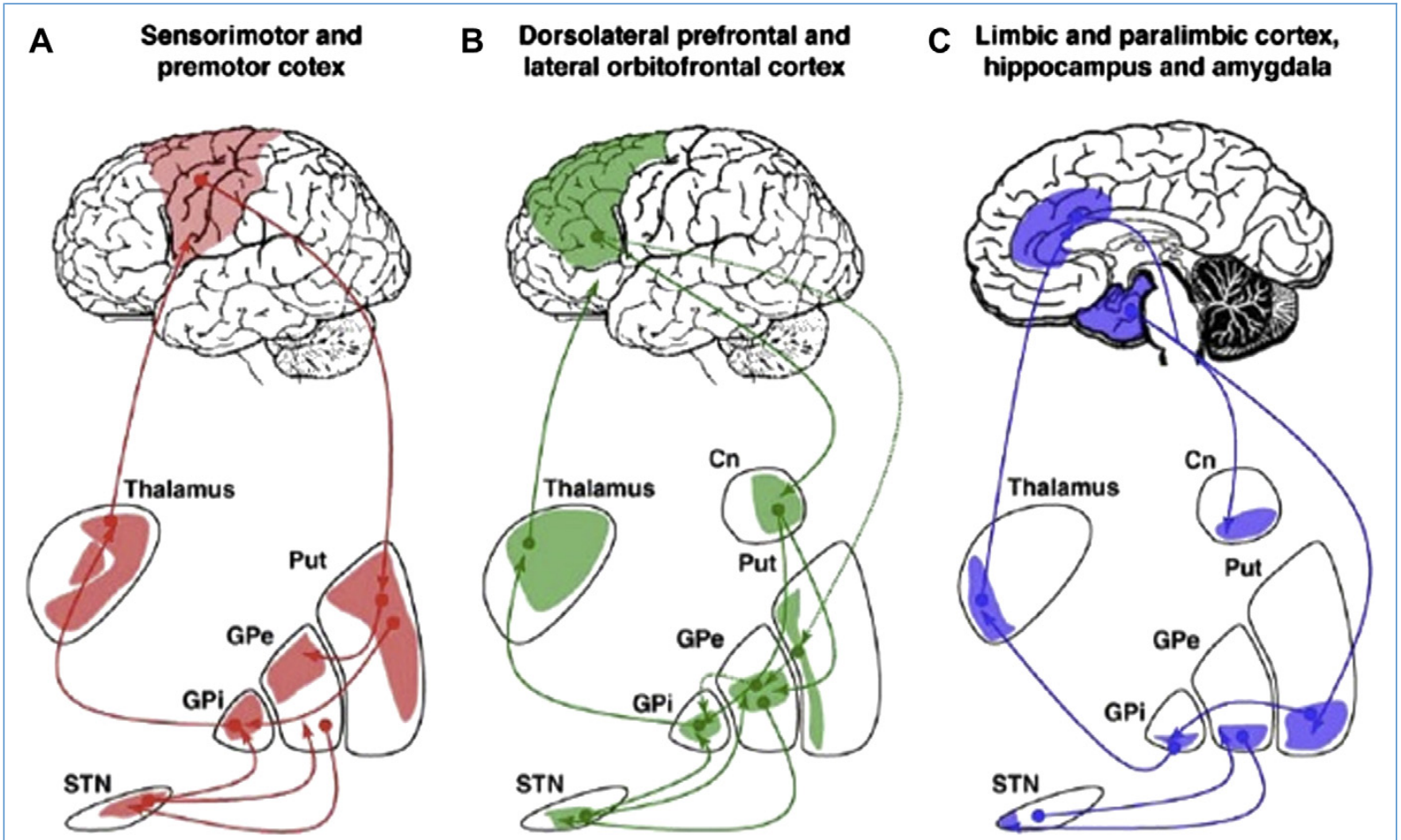


Figure 9. Schematic of cortico-striato-thalamocortical loops. An illustration of pathways in motor, associative, and limbic circuitry. (**A**) Motor circuit. Neurons from the sensorimotor cortex project to the posterolateral putamen (Put). The putamen sends two main projections onto the posterolateral region of the target nuclei: (i) the direct circuit to the globus pallidus pars interna (GPi) and (ii) the indirect circuit connecting the posterior putamen to the globus pallidus pars externa (GPe), the subthalamic nucleus (STN) and the GPi. The GPi is the primary output nucleus of the basal ganglia to the cortex via the ventrolateral thalamus. (**B**) Associative circuit. This circuit originates in the dorsolateral prefrontal and lateral orbitofrontal cortices, which project to the striatal caudate nucleus (Cn) and anteromedial portion of the putamen. From there, it projects to the dorsomedial region of the GPi and anteromedial portions of the GPe and STN. These in turn project onto the GPi and back to the cortex via the ventral anterior nuclei of the thalamus. (**C**) Limbic circuit. Here, the hippocampus, amygdala, paralimbic, and limbic cortices project to the ventral striatum (ventral portion of the caudate and putamen, including the nucleus accumbens [NAc]). The ventral striatum projects to the limbic portion of the GPe, medioventral STN, ventral GPi, and to the cortex via the mediodorsal nucleus of the thalamus. (Reproduced with permission from Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA: Deep brain stimulation: from neurology to psychiatry? Trends Neurosci 33:474-484, 2010.)

PeerJ

Integrating precision medicine in the study and clinical treatment of a severely mentally ill person

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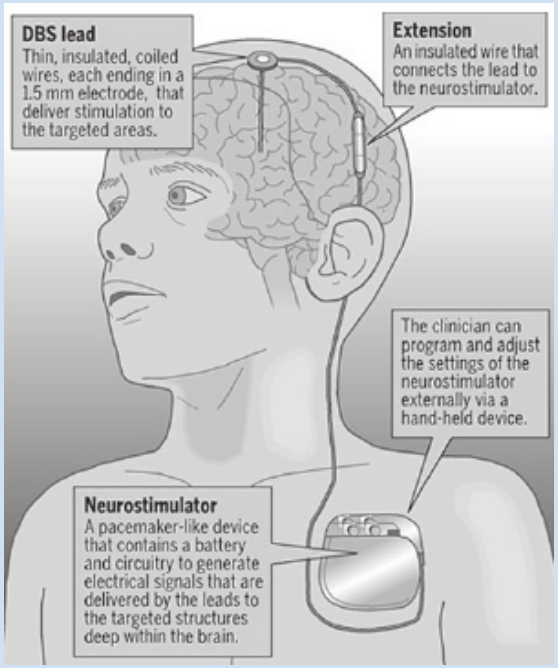

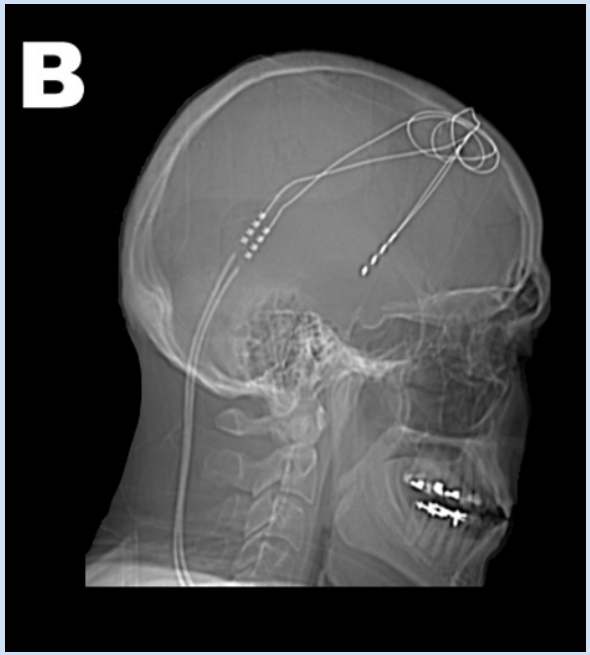

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Additional Information and Declarations can be found on page 18

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Severe Mental Illness (and other severe illness) in current system

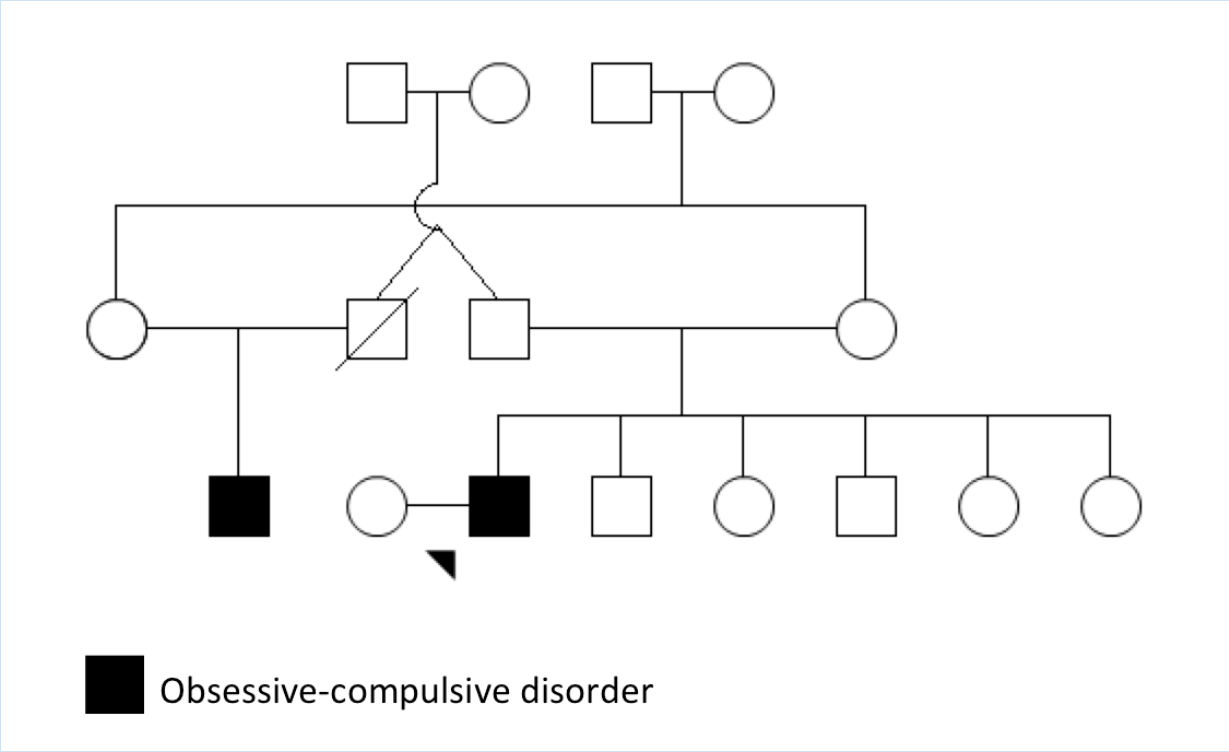
Current Standard of Care

Hospitalization
Therapy- counseling
Medication

A family in Utah, with a 40 year old Caucasian man with
very severe obsessive compulsive disorder, severe depression and intermittent psychoses, with symptoms that started around age 5.

Multiple medication trials failed over many years.
Considered treatment refractory.

Genetic architecture of mental illness?



Deep Brain Stimulation for Intractable Psychiatric Disorders

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History of Psychosurgery: A Psychiatrist's Perspective

Kyle A. B. Lapidus[1], Brian H. Kopell[1,2], Sharona Ben-Haim[2], Ali R. Rezai[3], Wayne K. Goodman[1]

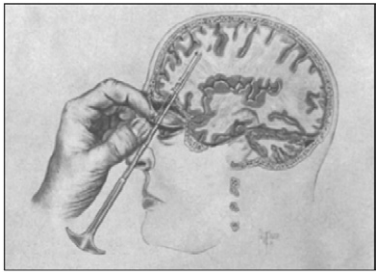

Figure 2. Transorbital or "ice pick" lobotomy technique. This procedure was developed by Freeman after severing ties with Watts. Here, frontal white matter is cut by a metal spike inserted through the thin bony orbit above the eye. (Reproduced with permission from Lerner BH: Last-ditch medical therapy—revisting lobotomy. N Engl J Med 353;119-121, 2005.)

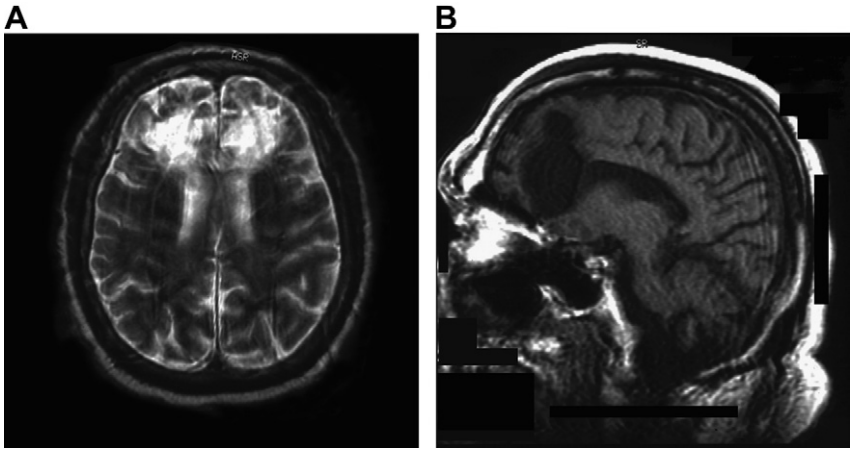

Figure 1. Lobotomy. (**A**) Axial T2-weighted and (**B**) sagittal T2-weighted images of lobotomy lesion.

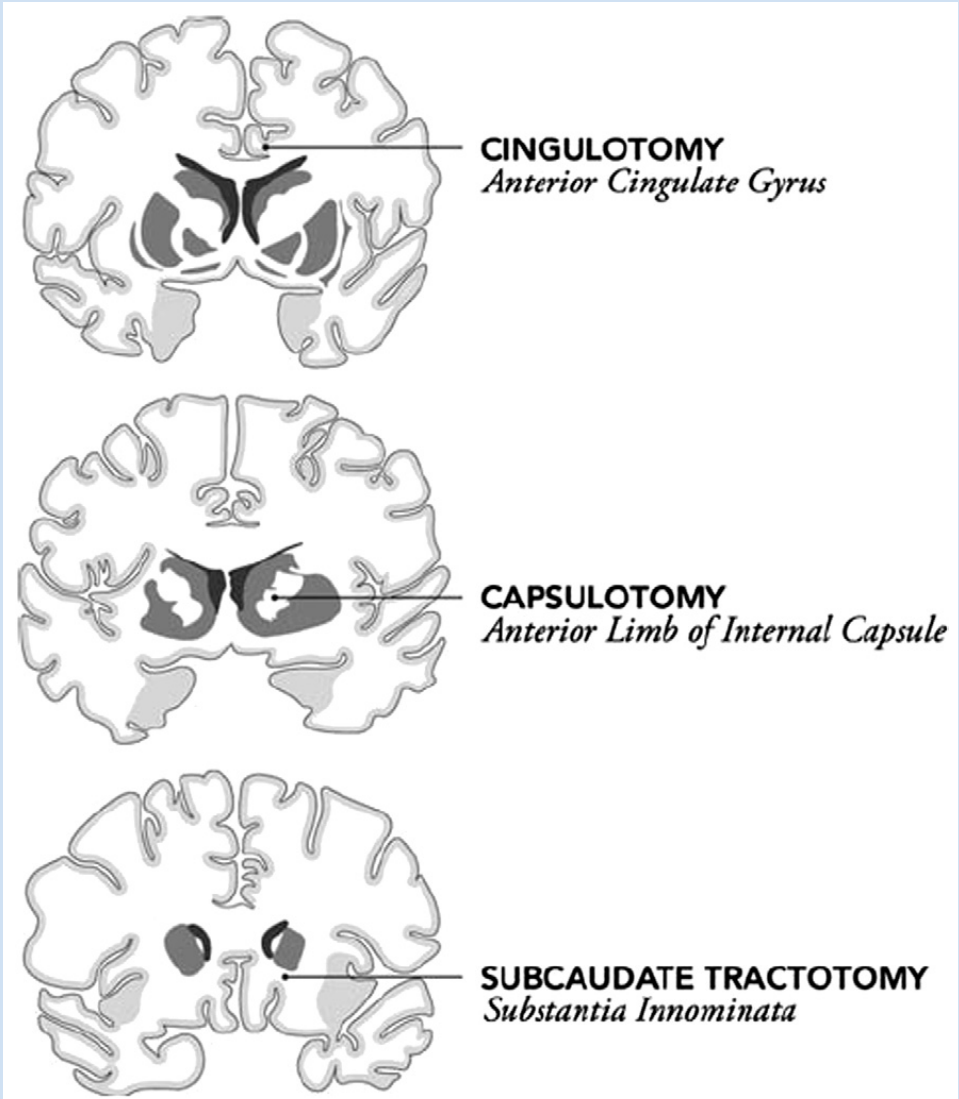

Figure 3. Illustration of stereotactic lesions. Illustration of anatomic locations of psychiatric neurosurgical procedures: anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy. Stereotactic limbic leucotomy combines cingulotomy and subcaudate tractotomy. (Reproduced with permission from Lipsman N, Neimat JS, Lozano AM: Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. Neurosurgery 61:1-13, 2007.)

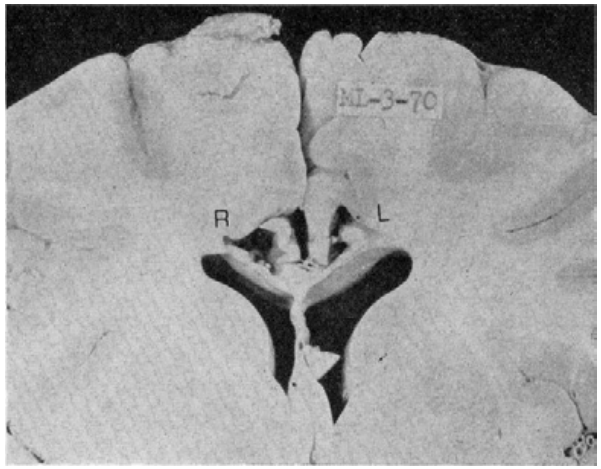

Figure 4. Cingulotomy pathology. Gross pathology of brain with cingulotomy lesion. The lesion is more complete on the right than the left side. (Reproduced with permission from Laitinen L, Livingston K: Surgical approaches in psychiatry. Proceedings of the 3rd International Congress of Psychosurgery. Baltimore: University Park Press; 1973.)

Table 1 Partial list of brain stimulation devices for treatment of psychiatric disorders

Device	Description of procedure	Uses: established or investigational	FDA regulatory status	Safety/tolerability of procedure	References
Electroconvulsive therapy (ECT)	Induction of generalized seizure with application of electricity to scalp Performed during anesthesia with cardiopulmonary support and use of muscle relaxants Typically 3 sessions per week for 2–4 weeks	MDD that is severe, accompanied by psychosis or suicidality, or refractory to other treatments Other indications include catatonia and schizophrenia	Currently categorized as a Class III device. FDA is reviewing whether ECT devices should remain in Class III (highest risk) or be downgraded to Class II (intermediate risk) devices for certain uses	Risks associated with general anesthesia Possible persistent autobiographical memory loss	(43, 68)
Repetitive transcranial magnetic stimulation (rTMS)	Fluctuating magnetic field from electromagnetic coil placed outside the skull induces an electrical current in the underlying cerebral cortex Typical course of treatment is five 40-min sessions per week for 4–6 weeks	Treatment-resistant depression Used off-label in clinical practice for other psychiatric disorders	Approved for narrow use in MDD patients who failed exactly one antidepressant medication in the current episode	Noninvasive and safe Minor scalp discomfort and headaches possible; very rarely seizures	(69, 70)
Vagus nerve stimulation (VNS)	Helical electrode is wrapped around left vagus nerve in the neck Connected to pulse generator under skin of chest that delivers ~30 s of stimulation every 5 min	Refractory epilepsy Treatment-resistant depression; benefit seen only after prolonged (up to 12 months) use	Approved as adjunctive therapy for refractory epilepsy Approved as adjunctive therapy for treatment-resistant depression (defined as ≥4 failed antidepressant treatments)	Invasive: requires surgery to attach electrode in neck and device under skin of chest Risks of general anesthesia; rarely infection or injury to recurrent laryngeal nerve causing hoarseness	(71, 72)
Deep brain stimulation (DBS)	Lead(s) implanted in brain anatomic target through burr hole(s) in cranium and locked in place Extension wires tunneled under skin and connected to pulse generator(s) implanted under skin of chest Programming of device settings performed wirelessly	Movement disorders Psychiatric disorders: Intractable OCD Treatment-resistant depression Tourette syndrome	Approved for essential tremor Approved for refractory Parkinson's disease Limited approval under HDE for dystonia and intractable OCD	Most invasive, highest risk: requires craniotomy and implantation of electrodes directly in brain parenchyma Risk of serious adverse events including intracerebral hemorrhage (~2%) and infection (~10%) More than 75,000 operations performed worldwide for movement disorders	See text

Abbreviations: MDD, major depressive disorder; OCD, obsessive-compulsive disorder; FDA, U.S. Food & Drug Administration; HDE, humanitarian device exemption.

Deep brain stimulation (DBS) at the interface of neurology and psychiatry

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University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, Florida, USA.

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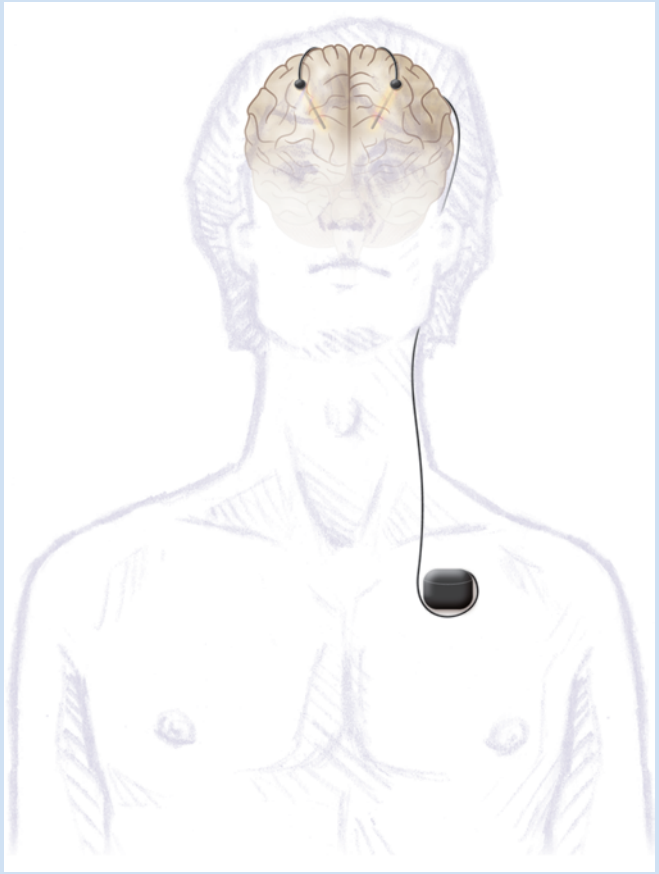


Figure 1
The modern version of the DBS system includes an electrode implanted into a deep brain target, which has been postulated to function as an important node that possesses the potential to modulate a dysfunctional brain circuit. The DBS lead is connected through an extension wire to an IPG (i.e., battery, neurostimulator), which is placed in the chest under the clavicle, or, less frequently, in the abdomen. The system is telemetrically programmed through the use of an external programming device to deliver pulses of electricity into the target region. These electrical pulses can modulate a circuit of interest to relieve disease symptoms. Schematic is not anatomically accurate.

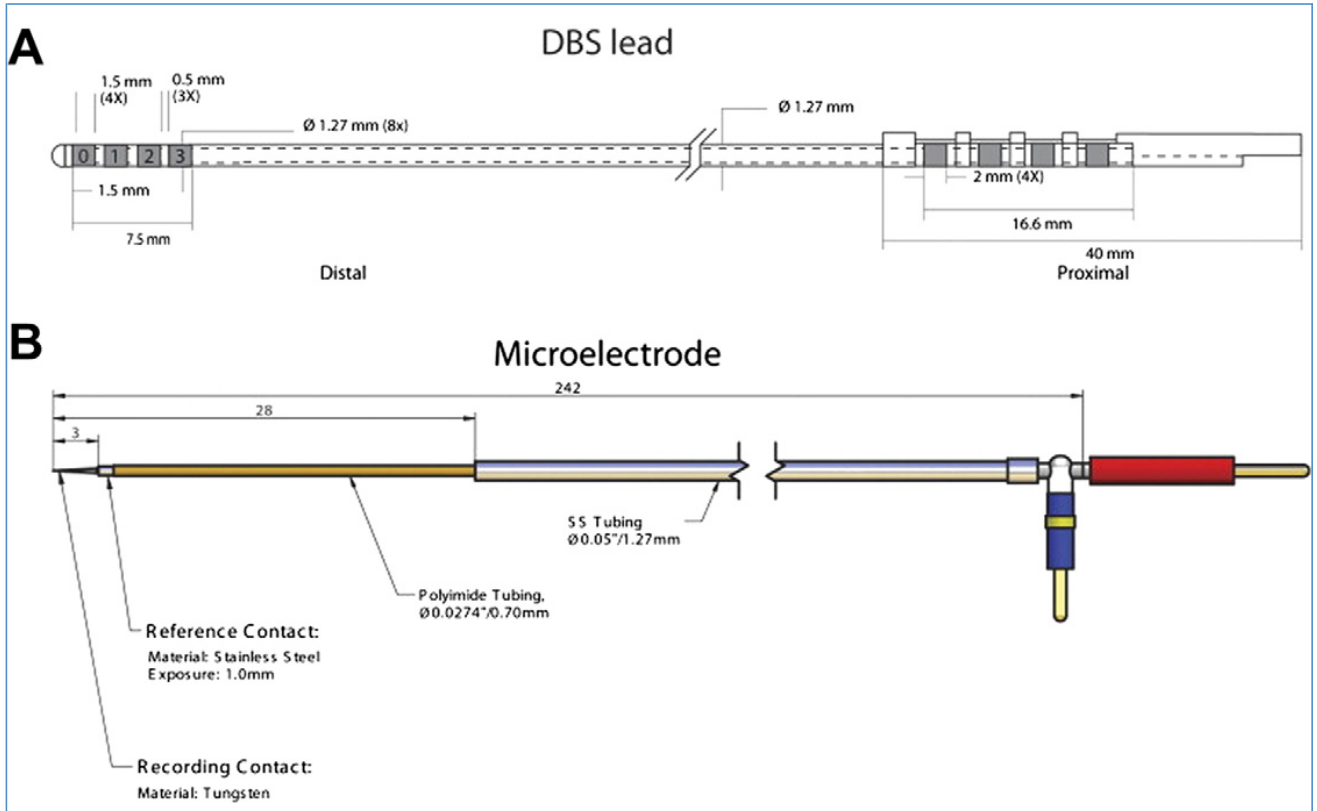


Figure 10. DBS electrode. Medtronic DBS lead and microelectrode. (Courtesy of Medtronic Inc.)

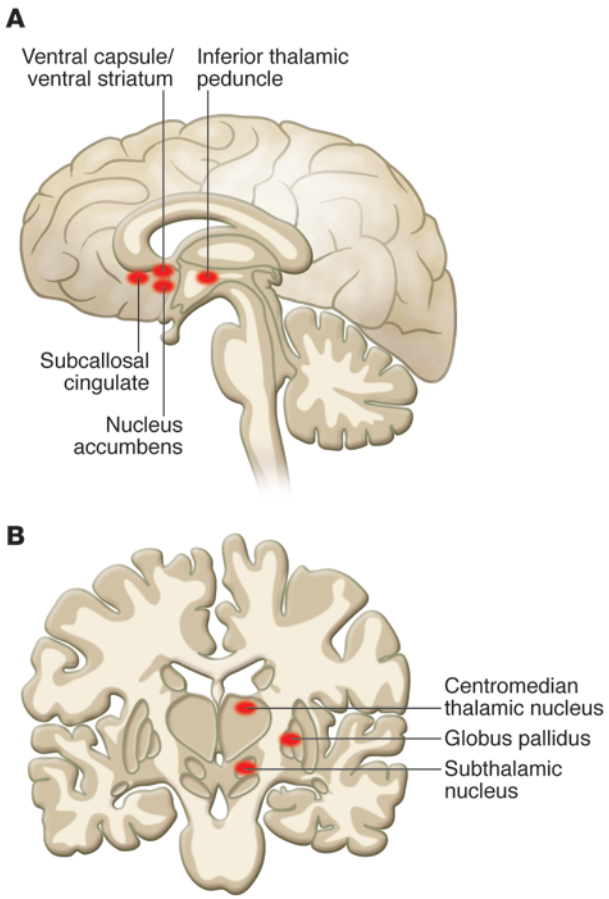
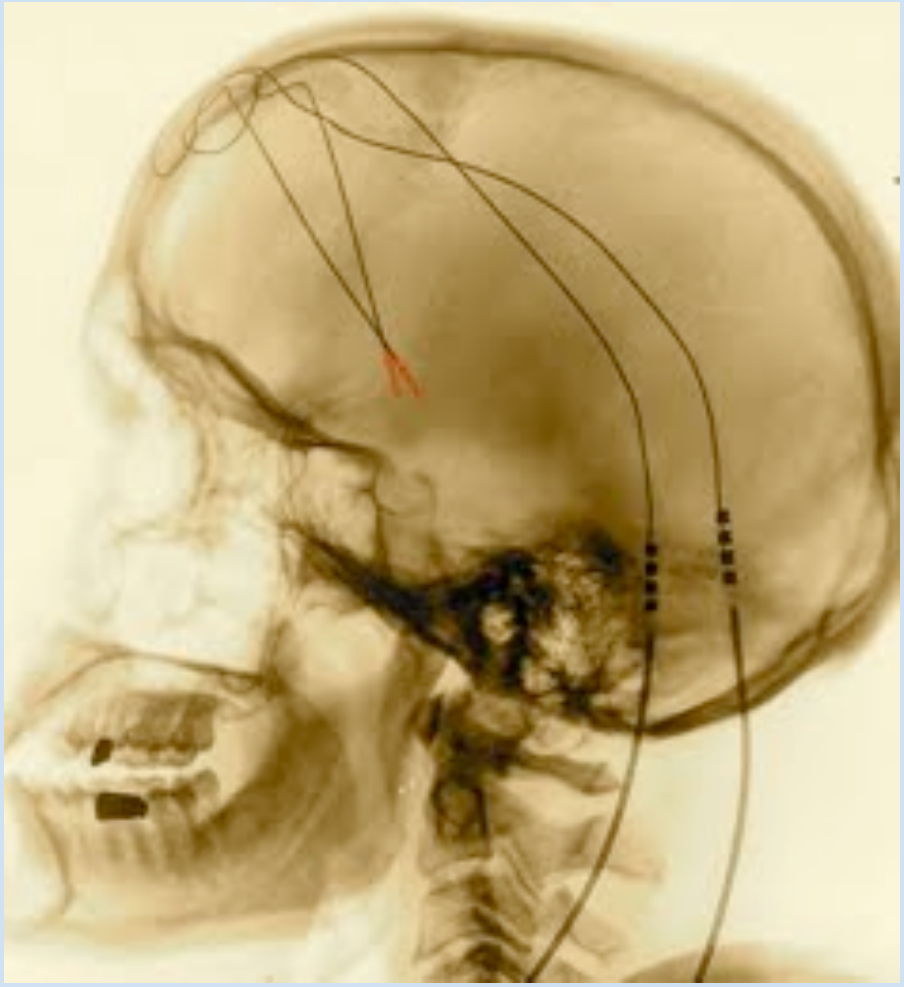
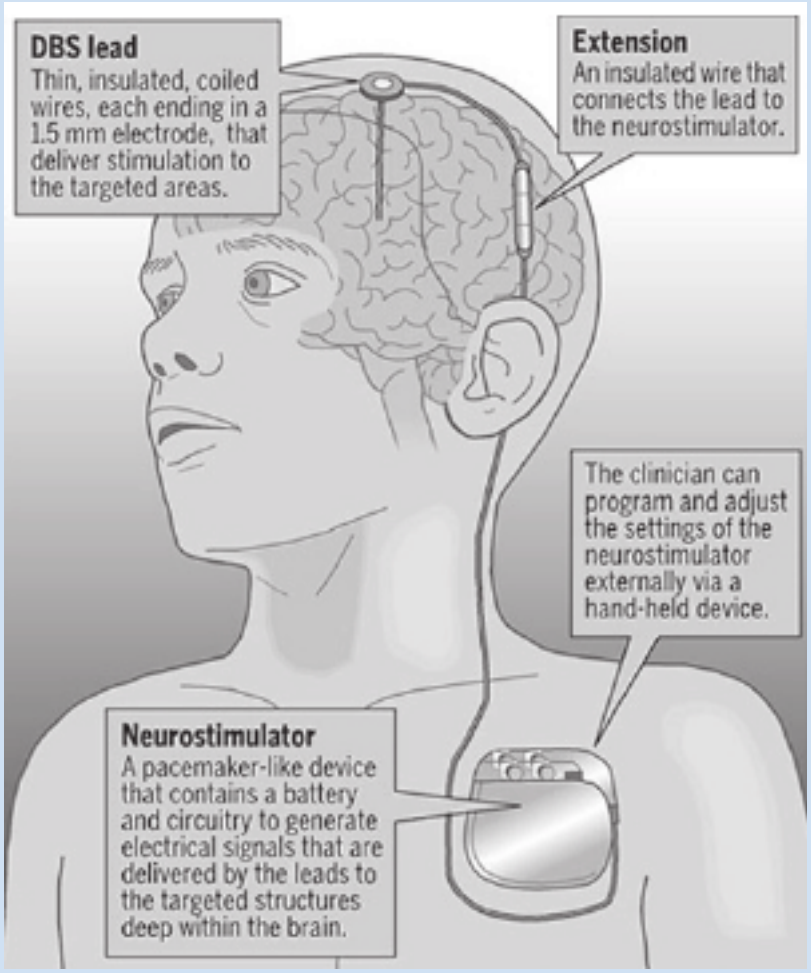


Figure 2
General schematic of DBS targets. (**A**) Sagittal view of DBS targets including VC/VS, STN, SCC, and ITP. (**B**) Coronal view of DBS targets including STN, GPi, and CM. Schematic is not anatomically accurate.

Humanitarian Device Exemption (HDE) for OCD





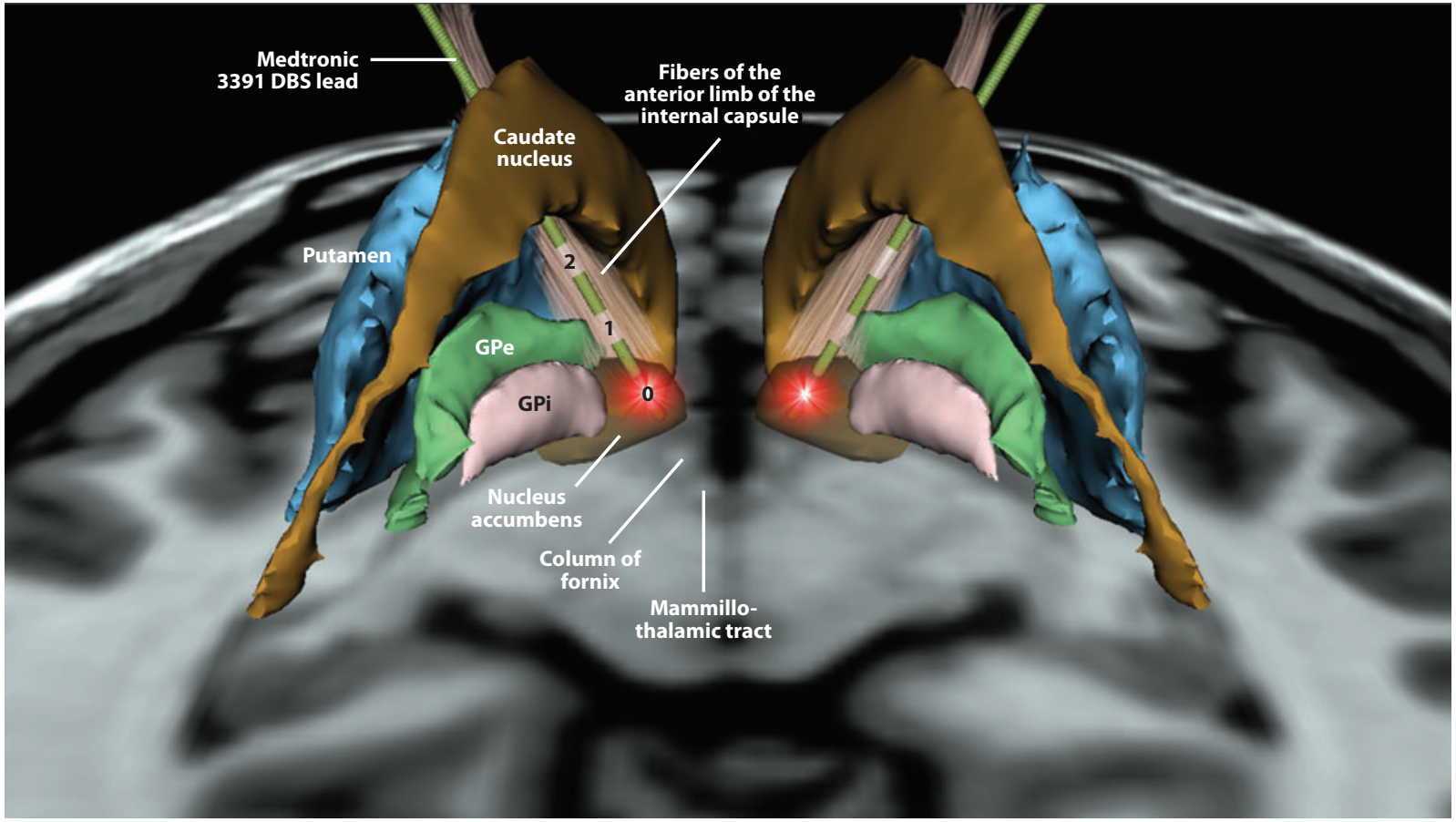


Figure 1

Three-dimensional (3D) illustration of bilaterally implanted deep brain stimulation (DBS) electrodes in the ventral capsule/ventral striatum. The 3D objects (leads and brain structures) are sitting on the axial plane 5 mm below the AC–PC plane as viewed posterior to anterior. The trajectory of the leads is down the barrel of the anterior limb of the internal capsule. Each lead has four contacts, but only three are shown (contacts #0, #1, and #2); contact #3 is hidden by the caudate nucleus. The most ventral #0 contact is active, as represented by red radiating stimulation fields. Abbreviations: AC–PC, anterior commissure–posterior commissure; GPe, globus pallidus externus; GPi, globus pallidus internus. Image courtesy of Kirk Finnis, PhD (Medtronic Inc., USA).

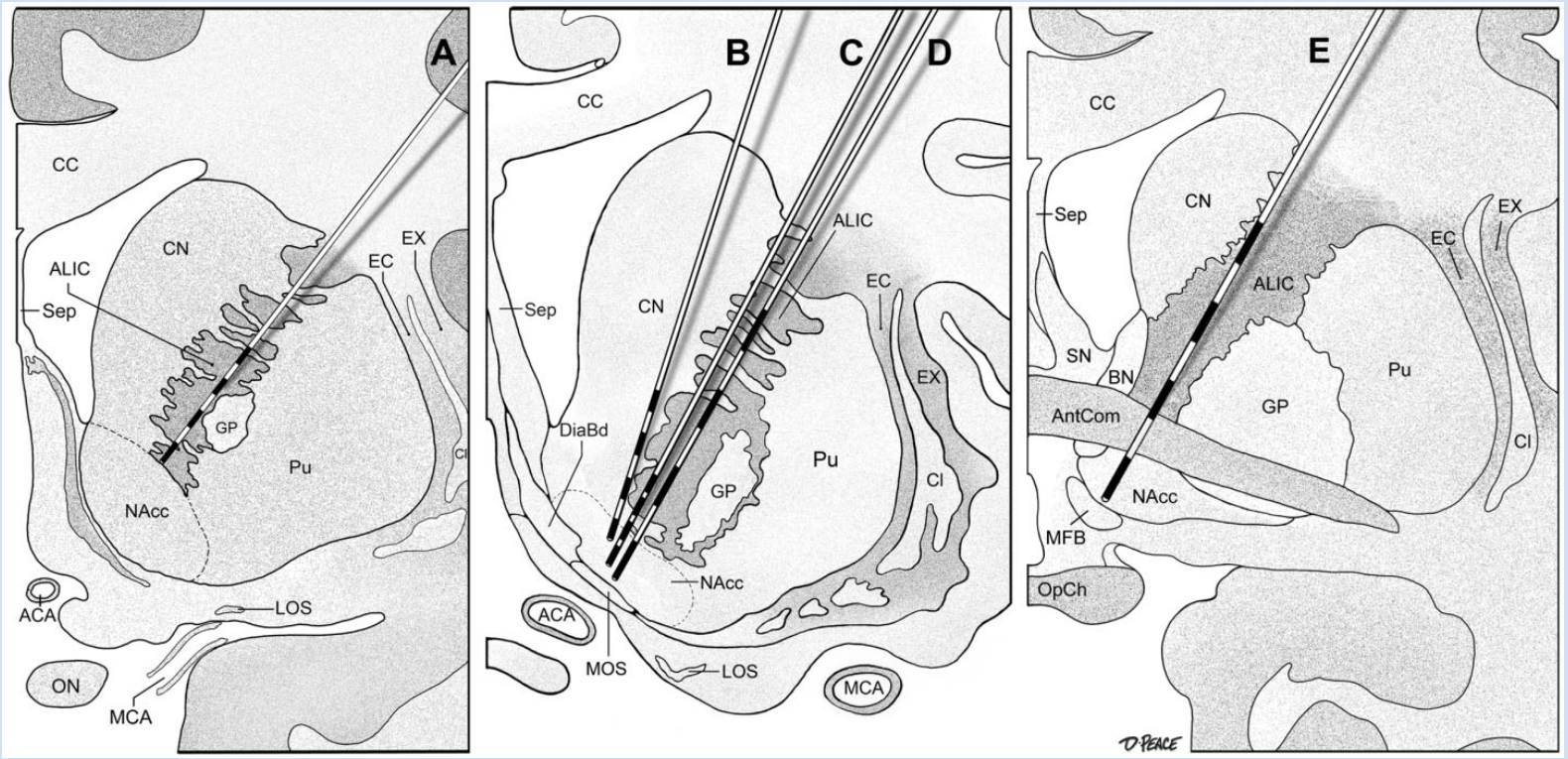


Figure 1. Anterior view of coronal sections of deep nuclear areas of the left hemisphere showing five different approaches for OCD DBS. Left: electrode placement in ALIC (a) for DBS. Middle: electrode placement targeting NAcc through ALIC utilizing three different trajectories (b, c, and d). Right: modified VC/VS trajectory (e). a: The ALIC trajectory (Anderson and Ahmed (2003) and Abelson et al. (2005)). b: Medial trajectory through the caudate nucleus to the NAcc utilizing Medtronic model 3387 electrode (each contact length = 1.5 mm, interelectrode spacing = 1.5 mm) by Aouizerate et al. (2004, 2007). c: VC/VS stimulation trajectory through the ALIC to the NAcc using a shorter length of stimulating electrode (Medtronic model 3389: each contact length = 1.5 mm, interelectrode spacing = 0.5 mm) by Denys et al. (2010). d: VC/VS trajectory through ALIC to the NAcc using a longer length of stimulating electrode (Medtronic model 3387 IES/3887: each contact length = 3 mm, interelectrode spacing = 4 mm) by Greenberg et al. (2006). e. VC/VS trajectory through ALIC to the NAcc using a longer length of stimulating electrode (Medtronic model 3387 IES/3887: each contact length = 3 mm, interelectrode spacing = 4 mm) by Greenberg et al. (2010). ACA, anterior cerebral artery; ALIC, anterior limb of the internal capsule; AN, anterior nucleus of the thalamus; AntCom, anterior commissure; BN, bed nucleus; CC, corpus callosum; CL, claustrum; CN, caudate nucleus; DBS, deep brain stimulation; DiaBd, diagonal band of Broca; EC, external capsule; EX, extreme capsule; GP, globus pallidus; LOS, lateral olfactory stria; MCA, middle cerebral artery; MFB, medial forebrain bundle; MD, mediodorsal nucleus of the thalamus; MOS, medial olfactory stria; NA, amygdala; NAcc, nucleus accumbens; OCD, obsessive compulsive disorder; OpCh, optic chiasm; Pu, putamen; Sep, septum pellucidum; SN, septal nucleus; STN, subthalamic nucleus; VC/VS, ventral capsule/ventral striatum.

Neuromodulation: Technology at the Neural Interface

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Surgical Neuroanatomy and Programming in Deep Brain Stimulation for Obsessive Compulsive Disorder

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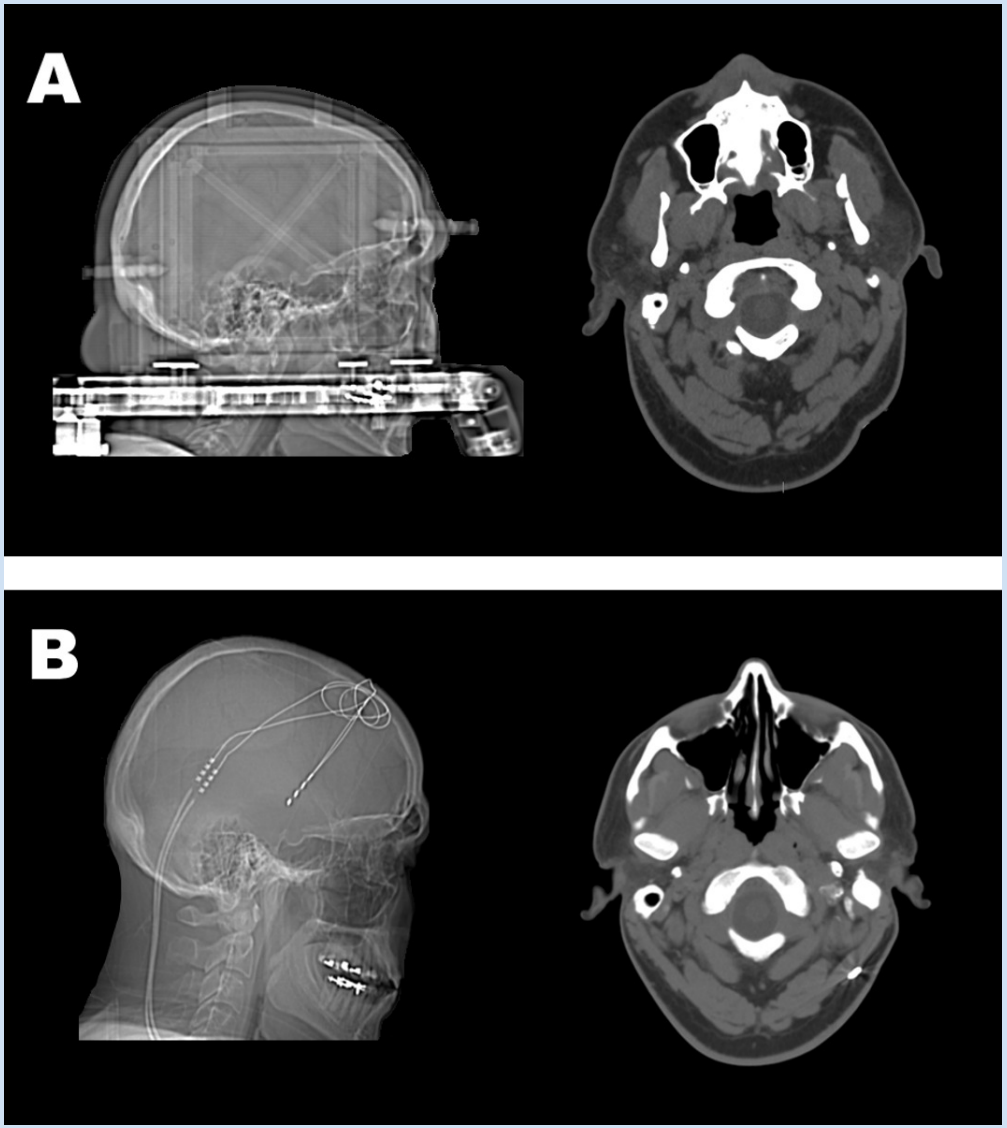
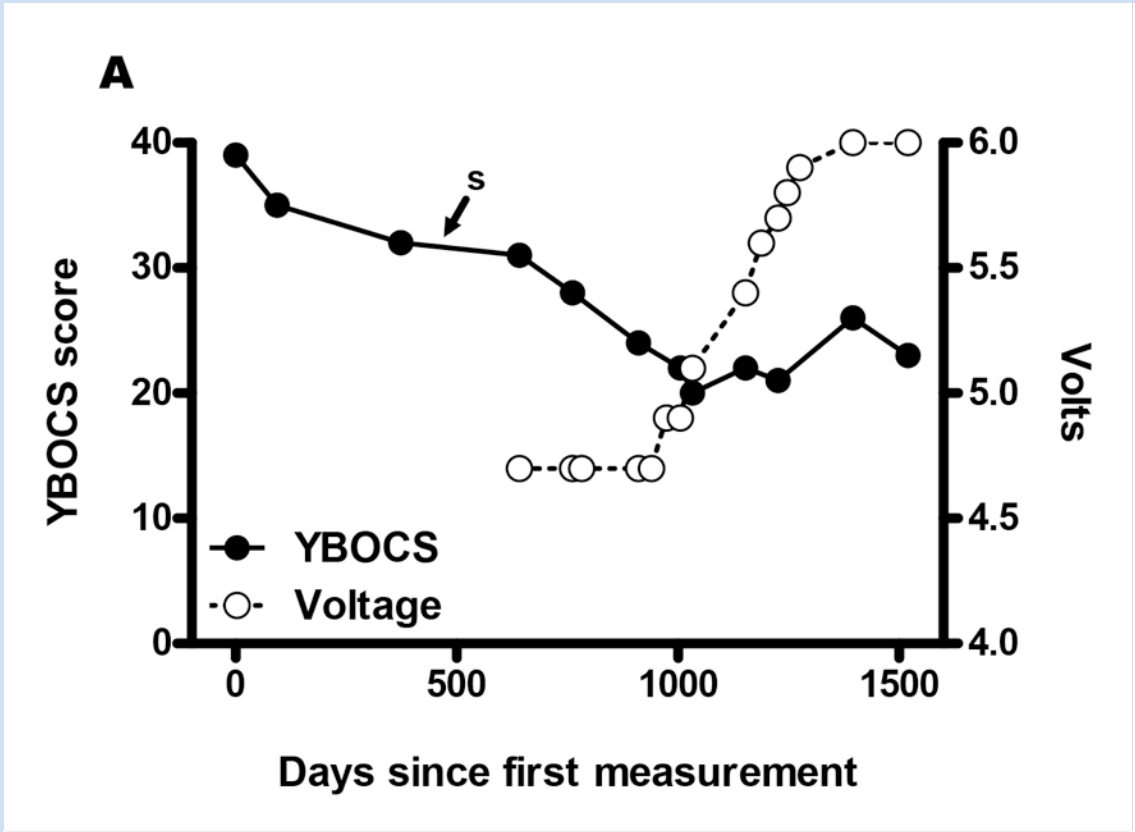


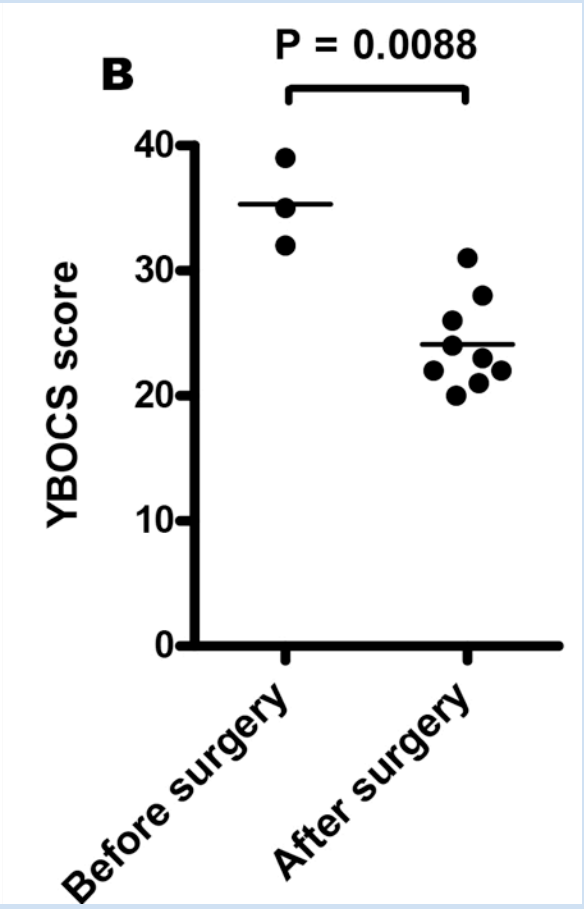
Figure 1 Sagittal and transverse computed tomography (CT) images of the brain and skull of MA. We show here sagittal and transverse sections taken from CT scans. Imaging was performed before (A) and after (B) MA received deep brain stimulation surgery for his treatment refractory OCD. Two deep brain stimulator probes can be seen to be in place from a bifrontal approach (B), with tips of the probes located in the region of the hypothalamus. Leads traverse through the left scalp soft tissues. Streak artifact from the leads somewhat obscures visualization of the adjacent bifrontal and left parietal parenchyma. We did not observe any intracranial hemorrhage, mass effect or midline shift or extra-axial fluid collection. Brain parenchyma was normal in volume and contour.

2.5 year follow-up

Global Assessment of Functioning (GAF) 0 to 100 scale

From 5-15 in 2008-2009 to 45-55 in 2013





Pulse width = 210, Frequency 130 Hz

Depleteable nature of battery

- Battery replaced with a rechargeable battery in January 2012.
- After the battery was turned off the first time, M.A. was not immediately under any pain. However, after 3 days, M.A. almost attempted suicide because of the increase in depression, anxiety, and physical pain. Even worse, M.A. had little to no insight into his disease, and had an increase in memory and congitive deficit and had thus forgotten the benefits that had been his just a few days prior.
- M.A. decided to kill himself since he was unable to connect the renewal of traumatic symptoms with the battery's termination. Before getting in his car to end his life in another planned car wreck, M.A. saw his battery modulator on the front seat of his car. The modulator could turn his pacemaker on and off. When M.A. saw it, he had a brief moment of clarity about feeling better in the past.
- Unsure if he was delusional or not, M.A. put the device up to his shoulder and turned the battery on. The change was instantaneous.

Supplementary video of subject M.A for Integrating precision medicine in the study and clinical treatment of a severely mentally ill person. PeerJ 1:e177

http://repository.cshl.edu/29337/

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journal homepage: www.elsevier.com/locate/atg

Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape

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Table 1
Processes involved in a CLIA-certified genetic test.

Preanalytic system
1) Test request and specimen collection criteria
2) Specimen submission, handling and referral procedures
3) Preanalytic systems assessment
Analytic system
1) A detailed step-by-step procedure manual
2) Test systems, equipment, instruments, reagents, materials and supplies
3) Establishment and verification of performance specifications
4) Maintenance and function checks
5) Calibration and calibration verification procedures
6) Control procedures, test records, and corrective actions
7) Analytic systems assessment
Post-analytic system
1) Test report, including (among other things):
a) interpretation
b) reference ranges and normal values
2) Post-analytic systems assessment

1. Sample Collection and handling

2. Sequencing/Analytics

3. Interpretation

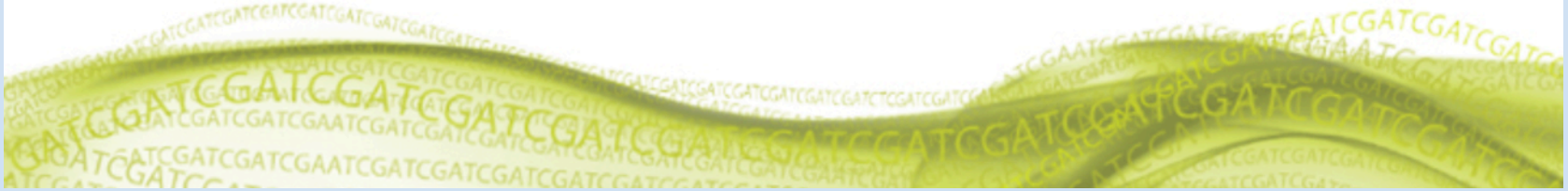
Individual Genome Sequencing Service

Available from Illumina's CLIA-certified laboratory.

"This laboratory test was developed, and its performance characteristics were determined by the Illumina Clinical Services Laboratory (CLIA-certified, CAP-accredited). Consistent with laboratory-developed tests, it has not been cleared or approved by the U.S. Food and Drug Administration. If you have any questions or concerns about what you might learn through your genome sequence information, you should contact your doctor or a genetic counselor. Please note that Illumina does not accept orders for Individual Genome Sequencing services from Florida and New York."

Understand Your Genome Symposium

During this two-day educational event, industry experts will discuss the clinical implementation of whole-genome next-generation sequencing (NGS) technology.



illumina®

Ordering Physician:
Gholson Lyon, MD
Steinmann Institute
10 West Broadway, Suite #820
Salt Lake City, UT 84101

Individual Genome Sequence Results

Clinical Report

www.everygenome.com
CLIA#: 05D1092911

Sample Collection and Handling

The Sample Collection kit includes barcoded collection tubes, a Test Requisition form, an Informed Patient Consent form, and a pre-paid shipping envelope. All paperwork must be completed and returned for sample processing. Requests for Sample Collection kits must be submitted by a physician.

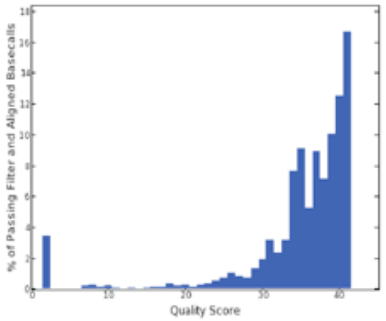
http://www.illumina.com/clinical/illumina_clinical_laboratory/igs_for_doctors/how_to_order.ilmn

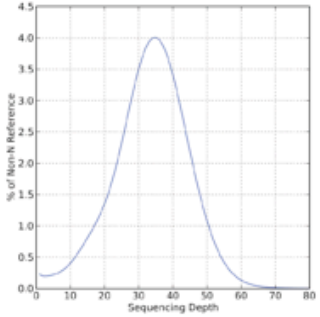
Sequencing and Analytics

Data Volume and Quality

	Yield (Gigabases)	% Bases ≥ Q30	% Bases Aligned
Passing Filter	113.10	87.10%	87.80%

	% Callable	% ≥ 5x depth	% ≥ 10x depth	% ≥ 20x depth	Mean depth(x)
Non-N Reference	93.28%	97.57%	96.22%	88.54%	33.35





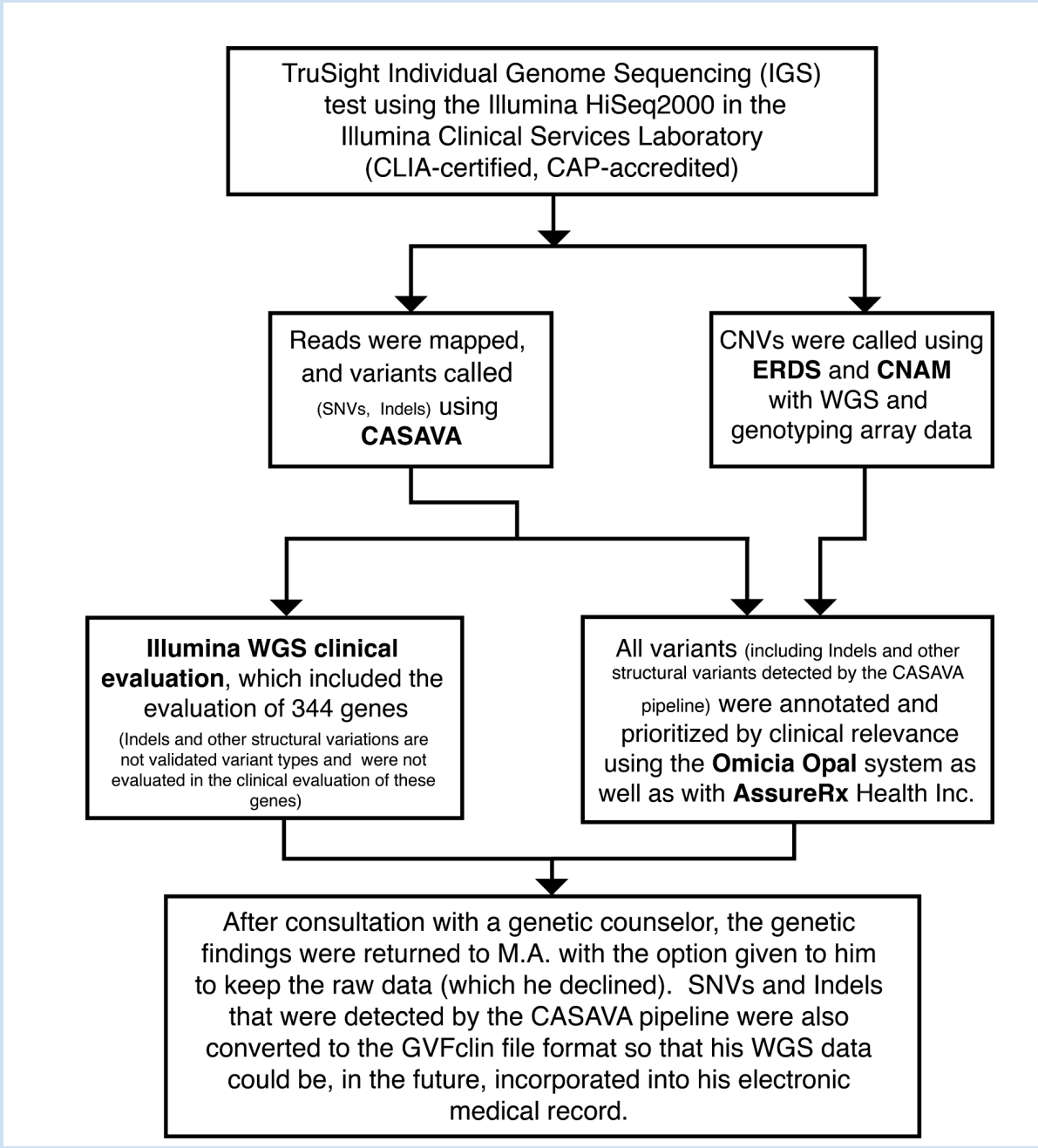
SNP Assessment

Total	Het/Hom	% in dbSNP	% in Genes	% in Coding
3,308,246	1.61	98.13%	45.47%	0.63%

Variant Statistics

	SNVs
Total Number	3,308,246
Number in Genes	1,504,121
Number in Coding Regions	20,879
Number in UTRs	24,946
Splice Site Region	2,917
Stop Gained	72
Stop Lost	16
Non-synonymous	9,884
Synonymous	10,907
Mature miRNA	36

From the Illumina Understand Your Genome Symposium October 2012


TruSight Individual Genome Sequencing (IGS) test using the Illumina HiSeq2000 in the Illumina Clinical Services Laboratory (CLIA-certified, CAP-accredited)
Reads were mapped, and variants called (SNVs, Indels) using **CASAVA**
CNVs were called using **ERDS** and **CNAM** with WGS and genotyping array data
Illumina WGS clinical evaluation, which included the evaluation of 344 genes (Indels and other structural variations are not validated variant types and were not evaluated in the clinical evaluation of these genes)
All variants (including Indels and other structural variants detected by the CASAVA pipeline) were annotated and prioritized by clinical relevance using the **Omicia Opal** system as well as with **AssureRx** Health Inc.
After consultation with a genetic counselor, the genetic findings were returned to M.A. with the option given to him to keep the raw data (which he declined). SNVs and Indels that were detected by the CASAVA pipeline were also converted to the GVFclin file format so that his WGS data could be, in the future, incorporated into his electronic medical record.

Previous report from Illumina (10/14/2012)

A total of **1247** variants were detected in the subset of genes for this patient. Each variant was evaluated for clinical significance and placed into one of five possible categories for classification, based on the American College of Medical Genetics and Genomics interpretation guidelines as outlined below and described at the end of this report.

Category		Number of Variants	Condition
Clinically Significant in Patient	Pathogenic	0	
	Likely Pathogenic	0	
Carrier Status for Patient	Pathogenic	0	
	Likely Pathogenic	1	Refsum Disease
Variants of Unknown Significance		284	
Likely Benign Variants		349	
Benign Variants		613	

Gene	Call	Amino Acid	Interpretation	Associated Condition	Mode of Inheritance
PHYH	c.734G>A	p.Arg245Gln	Likely Pathogenic	Refsum Disease	Autosomal Recessive

Refsum Disease

Refsum disease is an inherited condition that causes vision loss, anosmia, and a variety of other signs and symptoms. The vision loss is caused by retinitis pigmentosa. The first sign of retinitis pigmentosa is usually a loss of night vision, which often becomes apparent in childhood. Over a period of years, the disease disrupts peripheral vision and may eventually lead to blindness. Vision loss and anosmia are seen in almost everyone with Refsum disease, but other signs and symptoms vary. About one-third of affected individuals are born with bone abnormalities of the hands and feet. Features that appear later in life can include progressive myopathy; ataxia; hearing loss; and ichthyosis. Additionally, some people with Refsum disease develop arrhythmia and cardiomyopathies that can be life-threatening.

Refsum Disease?

- Found to have bilateral cataracts, large pupils, and loss of night vision.
- His mother and grandmother both have large pupils and loss of night vision. No cataracts known.
- Preventive measures implemented.
- Referred to optometry for further evaluation; **report showed normal fatty acids profile**.

Recent report from Illumina (12/16/2013)

Summary of Clinically Significant Findings		
Category	**# Variants**	**Condition**
Pathogenic	0	
Likely Pathogenic	0	
VUS - Suspicious	1	Malignant Hyperthermia Susceptibility

Summary of Findings Regarding Carrier Status		
Category	**# Variants**	**Condition**
Pathogenic	0	
Likely Pathogenic	1	Mannose-Binding Protein Deficiency
VUS - Suspicious	0	

Note:

In this individual's previous report dated 10/14/2012, one additional variant was called Likely Pathogenic: PHYH c.734G>A (p.Arg245Gln). Due to updated information, this variant has since been reclassified as a Variant of Unknown Significance and is no longer shown on this report. This variant and its updated classification can be found in the Clinical Variant Interpretation appendix.

Recent report from Illumina – Cont.

- **4182** more variants in additional **1256** genes were added into the more recent version of the clinical report.
- One variant of unknown significance (suspicious) and one likely pathogenic variant were reported.

Clinically Significant Findings			
Variant	**Interpretation**	**Associated Condition**	**Mode of Inheritance**
CACNA1S c.4060A>T (p.Thr1354Ser)	VUS - Suspicious	Malignant Hyperthermia Susceptibility	Autosomal Dominant

Note: However, this person has been prescribed general anesthesia before and had no significant side-effects. The allele frequency of c.4060A>T variant is ~1% in the 1000 Genomes database.

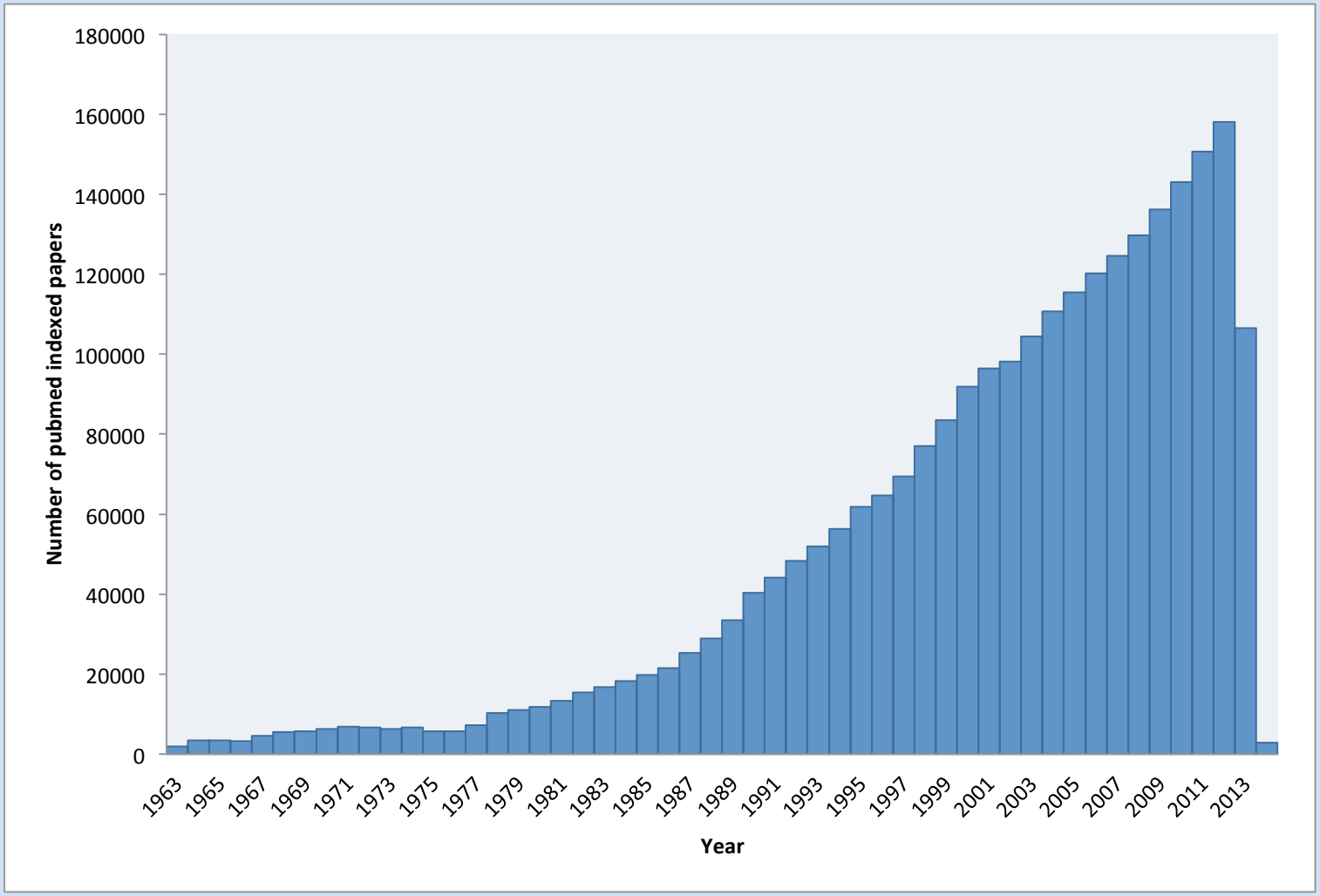
Recent report from Illumina – Cont.

Findings Regarding Carrier Status			
Variant	**Interpretation**	**Associated Condition**	**Mode of Inheritance**
MBL2 c.161G>A (p.Gly54Asp)	Likely Pathogenic	Mannose-Binding Protein Deficiency	Autosomal Recessive

Variants in the MBL2 gene have been associated with mannose-binding lectin deficiency. The c.161G>A (p.Gly54Asp) variant appears to be inherited in a co-dominant form, with heterozygotes displaying intermediate levels of mannose binding lectin levels. Multiple studies (Sumiya et al., 1991; Madsen et al., 1994; others) have demonstrated that this variant is likely to play a role in this common condition. It should be noted that many individuals who carry variants in MBL2 do not necessarily have clinical complications. The highest reported allele frequency for this variant is 0.185 in the Southern Han Chinese population in the 1000 Genomes database.

Note: This c.161G>A variant is classified as “Pathogenic” in ClinVar and classified as “with pathogenic allele” in dbSNP database.

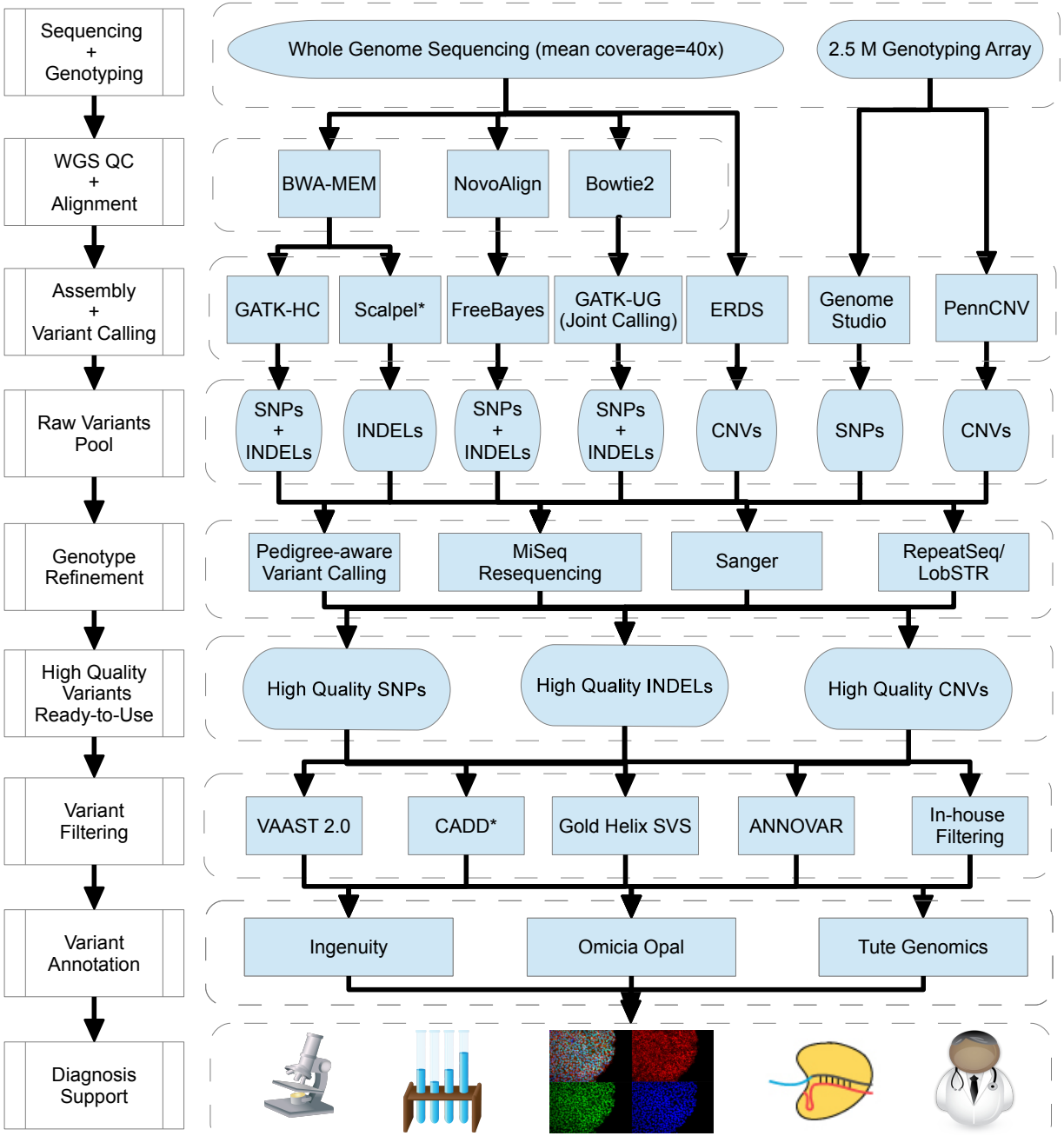
Pubmed indexed papers related to “Genetics”



Re-analyzing genomic data

- Significant improvements of bioinformatics pipelines in recent years
- Rapid increase of numbers of both publications and genomes sequenced
- “Refresh” views of genotype-phenotype relationship in an era of millions of genomes

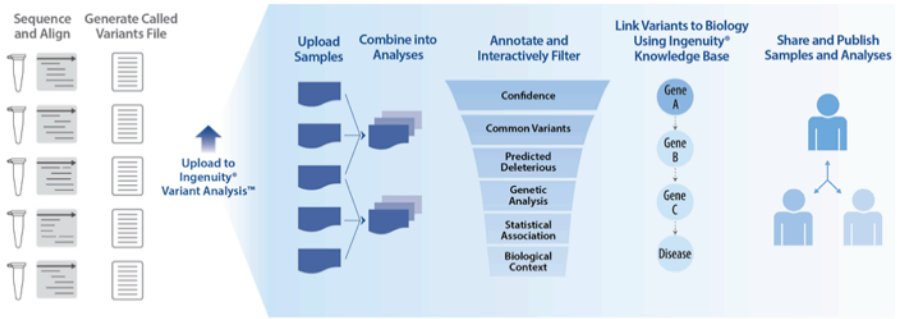
Variant Analysis Pipeline



* Scalpel (In press) http://schatzlab.cshl.edu/
* CADD (In press) http://cadd.gs.washington.edu/

Current popular genomic analysis online platforms and analysis suits

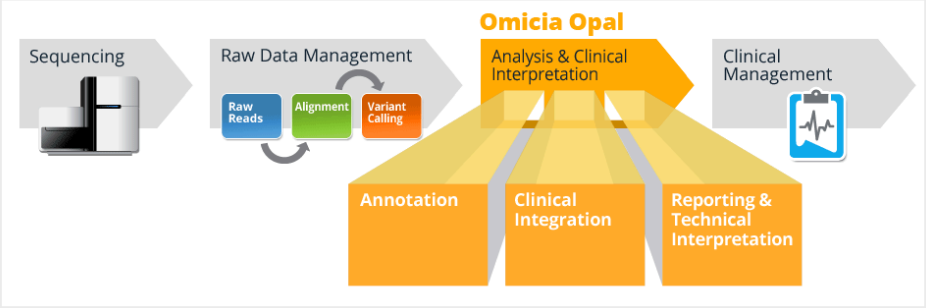
Identify causal variants from human sequencing data in just hours



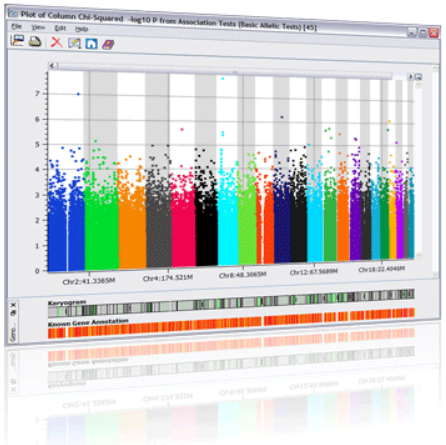
BIOLOGICAL INTERPRETATION OF HUMAN WHOLE GENOME, EXOME, AND TARGETED PANEL SAMPLES

Opal adds clinical context for genomic data

Omicia is unlocking individualized medicine by translating data derived from whole-genome sequencing into actionable information for researchers and clinicians.



Golden Helix Product Offerings



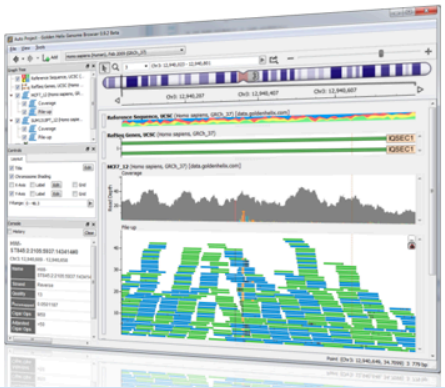
SNP & VARIATION SUITE 7

SNP & Variation Suite 7 is an integrated collection of user-friendly, yet powerful analytic tools for managing, analyzing, and visualizing multifaceted genomic and phenotypic data. SVS was created specifically to empower biologists and other researchers to easily perform complex analyses and visualizations, eliminating the need to rely exclusively on bioinformatics experts or cobble together difficult to use, incompatible freeware. With SVS you can focus on your research instead of learning to be a programmer or waiting in line for bioinformaticians.

Golden Helix GenomeBrowse™

Golden Helix GenomeBrowse® visualization tool raises the bar on the experience of exploring and finding key insights into your genomic data. Every component has been designed and optimized to give you a user-experience beyond imagination.

Find out more information about GenomeBrowse »



Easily select variants with prior evidence (called by both GATK and FreeBayes, but not by CASAVA)

Variant Class	Gene	Position dbSNP	Change	Zygosity Effect	Quality Coverage	Frequency	Omicia Score	Polyphen Mut-Taster	SIFT PhyloP	Evidence	
VUS (dg)	FCGR3A	chr1 161518333 rs10127939	A→A,C c.197T>G p.Leu66Arg	het non-synon	339.77 63:42:21	A:96% C:4%	0.109	damaging damaging	0.09 0.14	CV HGMD LSDB	Viral infections, recurrent, susceptibility to
VUS (dg)	AGT	chr1 230845794 rs699	A→G,G c.803T>C p.Met268Thr	hom non-synon	829.77 34:0:34	A:34% G:66%	0.086	benign benign	0.68 0.06	CV HGMD PGKB	Condition: Hypertension, essential, susceptibility to
VUS (other)	SLC22A1	chr6 160560881 rs35167514	ATG→-,ATG c.1258_1260del p.Ser420del	het nonframeshift deletion	693.76 30:15:15	-	0.424	- -	- 0.97	PGKB	Description: Reduced metformin uptake in transfected cells
VUS (other)	OR52B4	chr11 4389405 rs80193749	G→-,G c.121_121del p.Ser41del	het frameshift deletion	536.76 39:21:18	-	0.133	- -	- -0.77	HGMD	
VUS (other)	CHRFAM7A	chr15 30665281	CA→-,CA c.227_228del p.Ser76del	het frameshift deletion	422.76 51:39:12	-	0.321	- -	- 0.88	HGMD	
Known Pathogenic	XYLT1	chr16 17564311 rs61758388	C→A,C c.343G>T p.Ala115Ser	het non-synon	135.77 20:11:9	C:99% A:1%	0.187	benign benign	0.41 0.78	CV OMIM HGMD	Pseudoxanthoma elasticum
VUS (other)	P2RX5	chr17 3594277 rs5818907	G→-,- c.333_333del p.Ser111del	hom frameshift deletion	1114.76 33:0:33	-	0.247	- -	- -0.54	HGMD	
VUS (dg)	MAPT	chr17 44067382 rs112757188	T→C,C c.1321T>C p.Tyr441His	hom non-synon	531.77 17:0:17	T:68% C:32%	0.266	- -	0.26 0.43	LSDB	associated with shorter bleeding time and less response to aspirin.
VUS (other)	C17orf57	chr17 45360730 rs5918	T→C,T c.176T>C p.Leu59Pro	het non-synon	588.77 48:23:25	T:91% C:9%	0.089	benign benign	0.43 -3.9	CV HGMD PGKB LSDB	a higher risk of secondary coronary events which was reduced by pravastatin
VUS (other)	SLC14A2	chr18 43262359 rs3745009	G→A,A c.2638G>A p.Ala880Thr	hom non-synon	642.77 21:0:21	G:60% A:40%	0.546	benign benign	0.38 2.12	HGMD PGKB LSDB	associated with blood pressure response to nifedipine treatment.
VUS (dg)	TYK2	chr19 10463118 rs34536443	G→C,G c.3310C>G p.Pro1104Ala	het non-synon	435.77 45:23:22	G:99% C:1%	0.816	damaging damaging	- 3.89	HGMD	cancer-associated
VUS (dg)	PRNP	chr20 4680251 rs1799990	A→G,G c.385A>G p.Met129Val	hom non-synon	742.77 37:0:37	A:74% G:26%	0.302	damaging benign	0.02 0.66	CV OMIM HGMD PGKB GWAS	Description: Prion Disease, Susceptibility To Alzheimer Disease, Early-onset, Susceptibility To, Included,, Aphasia, Primary Progressive, Susceptibility To, Included

No rare variants or CNVs with high biological effect as related to mental illness.

3 common SNVs in this person that have been implicated in the literature as predisposing to mental illness.

Table 1 A summary of three clinically relevant alleles found in the sequencing results of MA. Variations in MTHFR, BDNF, and ChAT were found to be of potential clinical relevance for this person as they are all implicated in contributing to the susceptibility and development of many neuropsychiatric disorders that resemble those present within MA. A brief summary of the characteristics of each variation is shown, including the gene name, genomic coordinates, amino acid change, zygosity, variation type, estimated population frequency and putative clinical significance.

Gene name	Genomic coordinates	Amino acid change	Zygosity	Variation type	Population frequency	Clinical significance
MTHFR	chr1: 11854476	Glu > Ala	heterozygous	non-synon	T:77% G:23%	Susceptibility to psychoses, schizophrenia occlusive vascular disease, neural tube defects, colon cancer, acute leukemia, and methylenetetrahydrofolate reductase deficiency
BDNF	chr11: 27679916	Val > Met	heterozygous	non-synon	C:77% T:23%	Susceptibility to OCD, psychosis, and diminished response to exposure therapy
CHAT	chr10: 50824117	Asp > Asn	heterozygous	non-synon	G:85% A:15%	Susceptibility to schizophrenia and other psychopathological disorders.

Table 3 Description of the 22 genome-wide significant loci in the combined analysis

Chromosomal region	*P* value	Previous association[a]	Candidate gene in relation to index SNP[b]	Other genes in genomic region defined by LD[c]	eQTL[d]	Disease associations[e]
Chr. 6: 31,596,138–32,813,768	9.14×10^{-14}	SCZ	*HLA-DRB9*	MHC class II, many other genes, lincRNA	Many	Many
Chr. 10: 104,487,871–105,245,420	3.68×10^{-13}	SCZ	*C10orf32-AS3MT*	*CALHM1*, *CALHM2*, *CALHM3*, *CNNM2*, *CYP17A1*, *INA*, *MIR1307*, *NT5C2*, *PCGF6*, *PDCD11*, *SFXN2*, *ST13P13*, *TAF5*, *USMG5*, *WBP1L*	*ACTR1A*, *ARL3*, *AS3MT*, *C10orf32*, *C10orf78*, *NT5C2*, *TMEM180*, *TRIM8*, *WBP1L*	GWAS: blood pressure, CAD, aneurysm
Chr. 7: 1,827,717–2,346,115	5.93×10^{-13}	No	*MAD1L1*	*FTSJ2*, *NUDT1*, *SNX8*	*C7orf27*, *FTSJ2*, *MAD1L1*, *NUDT1*	
Chr. 1: 98,141,112–98,664,991	1.72×10^{-12}	SCZ	(*MIR137*, 37 kb)	*DPYD*, lincRNA	***DPYD***	*DPYD*: mental retardation
Chr. 12: 2,285,731–2,440,464	5.22×10^{-12}	SCZ, BPD	*CACNA1C*	–	No data	*CACNA1C*: autism, Timothy syndrome, Brugada syndrome 3
Chr. 10: 18,601,928–18,934,390	1.27×10^{-10}	5 disorders	*CACNB2*	*NSUN6*	No data	*CACNB2*: Brugada syndrome 4; GWAS: blood pressure
Chr. 8: 143,297,312–143,410,423	2.19×10^{-10}	No	*TSNARE1*	–	No data	
Chr. 1: 73,275,828–74,099,273	3.64×10^{-10}	No	(x10NST00000415686.1, 4 kb)	lincRNA	No data	
Chr. 11: 130,706,918–130,894,976	1.83×10^{-9}	No	(*SNX19*, 31 kb)	lincRNA	***SNX19***	
Chr. 5: 151,888,959–152,835,304	2.65×10^{-9}	No	ENST00000503048.1	lincRNA (*GRIA1*)	No data	
Chr. 5: 152,505,453–152,707,306	4.12×10^{-8}	No				
Chr. 19: 19,354,937–19,744,079	3.44×10^{-9}	BPD	(*MAU2*, 4 kb)	*CILP2*, *GATAD2A*, *GMIP*, *HAPLN4*, *LPAR2*, *MIR640*, *NCAN*, *NDUFA13*, *PBX4*, *SUGP1*, *TM6SF2*, *TSSK6*, *YJEFN3*	No data	GWAS: lipid levels

[a]Regions reported to meet genome-wide significance thresholds of association for schizophrenia (SCZ) or bipolar disorder (BPD). [b]The gene within which an index SNP is located is given. For intergenic index SNPs, the nearest gene is given in parentheses. [c]Other named genes in the genomic interval. [d]SNP-transcript associations with $q < 0.05$ in peripheral blood. eQTLs with the SNP with the strongest association are shown in bold. [e]Data from the NHGRI GWAS catalog[24], OMIM[43] and a compilation of genes related to autism[73] and mental retardation[43,74,75]. No data means no Affymetrix U219 probe sets or low expression in peripheral blood. The *CACNB2* association emerged when considering attention deficit/hyperactivity disorder (ADHD), autism, bipolar disorder, major depressive disorder and schizophrenia as affected[30]. CAD, coronary artery disease; HDL, high-density lipoprotein.

Indicates that M.A. is homozygous for the exact variant of genome significance

Indicates that M.A. is heterozygous for the exact variant of genome significance

Ripke et.al (2013) Nature Genetics

	Chr. 2: 37,422,072–37,592,628	6.78×10^{-9}	No	*QPCT*	*C2orf56*, *CEBPZ*, *PRKD3*, *SULT6B1* lincRNA	No eQTL	
	Chr. 5: 101,581,848–101,870,822	9.03×10^{-9}	No	*SLCO6A1*	lincRNA	No data	
	Chr. 3: 52,215,002–53,175,017	1.16×10^{-8}	SCZ, BPD	*ITIH3*	*ALAS1*, *ALDOAP1*, *BAP1*, *C3orf78*, *DNAH1*, *GLT8D1*, *GLYCTK*, *GNL3*, *ITIH1*, *ITIH4*, *MIR135A1*, *MIRLET7G*, *MUSTN1*, *NEK4*, *NISCH*, *NT5DC2*, *PBRM1*, *PHF7*, *PPM1M*, *RFT1*, *SEMA3G*, *SFMBT1*, *SPCS1*, *STAB1*, *TLR9*, *TMEM110*, *TNNC1*, *TWF2*, *WDR82*, lincRNA	No data (*ITIH1-ITIH3-ITIH4*)	*GLYCTK*: D-glyceric aciduria, mental retardation; *RTF1*: mental retardation; GWAS: adiponectin, height, waist-hip ratio
	Chr. 2: 145,139,727–145,214,607	1.19×10^{-8}	No	*ZEB2*	–	No eQTL	*ZEB2*: Mowat-Wilson syndrome, mental retardation
	Chr. 2: 200,628,118–201,293,421	1.21×10^{-8}	No	*FONG*	*C2orf47*, *C2orf69*, *SPATS2L*, *TYW5*, lincRNA	No data	GWAS: osteoporosis
	Chr. 18: 52,722,378–52,827,668	1.22×10^{-8}	No	(ENST00000565991.1, 21 kb)	lincRNA (*TCF4*)	No data	
	Chr. 2: 233,550,961–233,808,241	1.51×10^{-8}	No	*C2orf82*	*GIGYF2*, *KCNJ13*, *NGEF*	No data	
	Chr. 1: 243,593,066–244,025,999	1.80×10^{-8}	No	*AKT3*	*CEP170*	***AKT3***	
	Chr. 1: 243,418,063–243,627,135	2.53×10^{-8}	Yes	*SDCCAG8*		***SDCCAG8***	
	Chr. 12: 123,447,928–123,913,433	2.28×10^{-8}	No	*C12orf65*	*ABCB9*, *ARL6IP4*, *CDK2AP1*, *MIR4304*, *MPHOSPH9*, *OGFOD2*, *PITPNM2*, *RILPL2*, *SBNO1*, *SETD8*, lincRNA	*ARL6IP4*, *CDK2AP1*, *OGFOD2*, *SBNO1*	*C12orf65*: mental retardation; GWAS: HDL, height, head size
	Chr. 8: 89,188,454–89,761,163	3.33×10^{-8}	SCZ	Intergenic	*MMP16*, lincRNA	*MMP16*	
	Chr. 5: 60,484,179–60,843,706	3.78×10^{-8}	No	ENST00000506902.1	*ZSWIM6*, *C5orf43*, lincRNA	*C5orf43*, *ZSWIM6*	

Indicates that M.A. is homozygous for the exact variant of genome significance

Indicates that M.A. is heterozygous for the exact variant of genome significance

Ripke et.al (2013) Nature Genetics

Pharmacogenetics

- MA is homozygous for a p.Ile359Leu change in CYP2C9, and this variant has been linked to a reduction in the enzymatic activity of CYP2C9, a member of the cytochrome P450 superfamily of enzymes.
- Cytochrome P450 proteins are mono-oxygenases, which catalyze many reactions associated with drug metabolism as well as reactions associated with the synthesis of cholesterol, steroids and other lipids.
- Fluoxetine is commonly used in the treatment of OCD; it has been shown to be as effective as clomipramine and causes less side effects.
- CYP2C9 acts to convert fluoxetine to R-norfluoxetine, and so MA may not be able to adequately biotransform fluoxetine.
- It is notable that MA had no response to an 80 mg daily dose of fluoxetine.
- However, CYP2C9 does not play a rate-limiting role for other SSRIs or clomipramine

The FASEB Journal • Research Communication

Neurotrophic factor expression in expandable cell populations from brain samples in living patients with Parkinson's disease

Hu Xu, Louiza Belkacemi, Mandar Jog, Andrew Parrent, and Matthew O. Hebb[1]

Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada

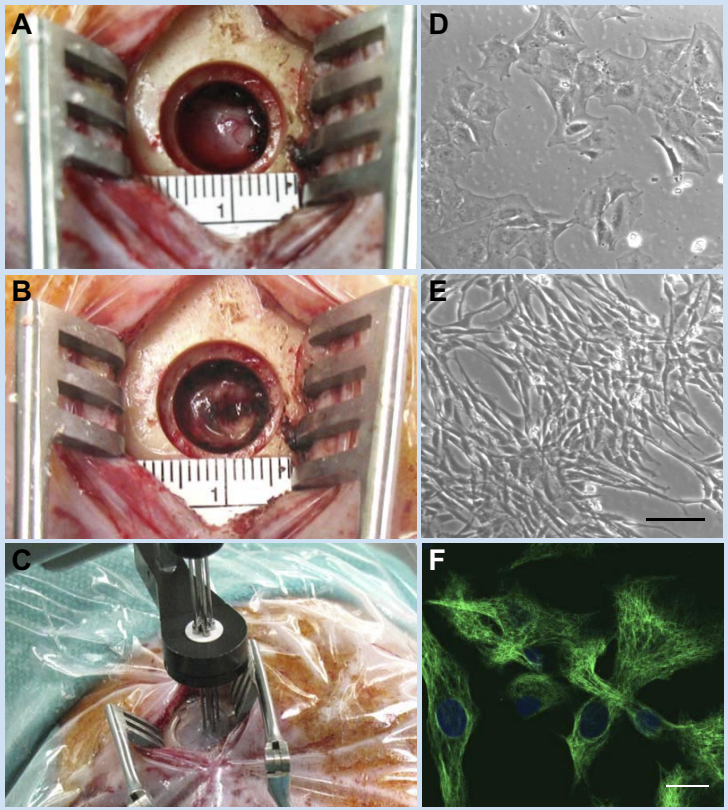
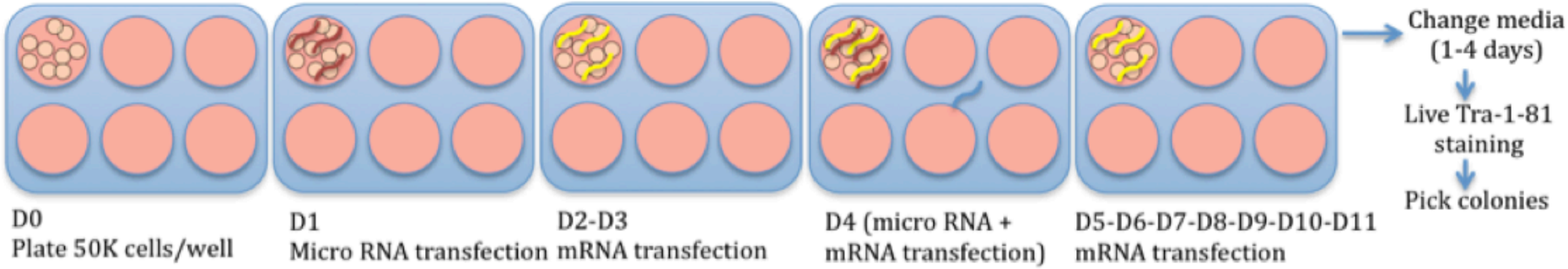
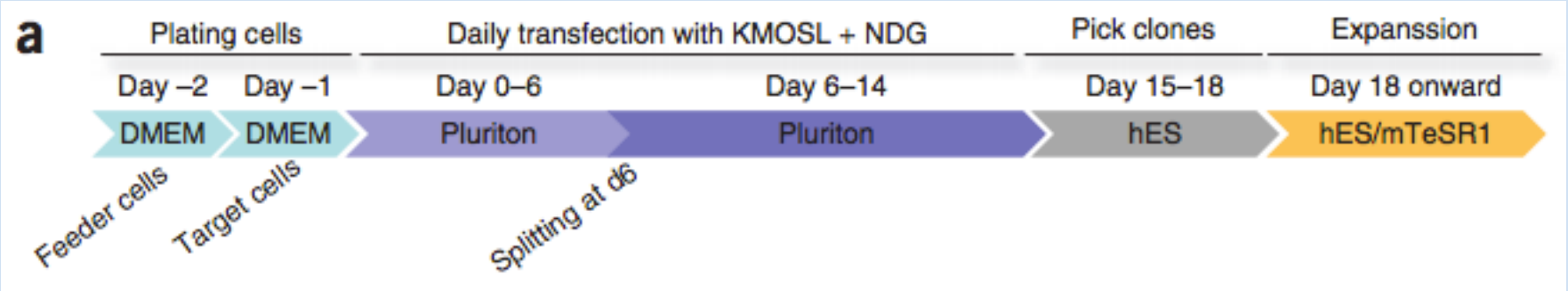


Figure 1. Brain biopsies in patients with PD yield expandable primary cell cultures. *A–C*) Operative images taken during DBS surgery in a patient with PD. *A*) The cortical exposure was achieved through a 14-mm burr hole and dural opening over the frontal lobe. *B*) Appearance of the brain following pial incision and brain biopsy. *C*) The biopsy site was used as the entry portal for the microelectrode array (shown) and subsequent DBS lead. The biopsy tissue yielded cultures with robust proliferative capacity and characteristic morphology. *D, E*) At subconfluence (*D*), cells were flat with broad polygonal somata and generous cytoplasm, while at higher densities (*E*), the cytoplasm was modest and somata spindle-shaped with fine lamellipodia. *F*) Cells exhibited robust expression of the progenitor marker, nestin. Scale bars = 50 μm (*D, E*); 20 μm (*F*).

Flowchart of mRNA reprogramming

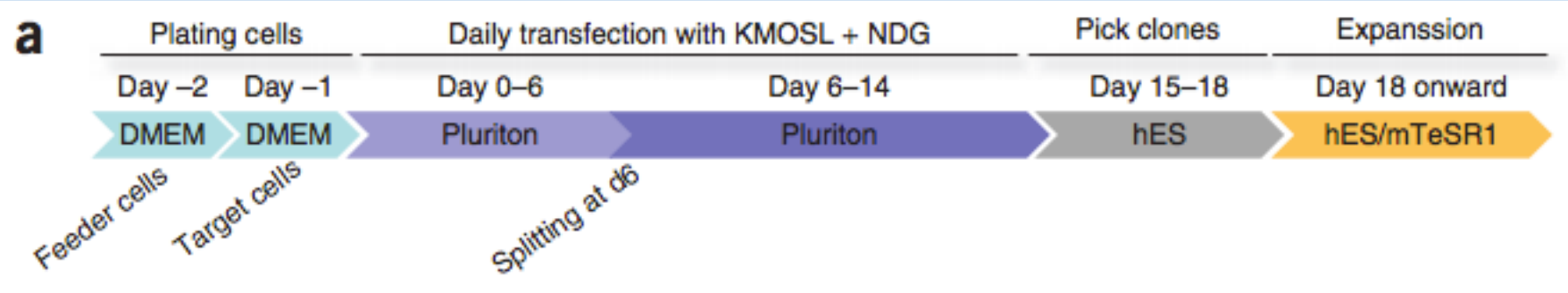


Protocol from MSSM based on Stemgent's.

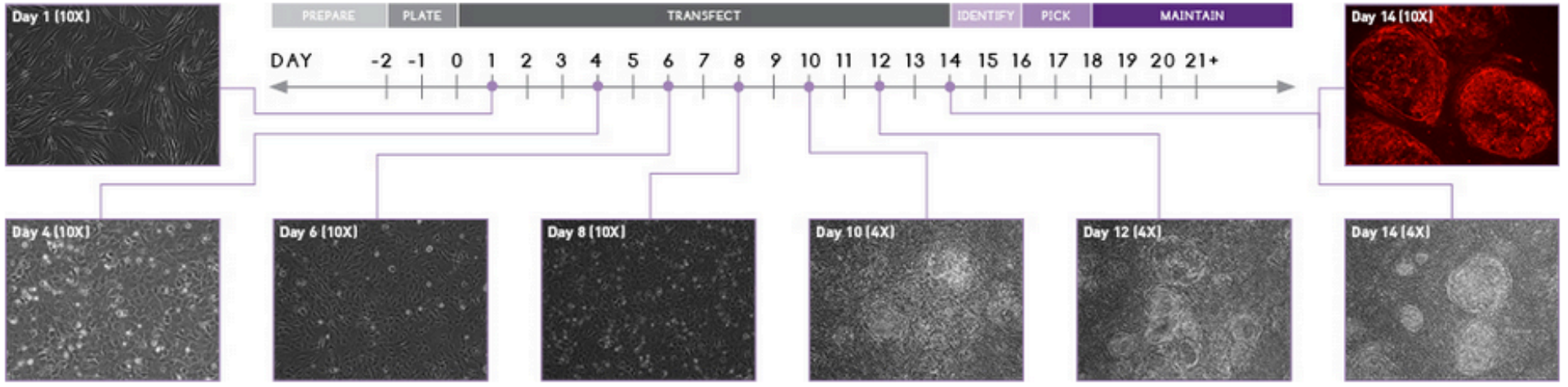


Mandal PK *et al*, Nat Protoc. 2013 Mar; 8(3): 568-82.

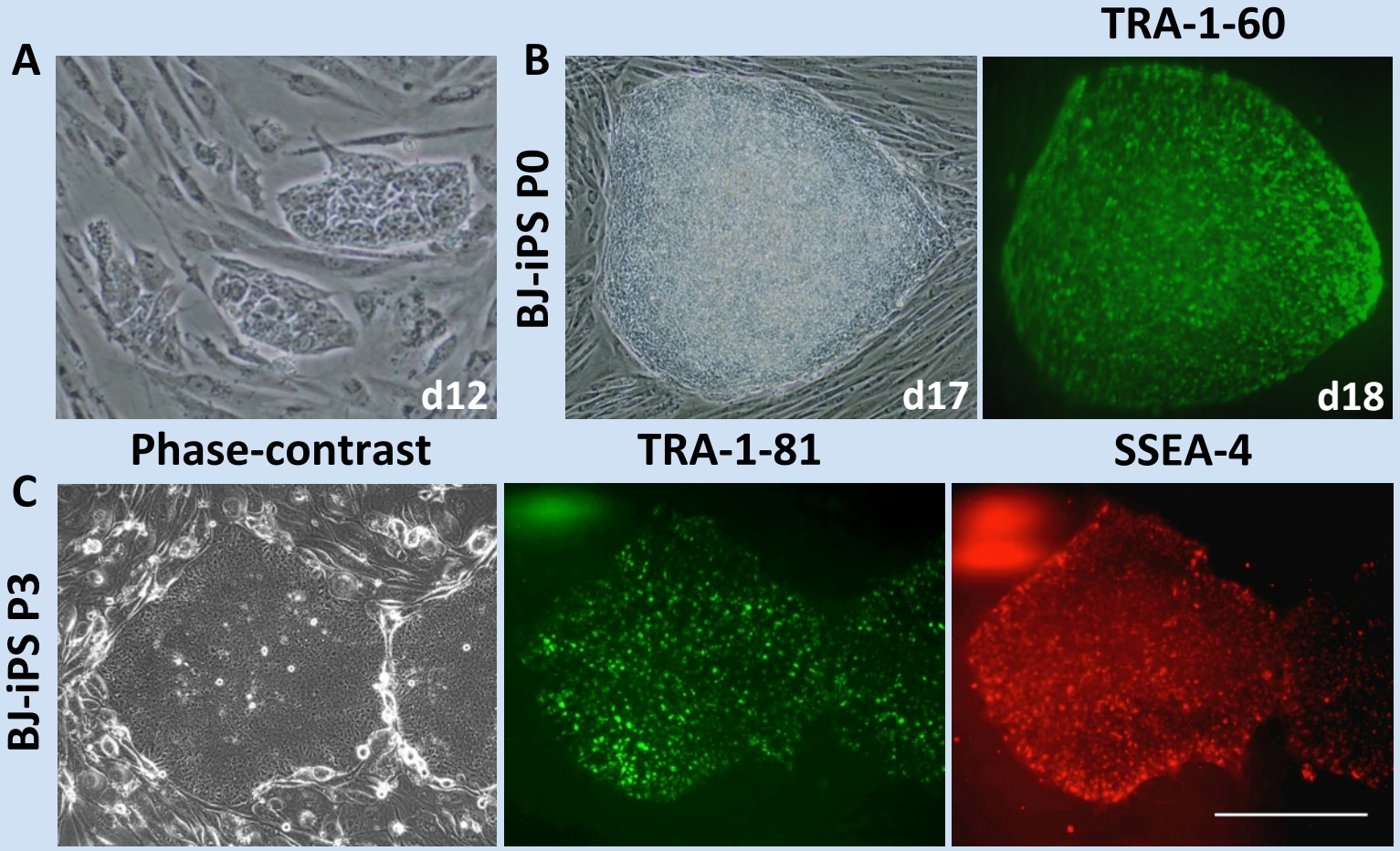
Flowchart of mRNA reprogramming



Mandal PK *et al*, Nat Protoc. 2013 Mar; 8(3): 568-82.

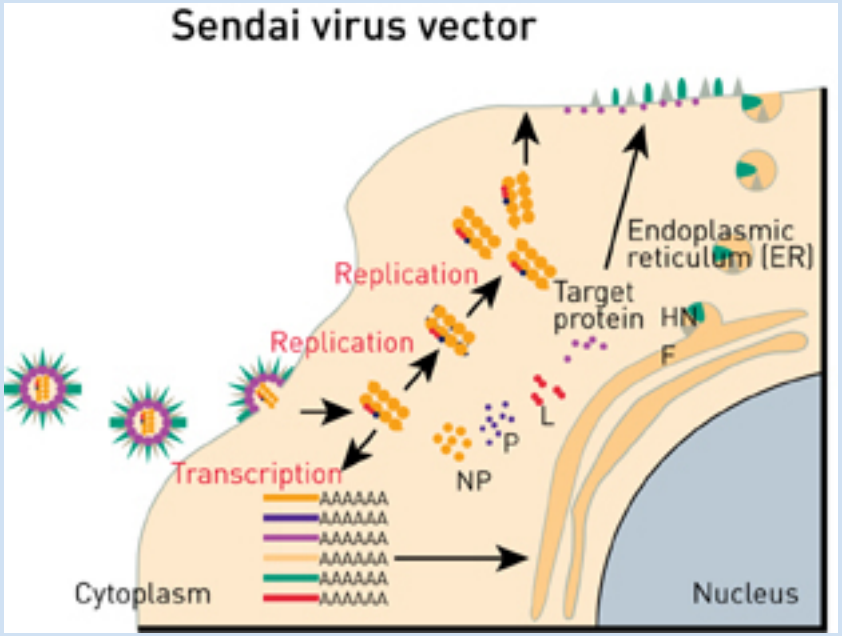


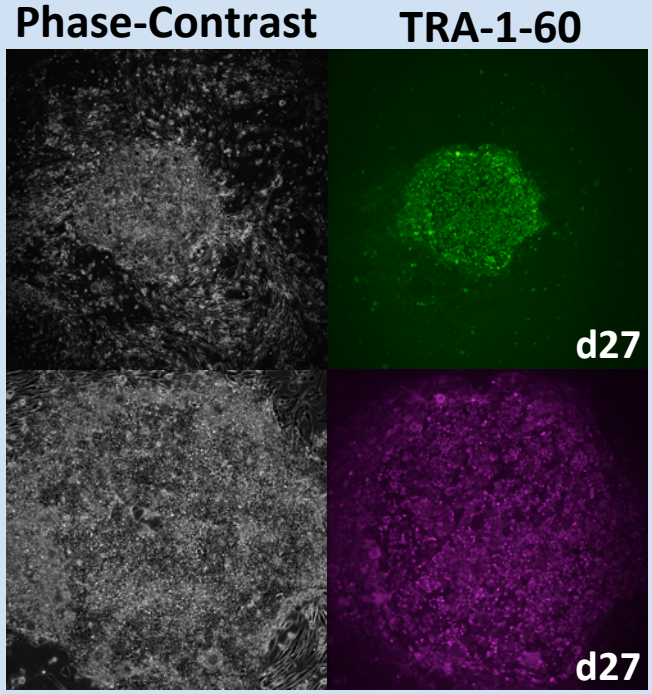
Protocol from Stemgent.

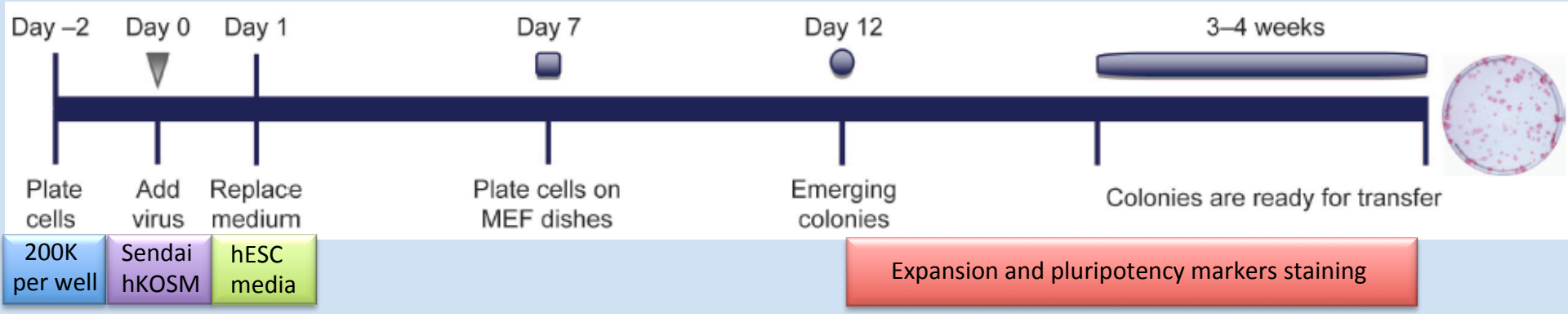


Generation of induced Pluripotent Stem Cells from wild-type (control) fibroblasts. (A) Bright-field images taken during the derivation in the new iPS facility of iPSCs from WT fibroblasts showing small hESC-like colonies (Day 12) and (B) appearance of a mature iPSC clone (Day 17). Immunocytochemical analysis of pluripotency marker TRA-1-60 on the same iPSC clone (Day 18). (C) Immunocytochemical showing expression of two additional pluripotency markers in iPSC clones (passage 3) after mechanical picking and expansion.
Scale bar represents 100 μm.

Flowchart of Sendai Virus mediated reprogramming







Based on CytoTune™ protocol from Invitrogen.

Summary

- first study in the clinical neurosciences that integrates detailed neuropsychiatric phenotyping, deep brain stimulation for OCD and clinical-grade WGS with management of genetic results in the medical treatment of one person with severe mental illness.
- Investigating iPS cells as one more way to understand the genetic architecture and phenotype.

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Dick McCombie

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Kai Wang

illumina®

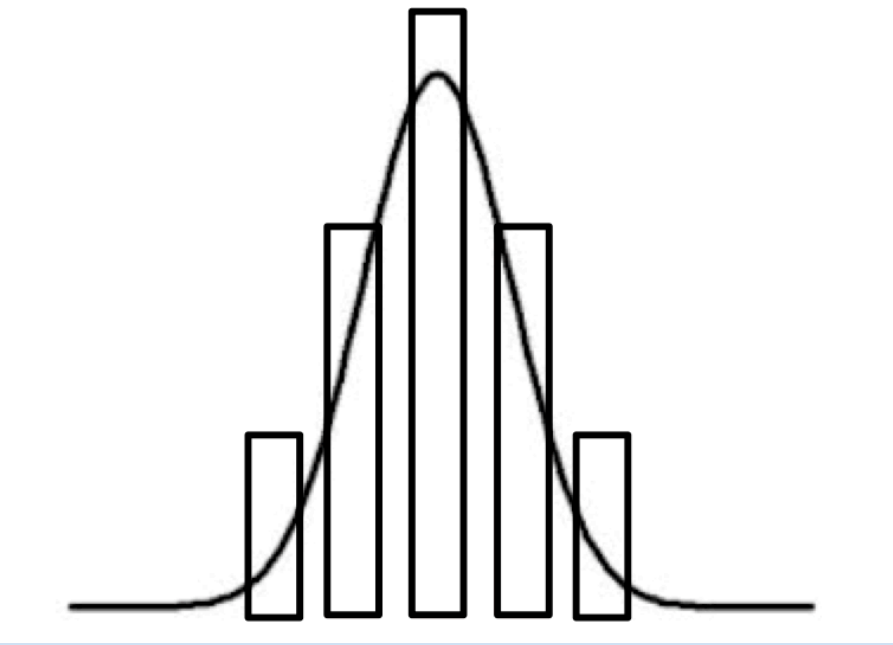
Tina Hambuch
Erica Davis
Dawn Barry

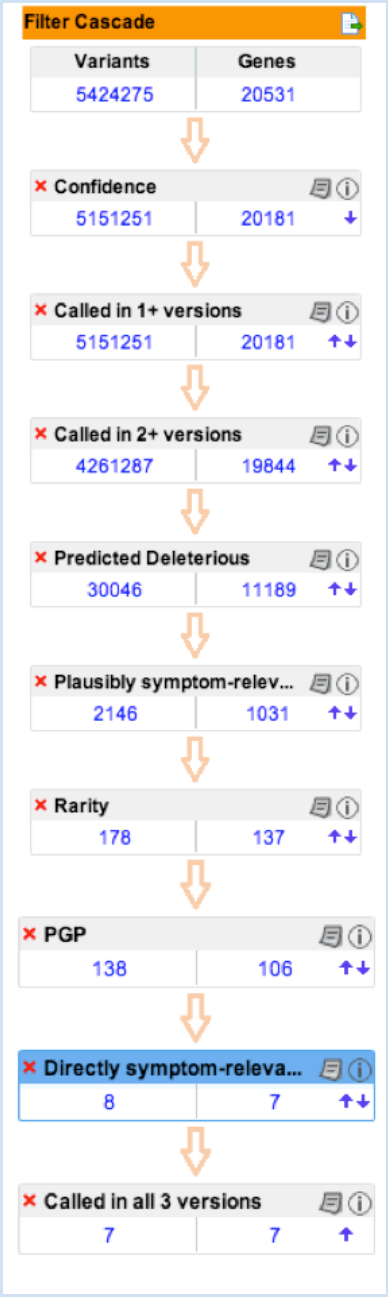
our study families

Extra Slides

Q: How frequent can we observe people with all three SNPs?

- Empirical genotype frequencies:
- 1000G: 3.20% (35 out of 1092, phenotypes unknown)
- UFBR: 4.58% (7 out of 153, including M.A. and M.A.'s father)





Identify of Refsum disease related variant in Ingenuity

Chr...	Position	Gene Region	Gene Symbol	Protein Variant	Case Samples	Translation Impact	SIFT Functio...	Variant Findings	dbSNP ID	1000 G...
4	629702	Exonic	PDE6B	p.Y219H		missense	Tolerated	1	62295357	0.37
4	3144528	Exonic	HTT	p.T996R		missense			190593027	0.24
7	92119098	Exonic	PEX1	p.T1189I		missense	Damaging			
8	77912596	Intronic, Promo	PEX2					73	148483807	
8	77913382	Promoter	PEX2					2	34704553	
9	104335619	Exonic	GRIN3A	p.N1062S		missense	Tolerated		71509734	0.55
10	13325784	Exonic	PHYH	p.R145Q, p.R24		missense	Tolerated	2	62619919	0.17
16	9858502	Exonic	GRIN2A	p.V967L		missense	Tolerated		61731465	0.41

nature medicine

ARTICLES

A primate-specific, brain isoform of *KCNH2* affects cortical physiology, cognition, neuronal repolarization and risk of schizophrenia

Stephen J Huffaker[1,2], Jingshan Chen[1,2], Kristin K Nicodemus[1,2], Fabio Sambataro[1,2], Feng Yang[3], Venkata Mattay[1,2], Barbara K Lipska[1,2], Thomas M Hyde[1,2], Jian Song[1,2], Dan Rujescu[4], Ina Giegling[4], Karine Mayilyan[5], Morgan J Proust[1], Armen Soghoyan[5], Grazia Caforio[6], Joseph H Callicott[1], Alessandro Bertolino[6], Andreas Meyer-Lindenberg[1,2,7], Jay Chang[2,3], Yuanyuan Ji[3], Michael F Egan[1], Terry E Goldberg[1,2], Joel E Kleinman[1,2], Bai Lu[2,3] & Daniel R Weinberger[1,2]

Organized neuronal firing is crucial for cortical processing and is disrupted in schizophrenia. Using rapid amplification of 5′ complementary DNA ends in human brain, we identified a primate-specific isoform (3.1) of the ether-a-go-go–related K^+ channel ***KCNH2*** that modulates neuronal firing. ***KCNH2***-3.1 messenger RNA levels are comparable to full-length ***KCNH2*** (1A) levels in brain but three orders of magnitude lower in heart. In hippocampus from individuals with schizophrenia, ***KCNH2***-3.1 expression is 2.5-fold greater than ***KCNH2***-1A expression. A meta-analysis of five clinical data sets (367 families, 1,158 unrelated cases and 1,704 controls) shows association of single nucleotide polymorphisms in ***KCNH2*** with schizophrenia. Risk-associated alleles predict lower intelligence quotient scores and speed of cognitive processing, altered memory-linked functional magnetic resonance imaging signals and increased ***KCNH2-3.1*** mRNA levels in postmortem hippocampus. KCNH2-3.1 lacks a domain that is crucial for slow channel deactivation. Overexpression of ***KCNH2-3.1*** in primary cortical neurons induces a rapidly deactivating K^+ current and a high-frequency, nonadapting firing pattern. These results identify a previously undescribed KCNH2 channel isoform involved in cortical physiology, cognition and psychosis, providing a potential new therapeutic drug target.

Huffaker et.al (2009) Nature Medicine

Marker	SNP rs# or ss#	Location (bp)	dbSNP	Alleles	CBDB Sibling Study (296 families) MAF	Minor Allele Direction of Association	empirical p-value	NIMHGI-C (71 families) MAF	Minor Allele Direction of Association	empirical p-value	German Case-Control Study (905 cases/1323 controls) Control MAF	Case MAF	p-value	Genotype	OR (95% CI)	p-value
M1	rs1805120	150280464	11225547	C/T	0.26	---	0.33	0.18	Negative	*0.09*	---	---	---	---	---	---
M2	ss74804664	150288028	11233111	G/A	0.23	---	0.5	0.19	---	0.32	---	---	---	---	---	---
M3	rs12668582	150288134	11233217	A/C	0.35	---	0.26	0.3	---	0.76	---	---	---	---	---	---
M4	rs6947240	150288142	11233225	G/A	0.23	---	0.42	0.2	---	0.4	---	---	---	---	---	---
M5	ss74804672	150288178	11233261	InsT	0.35	---	0.26	0.3	---	0.53	---	---	---	---	---	---
M6	ss74804669	150288335	11233418	T/C	0.03	---	0.11	0.058	---	0.75	---	---	---	---	---	---
M7	rs34657537	150288741	11233824	G/A	0.26	---	0.22	0.2	Negative	*0.076*	---	---	---	---	---	---
M8	rs3823587	150288823	11233906	T/G	0.26	---	0.42	0.19	---	0.13	---	---	---	---	---	---
M9	rs3807376	150289132	11234215	A/G	0.26	---	0.15	0.2	---	0.21	---	---	---	---	---	---
M10	rs35760656	150289611	11234694	G/A	0.26	---	0.34	0.2	---	0.12	---	---	---	---	---	---
M11	ss74804670	150289715	11234798	T/C	0.02	---	0.42	0.009	---	---	---	---	---	---	---	---
M12	ss74804671	150289729	11234812	G/A	0.04	---	0.43	0.019	---	0.82	---	---	---	---	---	---
M13	rs3778874	150289984	11235067	G/A	0.26	---	0.19	0.2	Negative	***0.042***	---	---	---	---	---	---
M14	rs2968857	150293263	11238346	T/C	0.38	---	0.68	0.42	---	0.65	---	---	---	---	---	---
M15	rs10236214	150299003	11244086	T/C	0.33	---	0.37	0.33	---	0.59	---	---	---	---	---	---
M16	rs11763131	150299115	11244198	G/A	0.31	Positive	***0.004***	0.31	---	0.38	0.27	0.29	***0.039***	2/2	1.54 (1.11, 2.15)	***0.010***
M17	rs3807374	150299279	11244362	A/C	0.3	Positive	***0.001***	0.31	---	0.65	0.27	0.30	***0.041***	2/2	1.54 (1.12, 2.13)	***0.009***
M18	rs4725984	150299447	11244530	C/T	0.32	---	0.28	0.3	---	0.72	---	---	---	---	---	---
M19	rs3807373	150299654	11244737	C/T	0.3	Positive	***0.0065***	0.29	---	0.47	0.27	0.29	*0.085*	2/2	1.46 (1.05, 2.02)	***0.024***
M20	rs3807372	150299990	11245073	C/T	0.14	Negative	*0.057*	0.17	---	0.5	0.14	0.15	0.239	2/2	1.63 (0.93, 2.87)	*0.088*
M21	rs41313101	150300253	11245336	C/T	0.02	---	0.56	0.02	Negative	*0.062*	---	---	---	---	---	---
M22	rs3778873	150300800	11245883	G/C	0.21	---	0.61	0.14	Negative	*0.068*	---	---	---	---	---	---
M23	rs41308993	150300839	11245922	G/C	0.03	---	0.34	0.057	---	0.75	---	---	---	---	---	---
M24	rs3778872	150300909	11245992	G/C	0.21	---	0.17	0.13	Negative	*0.065*	---	---	---	---	---	---
M25	ss74804667	150301321	11246404	C/T	0.01	---	0.26	0.014	---	0.24	---	---	---	---	---	---
M26	ss74804668	150301660	11246743	C/T	0.02	---	0.11	0.057	---	0.5	---	---	---	---	---	---
M27	rs3778871	150301705	11246788	T/G	0.15	---	0.36	0.089	Negative	***0.033***	---	---	---	---	---	---
M28	rs3778870	150301925	11247008	C/T	0.05	---	0.94	---	---	---	---	---	---	---	---	---
M29	rs3778869	150302031	11247114	C/T	0.14	---	0.26	---	---	---	---	---	---	---	---	---
M30	rs3800779	150302147	11247230	G/T	0.35	Positive	***0.0075***	0.33	---	0.93	0.31	0.34	***0.036***	2/2	1.46 (1.10, 1.94)	***0.010***
M31	rs748693	150302370	11247453	A/G	0.35	Positive	***0.019***	0.33	---	0.93	0.33	0.35	0.251	2/2	1.26 (0.96, 1.67)	*0.10*
M32	rs3807370	150304247	11249330	C/T	0.34	---	0.58	0.34	---	0.48	---	---	---	---	---	---
M33	rs1036145	150305363	11250446	G/A	0.35	Positive	***0.0035***	0.32	---	0.87	0.32	0.34	0.162	2/2	1.30 (0.98, 1.74)	*0.069*
M34	rs11771808	150306801	11251884	G/A	0.34	---	0.7	0.36	---	0.59	---	---	---	---	---	---
M35	rs2373885	150309013	11254096	A/G	0.27	---	0.37	0.34	---	0.37	---	---	---	---	---	---
M36	rs4496877	150311439	11256522	G/T	0.34	---	0.49	0.37	---	0.3	---	---	---	---	---	---
M37	rs10277237	150314277	11259360	A/G	0.26	---	0.27	0.25	---	0.3	---	---	---	---	---	---
M38	rs1800783	150320330	11265413	T/A	0.35	---	0.48	0.4	---	0.22	---	---	---	---	---	---
M39	rs1007311	150326941	11272024	A/G	0.48	---	0.36	0.45	---	0.95	---	---	---	---	---	---
M40	rs2566514	150335183	11280266	C/G	0.24	---	0.33	0.28	---	0.65	---	---	---	---	---	---
M41	rs743507	150338421	11283504	A/G	0.26	---	0.96	0.26	---	0.68	---	---	---	---	---	---
M42	rs891512	150339022	11284105	G/A	0.22	---	0.96	0.21	---	0.72	---	---	---	---	---	---
M43	rs1077872	150345679	11290762	C/G	0.34	---	0.68	---	---	---	---	---	---	---	---	---

Huffaker et.al (2009) Nature Medicine

Variant							Genotye			Call Quality				MAF		dbSNP
Chr	Position	REF	ALT	TYPE	Region	GENE	GATK	FREEBAYES	CASAVA	GATK	FREEBAYES	CASAVA	Read Depth	1000G	CG	ID
7	150668182	G	A	SNV	Intronic	KCNH2	Hom	Hom	Hom	1172	907	452	36	19.49%	22.22%	11763131
7	150668346	T	G	SNV	Intronic	KCNH2	Hom	Hom	Hom	1309	886	525	41	23.33%	25%	3807374
7	150668721	G	A	SNV	Intronic	KCNH2	Hom	Hom	Hom	1013	638	406	30	19.47%	21.29%	3807373
7	150671214	C	A	SNV	Intronic	KCNH2	Hom	Hom	Hom	1040	787	418	35	22.16%	21.29%	3800779
7	150671437	A	G	SNV	Intronic	KCNH2	Hom	Hom	Hom	2203	1331	746	70	24.03%	25.92%	748693
7	150674430	C	T	SNV	Intronic	KCNH2	Hom	Hom	Hom	1332	903	511	39	23.19%	26.85%	1036145

O'Rawe (2013) PeerJ

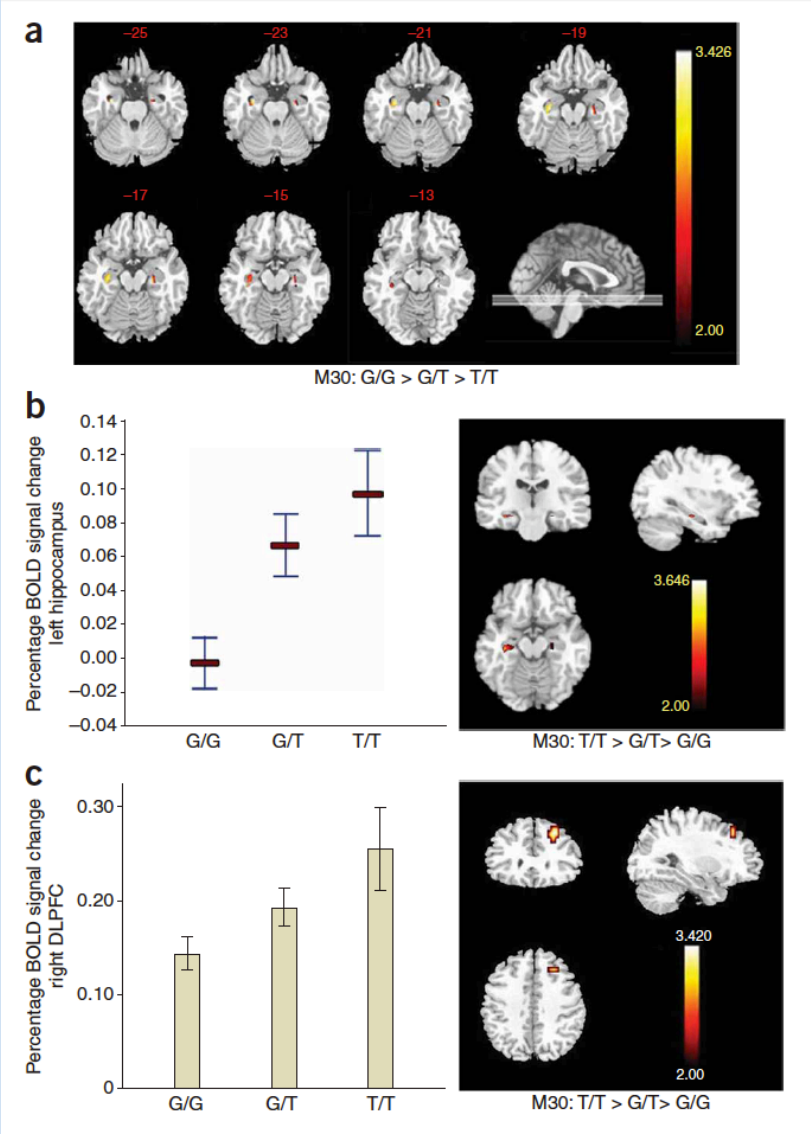


Fig 1. Association of risk SNPs with cognitive measures, brain structure volumes and regional brain activity during memery-based tasks.

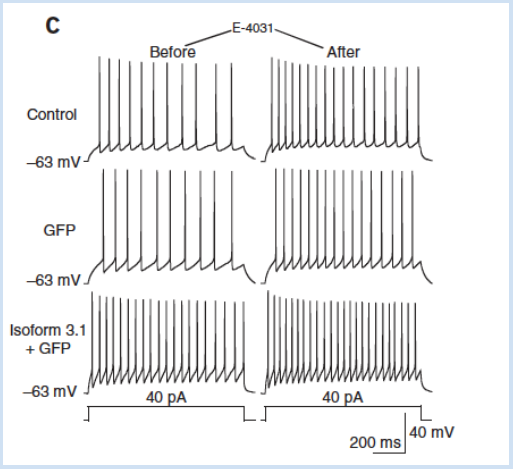


Figure2. Effect of KCNH2-3.1 overexpression in rat cortical neurons on action potential discharge evoked by long depolarizing pulse (40 pA, 1 s) before (left) and after (right) application of E-4031.

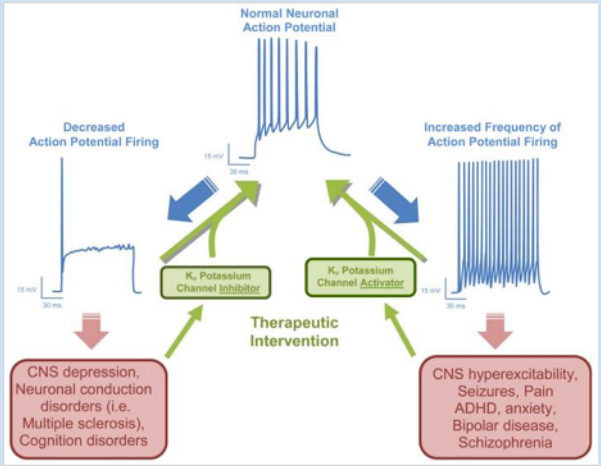
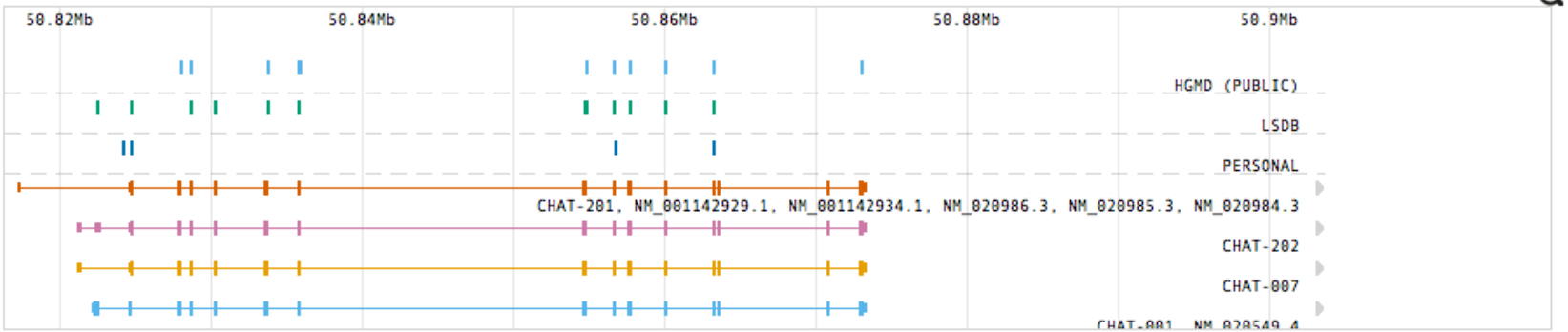


Fig 3. Theoretical effects of KV channel inhibitors and activators on pathologically altered neuronal activity

DBS:A pace-maker in this person's brain?

Huffaker et.al (2009) Nature Medicine
Wulff et.al (2009) Nat. Rev. Drug Discovery

Gene Summary for CHAT



Gene Overview	
Symbol	CHAT
Name	choline O-acetyltransferase
Location	10q11.2
Summary	This gene encodes an enzyme which catalyzes the biosynthesis of the neurotransmitter acetylcholine. This gene product is a characteristic feature of cholinergic neurons, and changes in these neurons may explain some of the symptoms of Alzheimer's disease. Polymorphisms in this gene have been associated with Alzheimer's disease and mild cognitive impairment. Mutations in this gene are associated with congenital myasthenic syndrome associated with episodic apnea. Multiple transcript variants encoding different isoforms have been found for this gene, and some of these variants have been shown to encode more than one isoform. [provided by RefSeq, May 2010]

Relevant Reference Resources	
NCBI Gene	http://www.ncbi.nlm.nih.gov/gene/1103
GeneTests	http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/gene/CHAT
Ensembl	http://www.ensembl.org/human/Gene/Summary?g=ENSG00000070748
UCSC Gene Browser	http://genome.ucsc.edu/cgi-bin/hgTracks?org=human&db=hg19&singleSearch=knownCanonical&position=CHAT
Genetics Home Reference	http://ghr.nlm.nih.gov/gene/CHAT

Associated Disease Categories

Category	Disease	Citation
DRUGS, CLINICAL PHARMACOLOGY AND ENVIRONMENT	Drug toxicity	Roden et al., 2002

Associated Knowledge Sets

Name	Type	Description
ODG - Alzheimers	disease	Omicia Disease Genes (ODG) Top 10 Neurological - Alzheimers
TruSight Exome	disease	Illumina's targeted rare genetic conditions exome test containing 2,761 genes covered in the HGMD database.
MitoGO	myset	
Longo - Phenomizer Fatty Acid Big	myset	A list of genes from phenomizer build from Patient Features HP:0004359. Long List ~3000 genes

Personal Variants in this Gene

Position	Transcript	Transcript HGVS	Protein	Protein HGVS	Zyg	Effect
50824117	NM_001142933.1	c.19G>A	NP_001136405	p.Asp7Asn	het	non-synon
50824619	NM_001142933.1	c.112G>A	NP_001136405	p.Ala38Thr	het	non-synon
50856652	NM_020549	c.1382G>A	NP_065574	p.Val461Met	hom	non-synon
50863147	NM_020549	c.1642T>C	NP_065574	p.His548His	hom	synonymous

Last Resort

Psychosurgery and the Limits of Medicine

Jack D. Pressman

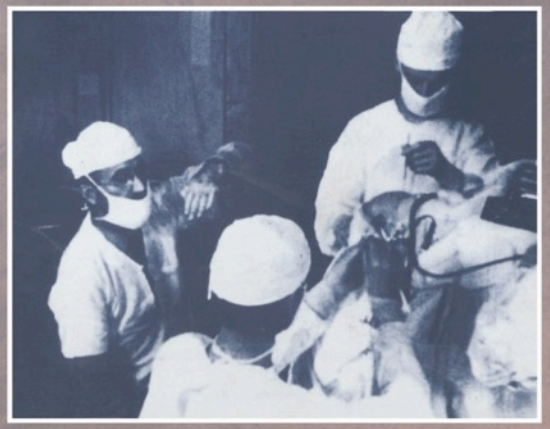


Table 1

Summary of studies of PD DBS, both DBS versus medical management and GPi DBS versus STN DBS

Study	No. patients	Target	F/u	Outcome Positive effects	Outcome Negative effects
Deuschl 2006 (ref. 50)	156	STN	6 mo	Significant PD symptom improvement and decrease of levadopa use	Weight gain and worsening of dyskinesias
Okun 2012 (ref. 165)	168	STN	3 mo	Significant PD symptom improvement and decrease of levadopa use	Dysarthria, depression, fatigue
Schuepbach 2013 (ref. 52)	251	STN	24 mo	Significant PD symptom improvement and decrease of levadopa use	Impulse control worsening, depression, suicide attempt
Okun 2009 (ref. 53)	52	23 GPi, 22 STN	7 mo	Significant PD symptom improvement	Significant decrease in verbal fluency and increase in anger
Williams 2010 (ref. 51)	183	STN or GPi	12 mo	Significant PD symptom improvement	Psychosis, anxiety, suicide
Follett 2010 (ref. 54)	299	152 GPi, 147 STN	24 mo	Significant PD symptom improvement and decrease of levadopa use	Slight decrease in memory function, NS
Odekerken 2012 (ref. 166)	128	65 GPi, 63 STN	12 mo	Significant PD symptom improvement and decrease of levadopa use	Slight increase in dementia score, NS

F/u, follow-up.

Table 2

Summary of studies of TS DBS including CM DBS and GPi DBS

Study	No. patients	Target	F/u	Outcome summary
Porta 2012 (ref. 70)	18	CM	5–6 yr	Tics, OCD, depression, and anxiety significantly decreased
Ackermans 2011 (ref. 72)	6	CM	12 mo	Tics significantly decreased; OCD, depression, and anxiety decreased, but NS
Maciunas 2007 (ref. 71)	5	CM	3 mo	Tics, OCD, depression, and anxiety decreased
Cannon 2012 (ref. 74)	11	GPi	4–30 mo	10 out of 11 had decreased TS symptoms, but one did not tolerate DBS and two had increased anxiety
Fernandez 2011 (ref. 73)	5	GPi	3–24 mo	Tics and OCD decreased

Table 3
Summary of studies of OCD DBS including VC/VS DBS and STN DBS

Study	No. patients	Response rate	F/u	DBS target	Outcome summary
Huff 2010 (ref. 110)	10	8/10 (80%)	12 mo	Unil NAc	YBOCS, HDRS, and GAF significantly improved;
Abelson 2005 (ref. 112)	4	2/4 (50%)	4–23 mo	Bil ant limb IC	HARS improved, but NS YBOCS, HARS, HDRS, and GAF improved; no data about significance
Greenberg 2006 (ref. 113)	8	6/8 (75%)	36 mo	Bil VC/VS	YBOCS, HARS, HDRS, and GAF significantly improved
Goodman 2010 (ref. 167)	6	4/6 (66.67%)	12 mo	Bil VC/VS	YBOCS an HARS significantly improved
Denys 2010 (ref. 168)	16	9/16 (56.25%)	12 mo	Bil NAc	YBOCS, HARS and HDRS significantly improved
Jimenez-Ponce 2009 (ref. 114)	5	5/5 (100%)	12 mo	Bil inf thal	YBOCS, HARS, HDRS, and GAF significantly improved
Greenberg 2010 (ref. 107)	26	19/26 (73.1%)	36 mo	Bil VC/VS	YBOCS and GAF significantly improved
Chabardès 2012 (ref. 108)	4	4/4 (100%)	6 mo	Bil STN	YBOCS improved; no data about significance
Mallet 2008 (ref. 115)	16	14/16 (87.5%)	3 mo	Bil STN	YBOCS and GAF significantly improved; HDRS improved, but NS

Unil, unilateral; Bil, bilateral; ant limb IC, anterior limb of the internal capsule; inf thal, inferior thalamic peduncle; GAF, global assessment of function.

Table 4
Summary of studies of depression DBS including NAc, VC/VS DBS and SCC DBS

Study	F/u	HDRS	MADRS	GAF	Clinical global impression	HAMA
Bewernick 2012 (ref. 102)	24 mo	Improved significantly	Improved significantly	No data	No data	Improved significantly
Malone 2009/2010 (refs. 97 and 98)	12 mo	Improved significantly	Improved significantly	Improved significantly	No data	No data
Holtzheimer 2012 (ref. 88)	24 mo	Improved significantly	No data	Improved significantly	No data	No data
Lozano 2012 (ref. 92)	12 mo	Improved significantly	No data	No data	Improved significantly	No data
Lozano 2008 (ref. 16)	12 mo	Improved significantly	No data	No data	Improved significantly	No data

Molecular Psychiatry (2008), 1–16

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ORIGINAL ARTICLE

Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience

BD Greenberg[1,2,10], LA Gabriels[3,4,10], DA Malone Jr[5], AR Rezai[5], GM Friehs[1,2], MS Okun[6,7,8], NA Shapira[6,7,8], KD Foote[6,7,8], PR Cosyns[3,4], CS Kubu[5], PF Malloy[1,2], SP Salloway[1,2], JE Giftakis[9], MT Rise[9], AG Machado[5], KB Baker[5], PH Stypulkowski[9], WK Goodman[6,7,8], SA Rasmussen[1,2] and BJ Nuttin[3,4]

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Table 5

Positive/negative neuropsychiatric effects from motoric/limbic DBS

Study	Symptom	Effect	Comments
Kosel et al. 2007[A] (ref. 127)	Depression	Improvement	Case report with 1 patient
Damier et al. 2007[A] (ref. 128)	Depression	Improvement in 1 of 10	
Fontaine et al. 2004 (ref. 125)	OCD	improvement	Case report with 1 patient
Okun 2009 (ref. 53)	Happy mood	Increase	NS
	Sad mood	Decrease	NS
	Tense mood	Increase	NS
Graff-Radford 2010 (ref. 169)	Tense mood	Decrease	Significant
Moum 2012 (ref. 134)	ICD	Resolved in 2 and appeared de novo in 2	2 out of 6 patients for both
	DDS	no change	
	Both	no change	
Chopra 2012 (ref. 135)	Mania	Resolved	12 out of 14 patients
Kluger 2012 (ref. 138)	Fatigue	58% of patients	
Voon 2008 (ref. 140)	Suicidal ideation	0.45% (24/5311) after DBS	
	Suicide attempt	0.90% (48/5311) after DBS	
Zahodne 2011 (ref. 139)	Binge eating	Increased	
	Subthreshold BED	increased	
Burdick 2011 (ref. 136)	Anger	Increased after STN, GPi; decreased after VIM	
	Confusion	Increased after GPi, decreased after VIM	
Kirsch-Darrow 2011 (ref. 137)	Apathy	Increased in middle aged, not in older patients	
Kuhn 2007 (ref. 148)	Alcohol abuse	Cessation	Case report with 1 patient
Kuhn 2009 (ref. 170)	Smoking	Cessation	3 out of 10
Mantione 2010 (ref. 146)	Smoking, overeating	Cessation	Case report with 1 patient
Zhou 2011 (ref. 171)	Heroin abuse	Cessation	Case report with 1 patient
	Smoking	Decrease	
Valencia-Alfonso 2012 (ref. 172)	Heroin abuse	Cessation	Case report with 1 patient
Shapira 2006 (ref. 151)	panic	Reproducible with stimulation of ventral-most contacts	Case report with 1 patient
Haq 2010 (ref. 89)	OCD, mania	Present with specific DBS settings	Case report with 1 patient
Flaherty 2004 (ref. 173)	Mania	High voltage in dorsal-most contacts	Case report with 1 patient
	Depression, apathy	High voltage in ventral-most contacts	
Nuttlin 2002 (ref. 174)	Memory function	Decrease	1 out of 4
	Hypomania	Present with specific DBS settings	2 out of 4
	Fear	Present with specific DBS settings	

ICD, impulse control disorder; DDS, dopamine dysregulation syndrome; BED, binge eating disorder; VIM, ventral intermediate nucleus of the thalamus.

Table 2 Published reports on deep brain stimulation for obsessive-compulsive disorder (OCD) and treatment-resistant depression (TRD) showing anatomic target[a] and number[b] of cases treated

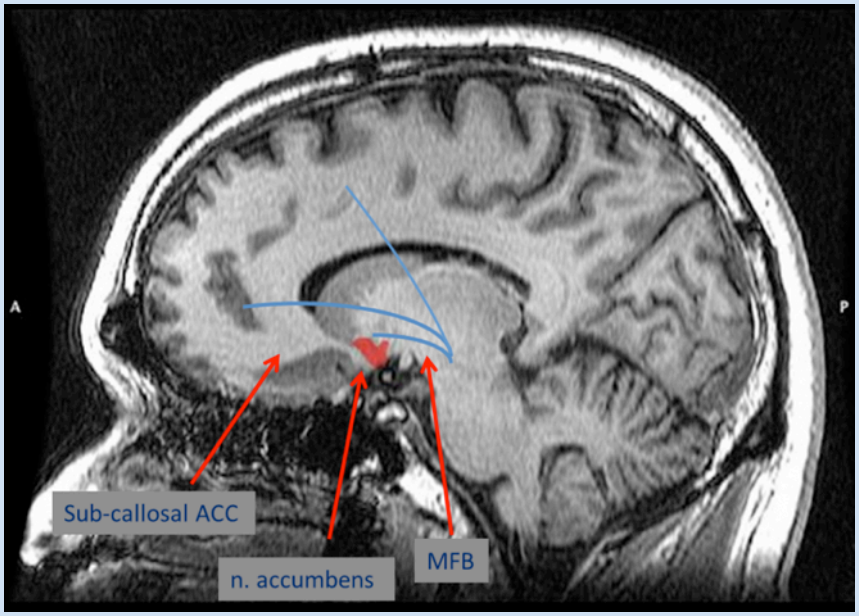
	ALIC	NAc	VC/VS	SCG	ITP	STN	HAB
OCD	N = 4 (1); N = 4 (27); N = 1 (49); N = 1 (73); N = 1 (15); N = 1 (51)	N = 2 (74); N = 2 (75); N = 5 (76); N = 16 (28); N = 1 (49); N = 10 (30)	N = 6 (29); N = 21 (32); N = 1 (77)	–	N = 5 (78)	N = 16 (31)	–
Totals	*N = 12*	*N = 36*	*N = 28*	–	*N = 5*	*N = 16*	–
TRD	–	N = 3 (79); N = 10 (80)	N = 15 (45)	N = 20 (46); N = 1 (81)	N = 1 (47)	–	N = 1 (48)
Totals	–	*N = 13*	*N = 15*	*N = 21*	*N = 1*	–	*N = 1*

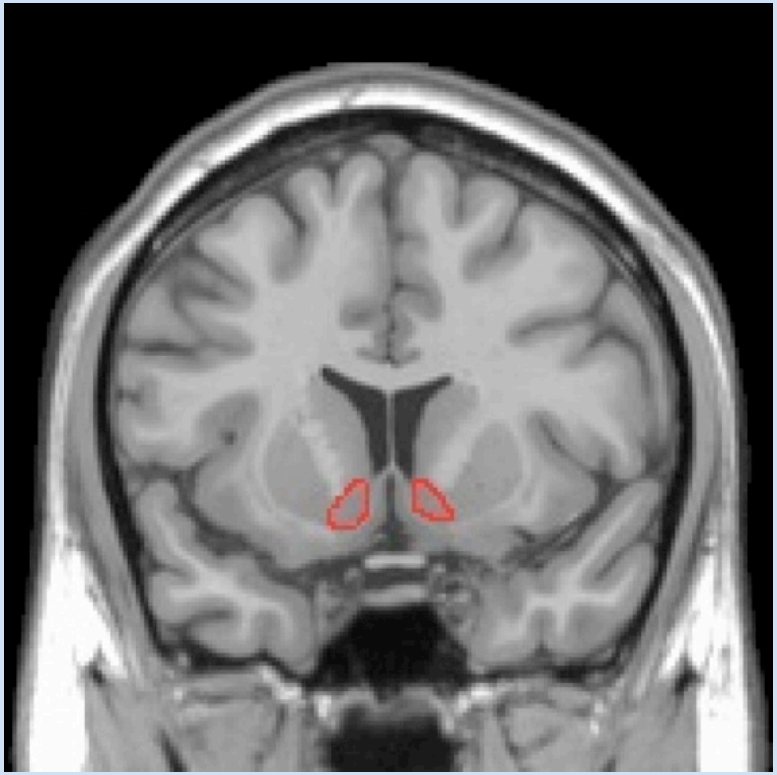
Abbreviations: ALIC, anterior limb of the internal capsule; OCD, obsessive-compulsive disorder; TRD, treatment-resistant depression; SCG, subcallosal cingulate gyrus (Brodmann's area 25); VC/VS, ventral capsule/ventral striatum; ITP, inferior thalamic peduncle; STN, subthalamic nucleus; NAc, nucleus accumbens; HAB, lateral habenula.

[a]Although the ALIC, VC/VS, and NAc are labeled as different targets, there is considerable overlap in these areas. Moreover, the actual position of the active electrode contact (or contacts), the specific stimulating lead used (which can differ in contact spacing), and the characteristics of the stimulation field account for considerable variance within a given intended target. For the purpose of this review, the name of the target used in each publication is retained, but it should be understood these targets might not be as distinct as the different names imply.

[b]Because counting the number of unique cases in the literature is challenging, these figures should be considered approximate. For example, some articles on long-term follow-up may not be clear as to how many cases are included from previous reports on acute response.

Nucleus accumbens





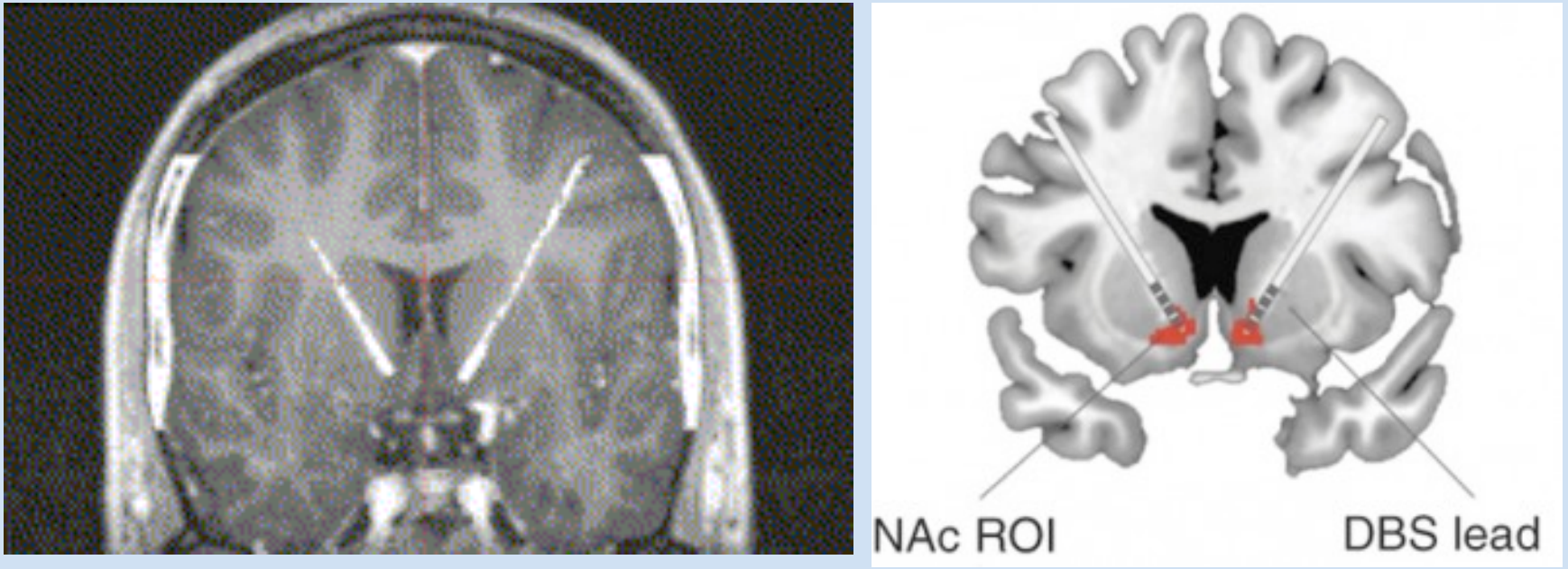


Fig. 1. Coronal section of the brain near the ALIC and nucleus accumbens with the track of the electrodes on the left and right side.

Neuropsychopharmacology (2006) 31, 2384–2393

www.neuropsychopharmacology.org

Three-Year Outcomes in Deep Brain Stimulation for Highly Resistant Obsessive–Compulsive Disorder

Benjamin D Greenberg*[,1,2], Donald A Malone[3,4], Gerhard M Friehs[1,2], Ali R Rezai[3,4], Cynthia S Kubu[3,4], Paul F Malloy[1,2], Stephen P Salloway[1,2], Michael S Okun[5,6], Wayne K Goodman[5,6] and Steven A Rasmussen[1,2]

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Deep brain stimulation (DBS) of the anterior limb of the internal capsule has been shown to be beneficial in the short term for obsessive–compulsive disorder (OCD) patients who exhaust conventional therapies. Nuttin *et al*, who published the first DBS for OCD series, found promising results using a capsule target immediately rostral to the anterior commissure extending into adjacent ventral capsule/ventral striatum (VC/VS). Published long-term outcome data are limited to four patients. In this collaborative study, 10 adult OCD patients meeting stringent criteria for severity and treatment resistance had quadripolar stimulating leads implanted bilaterally in the VC/VS. DBS was activated openly 3 weeks later. Eight patients have been followed for at least 36 months. Group Yale-Brown Obsessive Compulsive Scale (YBOCS) scores decreased from 34.6 ± 0.6 (mean $\pm$ SEM) at baseline (severe) to 22.3 ± 2.1 (moderate) at 36 months ($p < 0.001$). Four of eight patients had a $\geqslant 35\%$ decrease in YBOCS severity at 36 months; in two patients, scores declined between 25 and 35%. Global Assessment of Functioning scores improved from 36.6 ± 1.5 at baseline to 53.8 ± 2.5 at 36 months ($p < 0.001$). Depression and anxiety also improved, as did self-care, independent living, and work, school, and social functioning. Surgical adverse effects included an asymptomatic hemorrhage, a single seizure, and a superficial infection. Psychiatric adverse effects included transient hypomanic symptoms, and worsened depression and OCD when DBS was interrupted by stimulator battery depletion. This open study found promising long-term effects of DBS in highly treatment-resistant OCD.
Neuropsychopharmacology (2006) **31,** 2384–2393. doi:10.1038/sj.npp.1301165; published online 19 July 2006

Keywords: deep brain stimulation; obsessive–compulsive disorder; internal capsule; long-term treatment; neurosurgery

Table 1 Patient Characteristics

Patient	Age at surgery, gender	OCD onset	OCD duration	Baseline YBOCS	Primary symptoms	MDD?
BH1	32, M	10	22	32	CK, AR, CTM, PF	Y
BH2	40, F	16	24	34	WSH, INC, HRD	Y
BH3	39, M	12	27	35	CK, AR, GR, INC	Y
BH4	26, F	15	11	34	INC, PF	Y
BH5	32, M	10	22	33	CTM, DT, RE	Y
CC1[a]	59, F	19	40	38	CK, FH, CTM	N
CC2	35, F	12	23	36	INC, RP	Y
CC3	22, M	8	14	35	SYM, INC, OFF, WSH	Y
CC4	23, M	7	16	33	CK, SYM	Y
CC5	45, M	19	26	36	INC, CTM	N
Mean	35.3 years	12.8 years	22.5 years	34.6		
Min	22	7	11	32		
Max	59	19	40	38		

BH = Butler Hospital; CC = Cleveland Clinic.
OCD symptom abbreviations: CK = checking; AR = arranging/ordering; CTM = contamination fears; PF = perfectionism; WSH = washing; MDD = comorbid DSM-IV depression; INC = 'incompleteness' (Rasmussen and Eisen, 1992); HRD = hoarding; GR = grooming rituals; DT = doubt; RE = reassurance seeking; FH = fear of harming others; RP = repeating; SYM = symmetry obsessions/compulsions; OFF = fear of offending others.
[a]Patient CC1 died of recurrent breast cancer at 9 months. Her data were not carried forward in the analysis.

Table 2 Categorical Responses during Long-Term DBS for OCD

DBS duration	<25% YBOCS ↓ (no. of pts, %)	⩾25 <35% YBOCS ↓ (no. of pts, %)	⩾35% YBOCS ↓ (no. of pts, %)	Total *N*
1 month	7 (70)	2 (20)	1 (10)	10
3 months	5 (50)	2 (20)	3 (30)	10
6 months	4 (40)	4 (40)	2 (20)	10
12 months	4 (44)	2 (22)	3 (33)	9
18 months	3 (33)	3 (33)	3 (33)	9
24 months	2 (22)	3 (33)	4 (44)	9
30 months	3 (38)	1 (12)	4 (50)	8
36 months	2 (25)	2 (25)	4 (50)	8

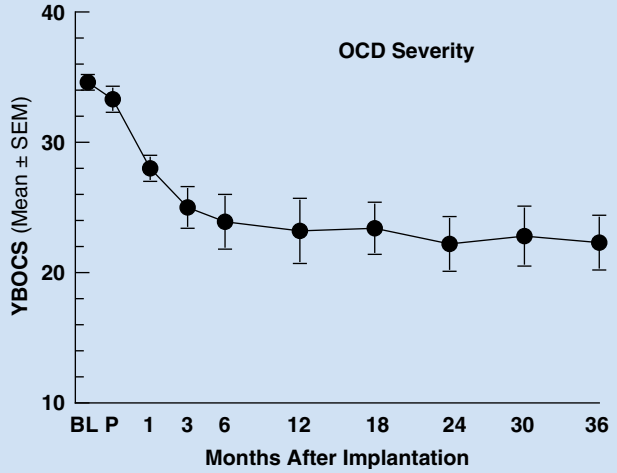


Figure 2 OCD severity (YBOCS) during long-term DBS.

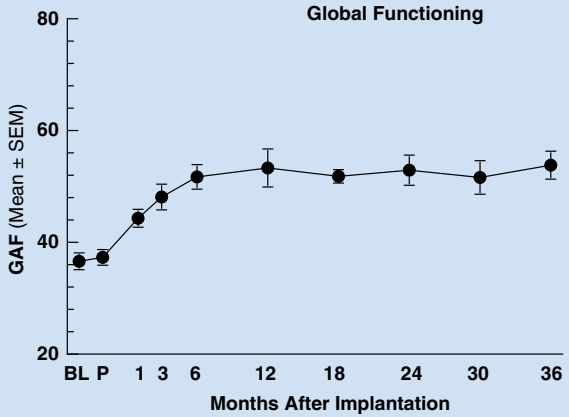


Figure 4 Global functioning during long-term DBS.

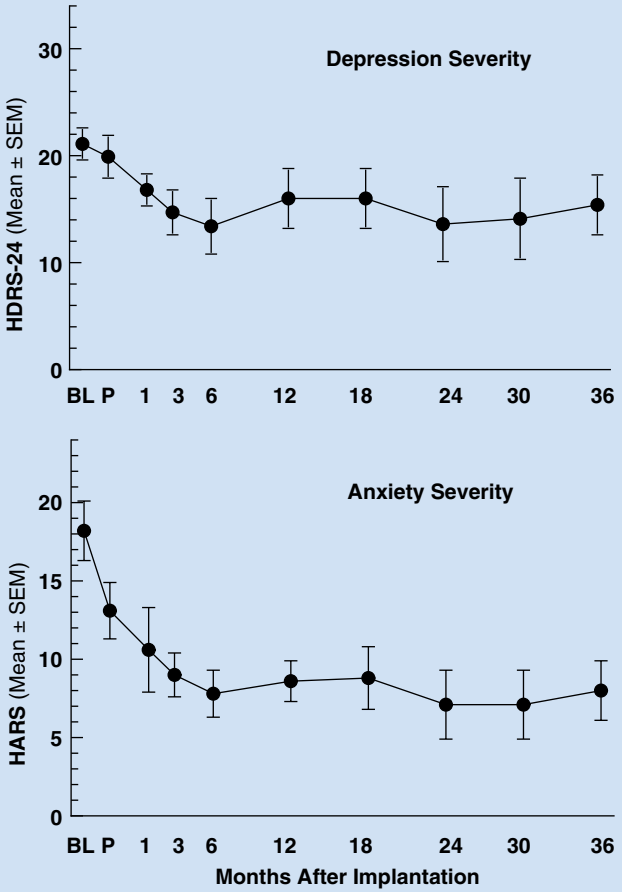


Figure 3 Depression (top) and anxiety (bottom) severity ratings during long-term DBS for OCD.

Table 3 Clinical Assessment of Functioning before and during Chronic DBS

	Baseline				During chronic DBS				
Pt.	**Working or in school?**	**Independent ADLs?**	**Able to live independently?**	**Social engagement**	**Working or in school?**	**Independent ADLs?**	**Able to live independently?**	**Social engagement**	**YBOCS ↓ (%)**
BH1	No	Extreme slowness	No	Limited	Finished degree program	Yes	Yes	Good	38
BH2	No	No	No	Minimal	Entered job training	Mainly	Yes	Limited	12[a]
BH3	No	No	No	Minimal	No	Mainly	Yes	Limited	31
BH4	No	No	No	Limited	No	No	No	Limited	12[a]
BH5	No	No	No	Minimal	Entered technical training	Mainly	No	Limited	33
CC1	No	Total care	No	Minimal			Deceased (at month 7)		
CC2	No	No	No	Limited	No	Mainly	Limited VN services	Dating, brief engagement	39
CC3	No	Yes	No	Limited	Works FT	Yes	Yes	Dating	49
CC4	No	Yes	No	Limited	Works FT	Yes	Yes	Engaged to marry	64
CC5	No	No; unable to leave room	No; assisted living	Minimal	Travels alone to day program	Improved	No	Limited	35

[a]The two patients who discontinued stimulation before the 36-month end point.

Table 1 Patient characteristics: demographic and clinical features of subjects

Patient (center)	*Age*	*M/F*	*OCD onset*	*OCD duration*	*Axis I comorbid*	*Axis II*	*Follow-up duration*
			(years)	(years)			(months)
Butler (BH)							
BH1	32	M	10	22	MDD	OCPD	36
BH2	40	F	16	24	BPII		36
BH3	39	M	12	27	Dysthymia		36
BH4	26	F	15	11	MDD		36
BH5	32	M	10	22	MDD		24
Cleveland Clinic (CC)							
CC1	59	F	19	40	None		6*
CC2	35	F	12	23	MDD		36
CC3	22	M	8	14	MDD	STYP(tr)	36
CC4	23	M	7	16	MDD		36
CC5	45	M	19	26	None		24
U of Florida (UF)							
UF1	32	F	24	8	MDD		24
UF2	50	M	34	16	MDD		12
UF3	38	M	22	16	MDD		12
UF4	32	M	10	22	MDD		6
UF5	32	F	15	17	MDD		3
Leuven (LV)							
LV1	35	M	12	23	MDD	HST(tr); NAR(tr)	12*
LV2	52	F	24	28	MDD; GAD		36
LV3	39	F	16	23	MDD; PD	DEP PD	36
LV4	35	M	12	23	MDD		36
LV5	40	F	14	26	MDD		36
LV6	37	M	16	21	MDD		36
LV7	39	F	15	24	MDD		24
LV8	40	M	14	26	MDD; PD		24
LV9	23	M	12	11	MDD		12
LV10	30	F	9	21	None		6
LV11	57	F	16	41	MDD		3
Mean	37.1		15.1	22.0			31.4
s.e.m.	1.9		1.6	1.5			4.1

Abbreviations: BPII, bipolar II mood disorder; DEP PD, dependent personality disorder; F, female; GAD, generalized anxiety disorder; HST(tr), histrionic traits; M, male; MDD, major depressive disorder; NAR(tr), narcissistic traits; OCD, obsessive-compulsive disorder; OCPD, obsessive-compulsive personality disorder; PD, panic disorder; STYP(tr), schizotypal traits.
*Details in text.

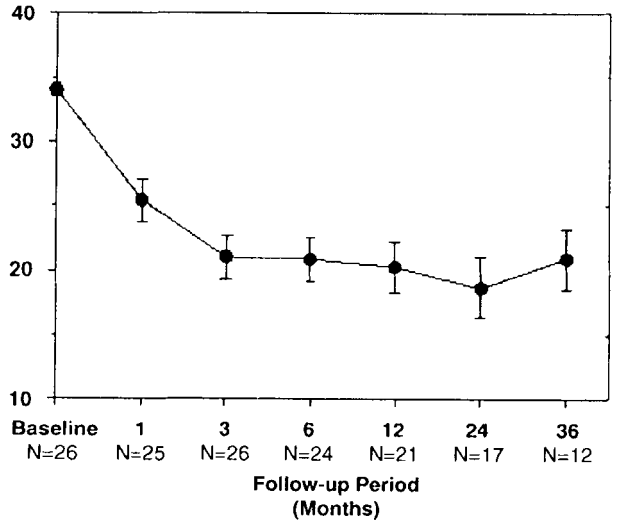


Figure 4 Mean (±s.e.m.) Yale–Brown Obsessive Compulsive Scale (YBOCS) severity scores pretreatment and at each deep brain stimulation (DBS) treatment rating point.

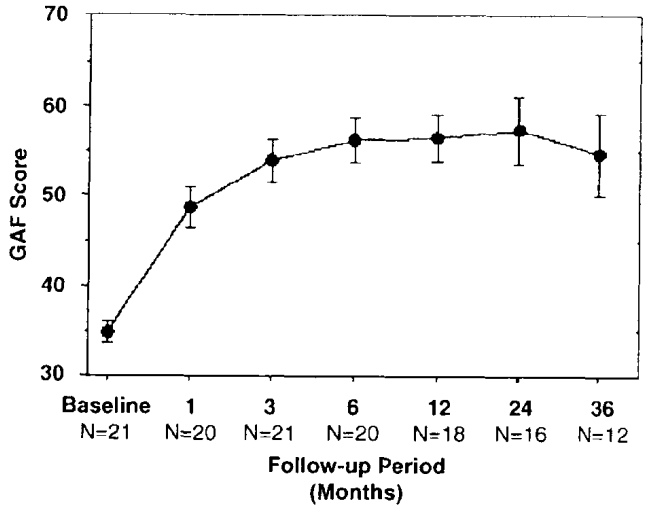
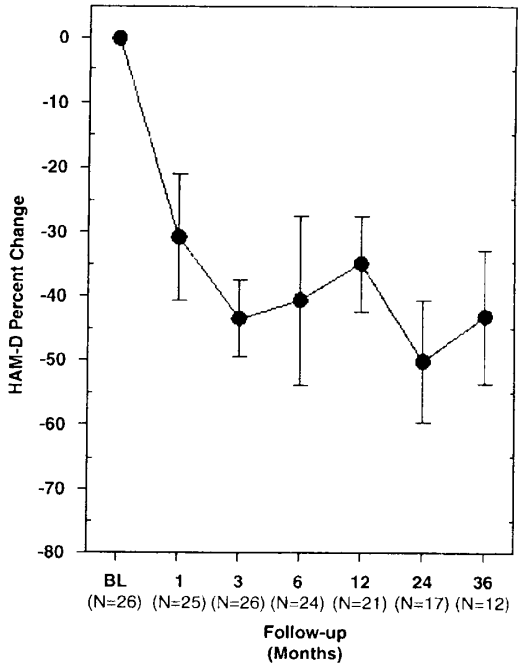


Figure 6 Average (±s.e.m.) Global Assessment of Functioning (GAF) scores over time.



Deep Brain Stimulation for Intractable Obsessive Compulsive Disorder: Pilot Study Using a Blinded, Staggered-Onset Design

Wayne K. Goodman, Kelly D. Foote, Benjamin D. Greenberg, Nikki Ricciuti, Russell Bauer, Herbert Ward, Nathan A. Shapira, Sam S. Wu, Candy L. Hill, Stephen A. Rasmussen, and Michael S. Okun

Background: Prior promising results have been reported with deep brain stimulation (DBS) of the anterior limb of the internal capsule in cases with severe obsessive compulsive disorder (OCD) who had exhausted conventional therapies.

Methods: In this pilot study, six adult patients (2 male; 4 female) meeting stringent criteria for severe (minimum Yale-Brown Obsessive Compulsive Scale [Y-BOCS] of 28) and treatment-refractory OCD had DBS electrode arrays placed bilaterally in an area spanning the ventral anterior limb of the internal capsule and adjacent ventral striatum referred to as the ventral capsule/ventral striatum. Using a randomized, staggered-onset design, patients were stimulated at either 30 or 60 days following surgery under blinded conditions.

Results: After 12 months of stimulation, four (66.7%) of six patients met a stringent criterion as "responders" ($\geq$35% improvement in the Y-BOCS and end point Y-BOCS severity $\leq$16). Patients did not improve during sham stimulation. Depressive symptoms improved significantly in the group as a whole; global functioning improved in the four responders. Adverse events associated with chronic DBS were generally mild and modifiable with setting changes. Stimulation interruption led to rapid but reversible induction of depressive symptoms in two cases.

Conclusions: This pilot study suggests that DBS of the ventral capsule/ventral striatum region is a promising therapy of last resort for carefully selected cases of severe and intractable OCD. Future research should attend to subject selection, lead location, DBS programming, and mechanisms underpinning therapeutic benefits.

BIOL PSYCHIATRY 2010;67:535–542

Table 1. DBS Programming and Lead Locations at 12 Months of Chronic Stimulation

Patient	DBS Setting	Lateral	AP	Axial
1[a]	Rt 1-C+, 5 V, 210 μs, 135 Hz	10.4	16.2	1.7
	Lt 0-C+, 4 V, 210 μs, 135 Hz	6.3	13.7	−3.8
2	Rt 2-C+, 3.5 V, 210 μs, 135 Hz	10.5	17.3	8.4
	Lt 2-C+, 3.5 V, 210 μs, 135 Hz	12.8	18.1	9.4
3[a]	Rt 0-1-C+, 8.5 V, 150 μs, 130 Hz	4.8 (0 contact)	18.0	−3.8
	Lt 0-1-C+, 7.5 V, 150 μs, 130 Hz	10.4 (0 contact)	18.8	−3.8
4	Rt 1-C+, 6.5 V, 180 μv, 135 Hz	8.9	12.4	−2.6
	Lt 1-C+, 6.5 V, 180 μv, 135 Hz	13.4	16.0	−2.3
5[a]	Rt 0-1-C+, 2.5 V, 210 μv, 135 Hz	9.2 (0 contact)	12.2	−1.7
	Lt 1-C+, 2.5 V, 210 μv, 135 Hz	12.2 (1 contact)	14.8	4.8
6[a]	Rt 1-O+, 3.5 V, 90 μs, 135 Hz	9.4	15.9	1.5
	Lt 1-O+, 3.3 V, 90 μs, 135 Hz	11.2	15.2	.9

Table shows patients 1 through 6 with chronic DBS settings at the active contact at 12 months of DBS. The DBS settings show right side, left side, volts, pulse width, and rate. The lateral, anteroposterior, and axial coordinates of the center of the active contact relative to the mid-commissural point are provided.

AP, anteroposterior; DBS, deep brain stimulation; Hz, rate; Lt, left side; μ, pulse width; Rt, right side; V, volts; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a]Patients who had a clinical response based on Y-BOCS criteria.

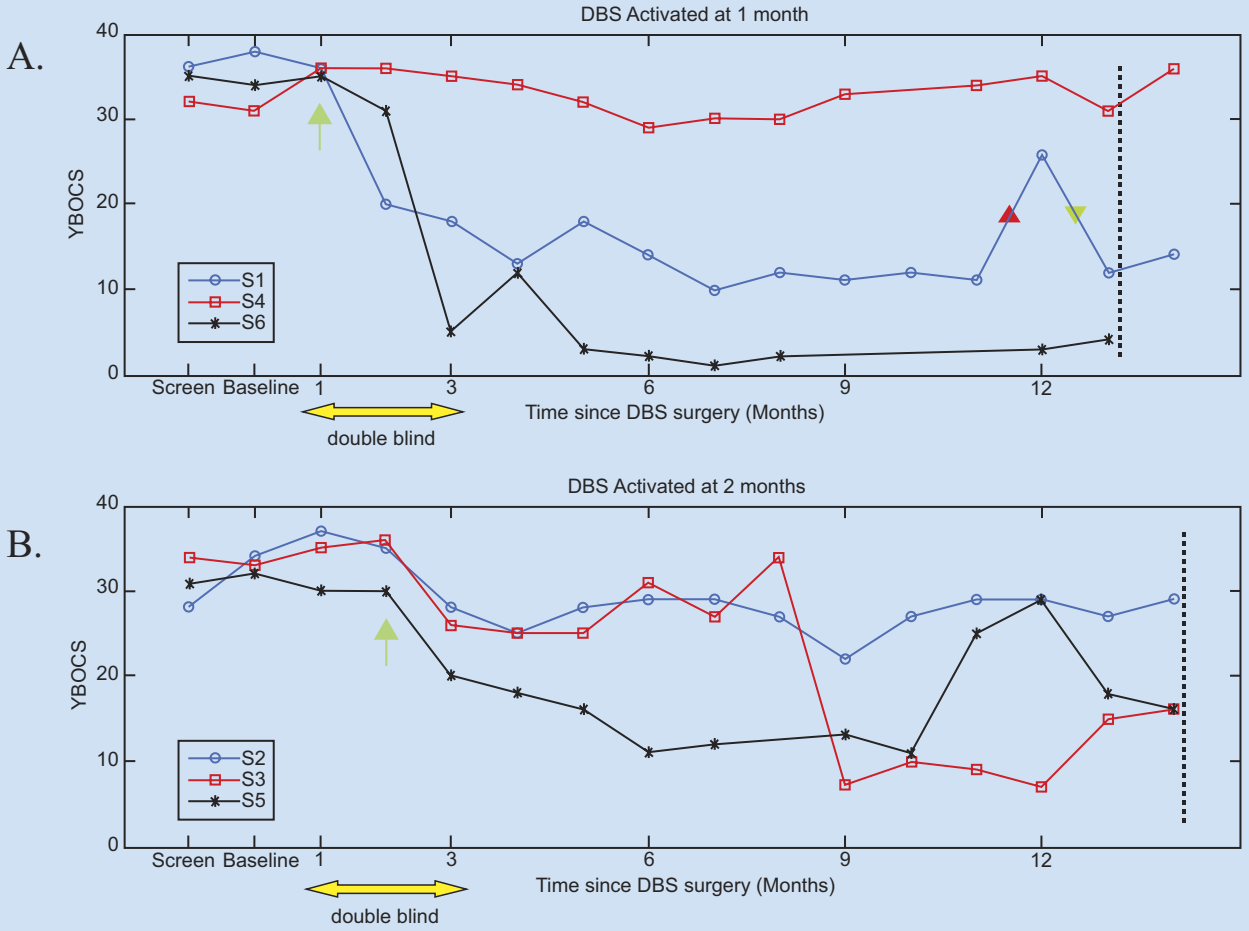


Figure 1. Patients and raters were blind to treatment condition (sham vs. active) for the 90-day period starting with the first postoperative visit as noted by the yellow double arrow. **(A)** Three patients (S1, S4, and S6) randomized to active DBS at 1 month postimplantation (denoted by green arrow); **(B)** three patients (S2, S3, and S5) randomized to active at month 2 (denoted by green arrow). In **(A)** patients received 12 months of active DBS at 13 months postimplantation (marked by dotted vertical line), whereas in **(B)** patients received 12 months of active DBS at 14 months postimplantation (marked by dotted vertical line). Unbeknownst to subject 1 or the research treatment team, this individual's right-sided battery was depleted between 11 and 12 months (red triangle) following surgery. This event was closely followed by an exacerbation in OCD symptoms that normalized shortly after device replacement (green triangle). Subject 3 did not show a response until after major changes in DBS settings at week 8 status post surgery (see text for details). The reasons for the temporary worsening of subject 5 between months 10 and 12 postimplantation are unclear. Possibilities include impact of significant life events or setting changes at month 10 that improved mood but lowered threshold for panic attacks. These settings were further modified at month 12. DBS, deep brain stimulation; OCD, obsessive compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 2. Analyses of Changes in Primary and Secondary Rating Scales During 12 Months of DBS Activation for All Participants ($n = 6$)

Variable	Num *df*	Den *df*	*F* Value	Pr > *F*
Y-BOCS[a]	12	55	2.02	.0392[a]
POMS Total	9	32	2	.0723
POMS T	7	20	1.23	.3347
POMS-D	7	20	1.75	.1550
POMS-A	7	20	1.49	.2256
POMS-V[a]	7	20	4.21	.0053[a]
POMS-F[a]	7	20	3.08	.0228[a]
POMS-C	7	20	1.15	.3743
HAM-D17[a]	12	50	2.22	.0249[a]
SF-36 PF	9	22	1.52	.2025
SF-36 RP	9	22	.94	.5143
SF-36 BP	9	21	2.27	.0587
SF-36 GH	9	22	.98	.4861
SF-36 V[a]	9	22	3.5	.0079[a]
SF-36 SF	9	22	1.77	.1326
SF-36 RE	9	22	1.63	.1680
SF-36 MH	9	22	1.39	.2536
SF-36 Total	9	22	.82	.6038

DBS, deep brain stimulation; HAM-D17, Hamilton Depression 17-Item Rating Scale; POMS-A, Profile of Mood States anger-hostility subscore; POMS-C, Profile of Mood States confusion-bewilderment subscore; POMS-D, Profile of Mood States depression-dejection subscore; POMS-F, Profile of Mood States fatigue-inertia subscore; POMS T, Profile of Mood States tension subscale; POMS Total, Profile of Mood States total score; POMS-V, Profile of Mood States vigor-activity subscore; SF-36 BP, Medical Outcomes Study Short Form Health Survey bodily pain subscale; SF-36 GH, Medical Outcomes Study Short Form Health Survey general health subscale; SF-36 MH, Medical Outcomes Study Short Form Health Survey mental health subscale; SF-36 PF, Medical Outcomes Study Short Form Health Survey physical functioning subscale; SF-36 RE, Medical Outcomes Study Short Form Health Survey role limitations due to emotional problems subscale; SF-36 RP, Medical Outcomes Study Short Form Health Survey role limitations due to personal health problems subscale; SF-36 SF, Medical Outcomes Study Short Form Health Survey social functioning subscale; SF-36 Total, Medical Outcomes Study Short Form Health Survey total score; SF-36 V, Medical Outcomes Study Short Form Health Survey vitality subscale; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a]Significant difference on analysis of variance for repeated measures obtained during the first 12 months of DBS activation.

Table 3. Categorical Responses and End Point Severity During DBS for OCD ($n = 6$)

Duration of DBS Activation (months)	Total *n*	<25% Y-BOCS ↓ (*n*, %)	25%–35% Y-BOCS ↓ (*n*, %)	≥35% Y-BOCS ↓ (*n*, %)	Severity Y-BOCS ≤ 16 (*n*, %)
1	6	4 (67)	0 (0)	2 (33)	0 (0)
2	6	2 (33)	1 (17)	3 (50)	1 (17)
3	6	3 (50)	0 (0)	3 (50)	3 (50)
4	6	3 (50)	0 (0)	3 (50)	2 (33)
5	6	3 (50)	0 (0)	3 (50)	3 (50)
6	5	3 (60)	0 (0)	2 (40)	2 (40)
7	6	1 (17)	0 (0)	5 (83)	4 (67)
8	5	2 (40)	0 (0)	3 (60)	3 (60)
9	4	2 (50)	0 (0)	2 (50)	2 (50)
10	5	3 (60)	0 (0)	2 (40)	2 (40)
11	6	2 (33)	0 (0)	4 (67)	3 (50)
12	6	2 (33)	0 (0)	4 (67)	4 (67)

Categorical response is shown against duration of DBS activation, which is not the same as time since implantation. Number of nonresponse is indicated in the column labeled <25% reduction on the Y-BOCS. Number of responders is shown using two different criteria: 25%–35% reduction on the Y-BOCS and the more stringent definition of ≥35% reduction on the Y-BOCS. The last column shows the number of individuals who had a Y-BOCS score ≤16 at that time point.

DBS, deep brain stimulation; OCD, obsessive compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 4. Reliable Changes in Neuropsychological Performance from Baseline Among Responders and Nonresponders

		6 Month						1 Year					
		Responders (3)			Nonresponders (3)			Responders (4)			Nonresponders (2)		
	Baseline Mean (SD)	+	nc	—	+	nc	—	+	nc	—	+	nc	—
WAIS 3 DS													
Forward	7.00 (1.9)	0	3	0	0	3	0	0	4	0	0	2	0
Backward	5.33 (1.6)	0	3	0	0	3	0	0	4	0	0	2	0
WAIS raw	19.33 (6.0)	0	3	0	0	2	1	0	4	0	0	1	1
Verbal Fluency CFL	44.50 (15.64)	0	3	0	1	2	0	0	3	1	1	1	0
Wisconsin Card Sort													
Categories	5.67 (.82)	0	3	0	0	3	0	0	4	0	0	2	0
Persev errors	6.33 (2.58)	0	3	0	0	3	0	0	4	0	0	2	0
Persev responses	6.33 (2.58)	0	3	0	0	3	0	0	4	0	0	2	0
Tower of London													
Movement count	44.50 (19.77)	0	3	0	1	2	0	0	4	0	1	1	0
Total time	415.17 (199.36)	2	1	0	2	1	0	2	1	1	1	1	0
Grooved Pegboard													
Dominant	101.83 (28.62)	2	1	0	1	2	0	3	1	0	0	2	0
Nondominant	124.17 (41.90)	2	1	0	1	1	1	3	1	0	0	1	1
Hopkins VLT													
Total	26.33 (3.33)	0	3	0	2	1	0	1	3	0	0	2	0
Delayed recall	8.67 (2.80)	0	3	0	1	2	0	1	3	0	0	2	0
Recog discrimination	11.17 (1.17)	0	2	1	0	2	1	0	3	1	0	1	1

+, improvement beyond the 90% confidence interval for reliable change; —, decline in performance beyond the 90% confidence interval for reliable change; nc, no change from baseline; Persev, perseveration errors; Recog, recognition; VLT, verbal learning task; WAIS, Wechsler Adult Intelligence Scale; WAIS 3 DS, Wechsler Adult Intelligence Scale version 3 Digit Span.

REVIEW ARTICLE

Deep Brain Stimulation for the Treatment of Severe, Medically Refractory Obsessive-Compulsive Disorder

Mark Sedrak, MD; William Wong, MD; Paul Wilson, MD; Diana Bruce, PA-C, MSHS; Ivan Bernstein, PA-C, MSPAS, MPH; Suketu Khandhar, MD; Conrad Pappas, MD, PhD; Gary Heit, MD, PhD; Eric Sabelman, PhD

Perm J 2013 Fall;17(4):47-51

http://dx.doi.org/10.7812/TPP/13-005

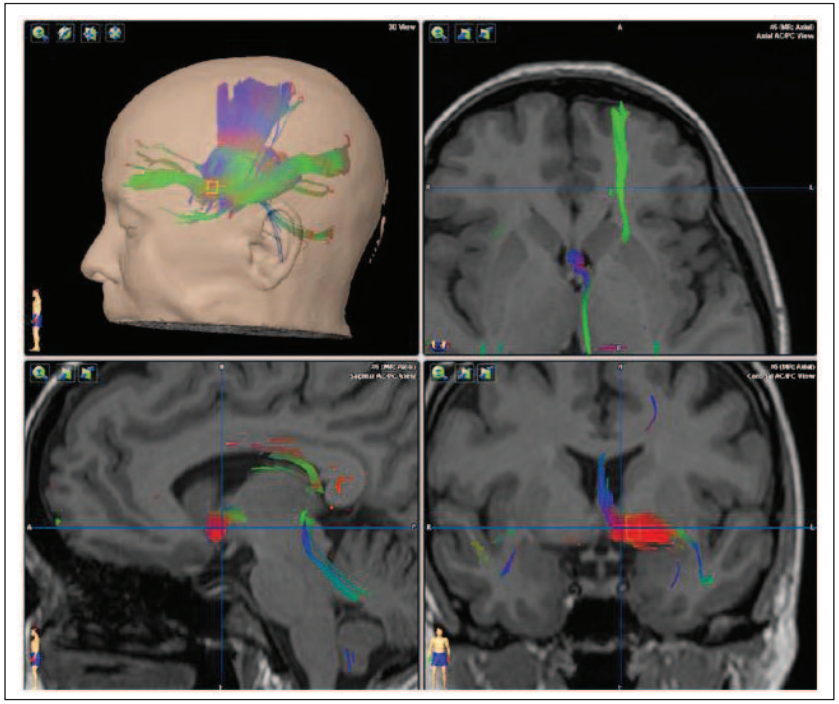


Figure 1. Diffusion tensor image demonstrating connections between prefrontal cortex regions and the ventral portion of the anterior limb of the internal capsule (ALIC) and the adjacent ventral capsule ventral striatum (VC/VS). Yellow box in upper left corner is a 3x3mm voxel seed point. Tractography was set at threshold of 0.15 and minimal fiber length of 15mm. Intense orbitofrontal connections are seen. Other fiber pathways include dorsolateral prefrontal cortex, supplementary motor, sensorimotor, uncinate fasciculus, inferior occipitofrontal fasciculus, thalamus, and various dorsal mesencephalic pathways.

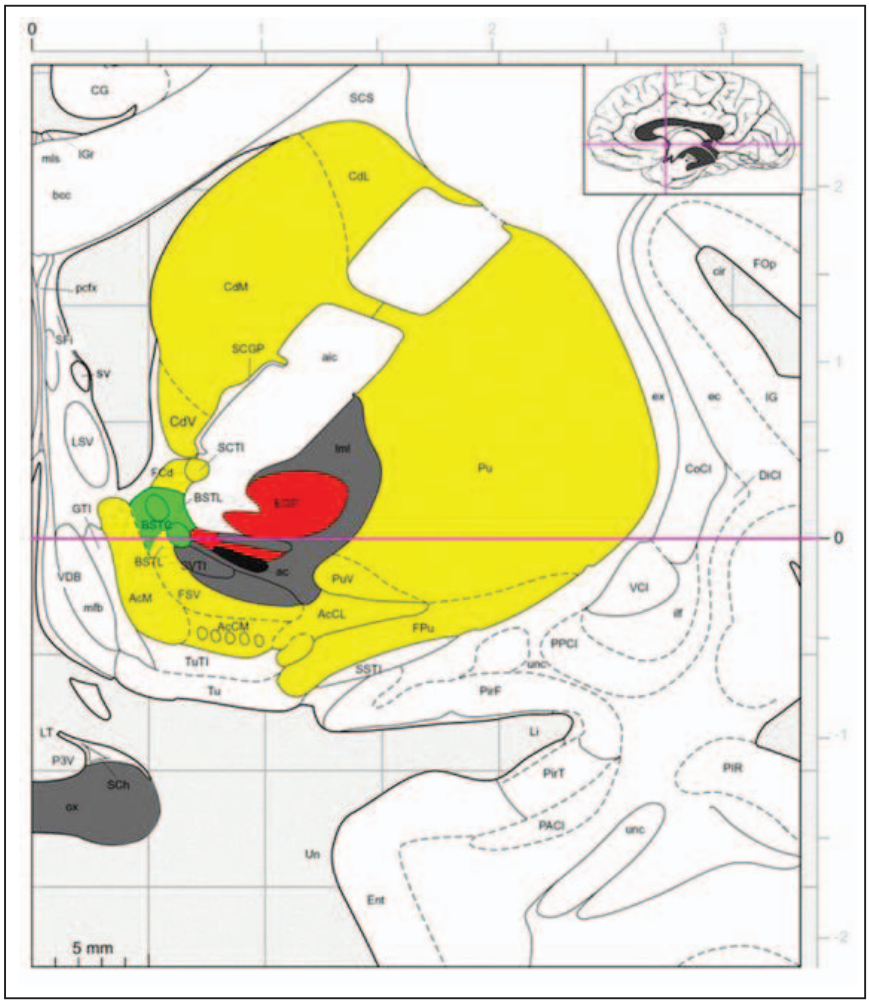


Figure 2. Frontal section through the target area, giving the topographic relations between internal capsule, nucleus accumbens, and bed nucleus of stria terminalis. Target point: 3 mm rostral CA, 7 mm right lateral of midline. 3-4 mm ventral of AC-PC line. Green: rostral edge of bed nucleus of stria terminalis. White: caudal part of anterior limb of internal capsule.[1]

1. Sturm V, Lenartz D, Koulousakis A, et al. The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. J Chem Neuroanat 2003 Dec;26(4):293-9.
DOI: http://dx.doi.org/10.1016/j.jchemneu.2003.09.003

Table 1. Outcomes of deep brain stimulation for obsessive-compulsive disorder

Study	Jadad score	Double-blind	Started/ finished, n	Final observation, mo	Cerebral blood flow	Clinical scales	DBS location	Adverse effects[a]	Improved, n (%)	Recovered, n (%)
Nuttin[1]	3	Yes	6/4	21	fMRI, PET	POMS	AL/IC		3 (75)	
Gabriëls[2]	0	No	3/3	33-39		BPRS, POMS, Y-BOCS	AL/IC		2 (67)	
Nuttin[3]	4	Yes	6/4	21	fMRI, PET	CGI, Y-BOCS	AL/IC, DMNT		3(75)	
Sturm[4]	0	No	4/4	30-34	fMRI, PET		Right NA		4 (100)	
Abelson[5]	3	No	4/4	10	PET	GAF, HDRS	AL/IC	Mild dizziness	3 (75)	1 (25)
Greenberg[6]	4	Yes	10/8	36		HDRS, Y-BOCS	AL/IC, VC/C	Seizure, hypomania, relapse with battery failure	2 (25)	4 (50)
Jiménez[b7]	0	Yes	1/1			GAF	ITP		1 (100)	1 (100)
Mallet[8]	4	Yes	18/16	3		GAF, CGI, MADRAS, MDRS, MINI, Y-BOCS	STN	15 major including a brain hemorrhage; 22 minor	10 (62)	4 (25)
Nuttin[9]	4	Yes	6/6	21	PET	CGI, Y-BOCS	AL/IC		3 (50)	

[a] other than minor surgical effects.

[b] In this study, one patient with obsessive-compulsive disorder and another with treatment resistant depression underwent DBS.

AL/IC = anterior limbs of internal capsule; BPRS = Brief Psychiatric Rating Scale; DBS = deep brain stimulation; CGI = Clinical Global Impressions; DMNT = dorsa-medial nucleus of the thalamus; fMRI = functional magnetic resonance imaging; GAF = Global Assessment of Scale; HDRS = Hamilton Depression Rating Scale; ITP = inferior thalamus peduncle; MADRS = Montgomery-Asberg Depression Rating Scale; MDRS = Mattis Dementia Rating Scale; MINI = Mini International Neuropsychiatric Interview; mo = month; NA = nucleus accumbens;
PET = positron-emission tomography; POMS = Profile of Mood States; STN = subthalamic nucleus; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

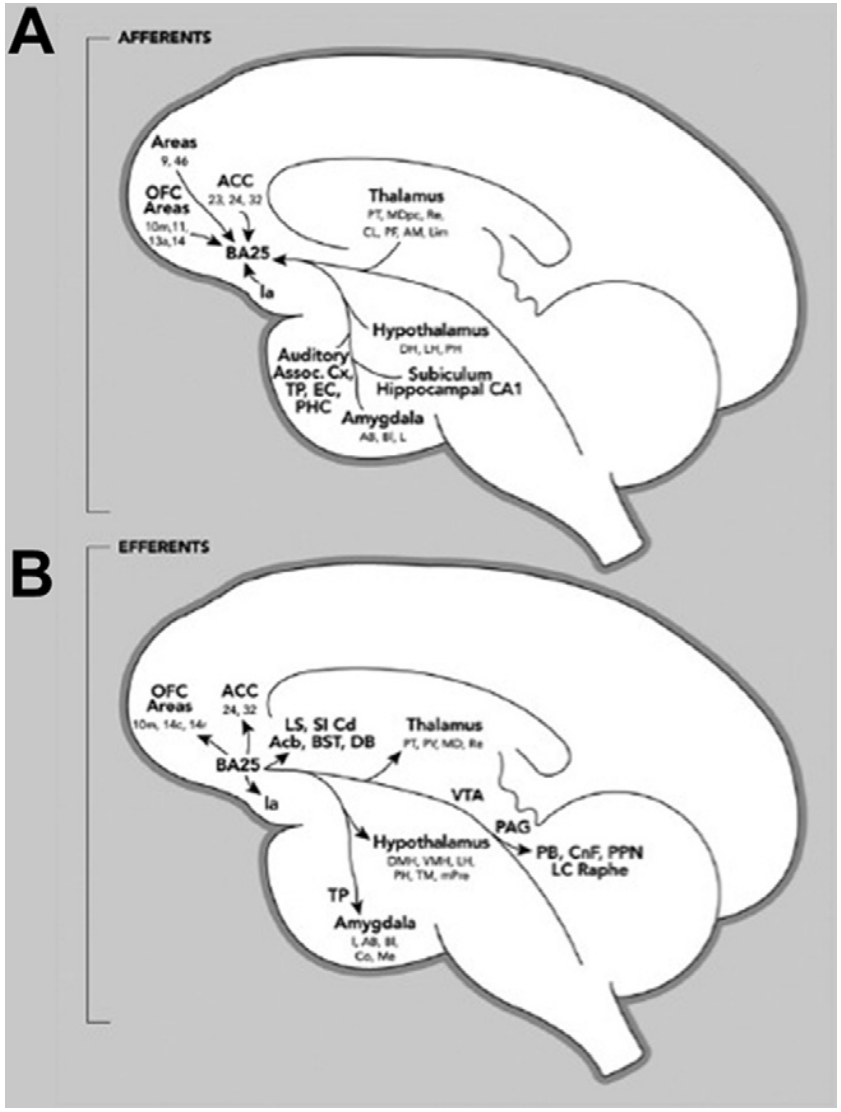


Figure 12. Brodmann area 25 circuitry. Schematic diagram and the main (**A**) afferent and (**B**) efferent from and to Brodmann area 25. Acb, nucleus accumbens; ACC, anterior cingulate cortex; amygdala (AB, accessory basal nucleus; BI, basolateral nucleus; Co, cortical nucleus; I, intercalated nucleus; L, lateral nucleus; Me, medial nucleus); BST, bed nucleus of the stria terminalis; Cd, caudate nucleus; CnF, cuneiform nucleus; DB, diagonal band of Broca; EC, entorhinal cortex; hypothalamus (DH, dorsal hypothalamus; DMH, dorsomedial hypothalamus; LH, lateral hypothalamus; PH, posterior hypothalamus; Mpre, medial preoptic area; TM, tuberomammillary nucleus; VMH, ventromedial hypothalamus); Ia, agranular insular cortex; LC, locus coeruleus; LS, lateral septal nucleus; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PB, parabrachial nucleus; PHC, parahippocampal cortex; PPN, pedunculopontine nucleus; SI, substantia innominata; TP, temporal pole; thalamus (AM, anteromedial nucleus; MD, mediodorsal nucleus; MDpc, parvicellular portion of the mediodorsal nucleus; PT, parataenial nucleus; Re, nucleus reuniens; CL, central lateral nucleus; lim, nucleus limitans; PF, parafascicular nucleus; PV, paraventricular nucleus); VTA, ventral tegmental area. (Reproduced with permission from Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM: The subcallosal cingulate gyrus in the context of major depression. Biol Psychiatry 69:301-308, 2011.)

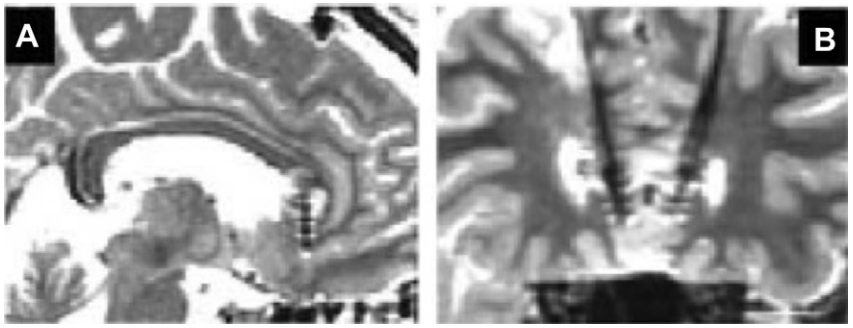


Figure 13. DBS electrode in Brodmann area 25. Postoperative magnetic resonance image (MRI). T2-weighted (**A**) sagittal and (**B**) coronal MRI images of a deep-brain stimulation electrode in Brodmann area 25. (Reproduced with permission from Mayberg H, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH: Deep brain stimulation for treatment-resistant depression. Neuron 45:651-660, 2005.)

Disruptive developments in Medicine

Prevention efforts, genomics-guided

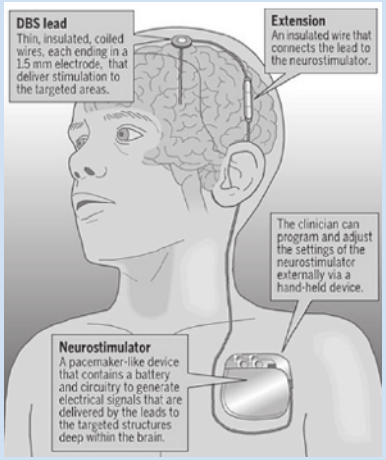
PatientsLikeMe

23andMe

ancestry.com

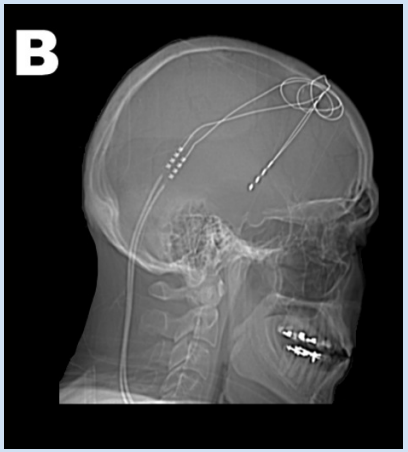
Google

More direct action on the brain itself



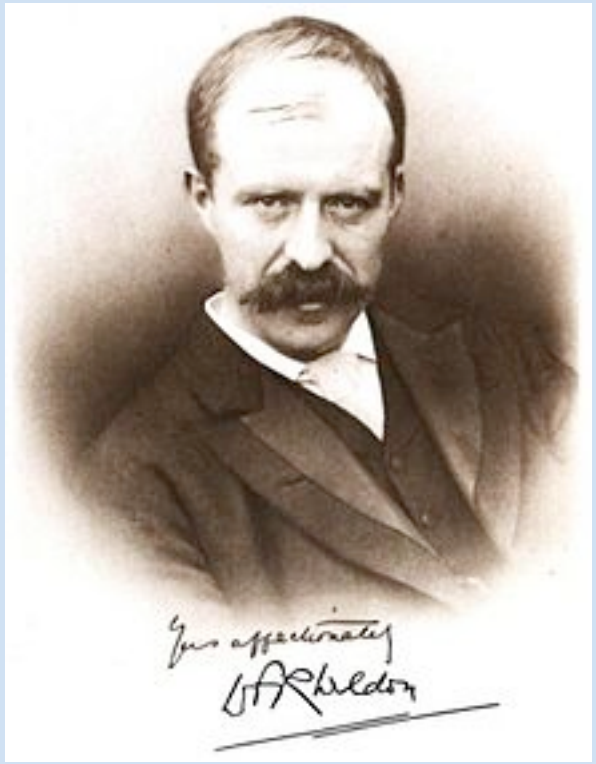
Medtronic

When Life Depends on Medical Technology



Complexity

- There are ~25-100 TRILLION cells in each human body, with ~6 billion nucleotides per cell.
- There is extensive modification of DNA, RNA and proteins both spatially and temporally.
- There are higher level mechanisms of somatic mosaicism, heterosis, and likely ancestral inheritance.



Vs.

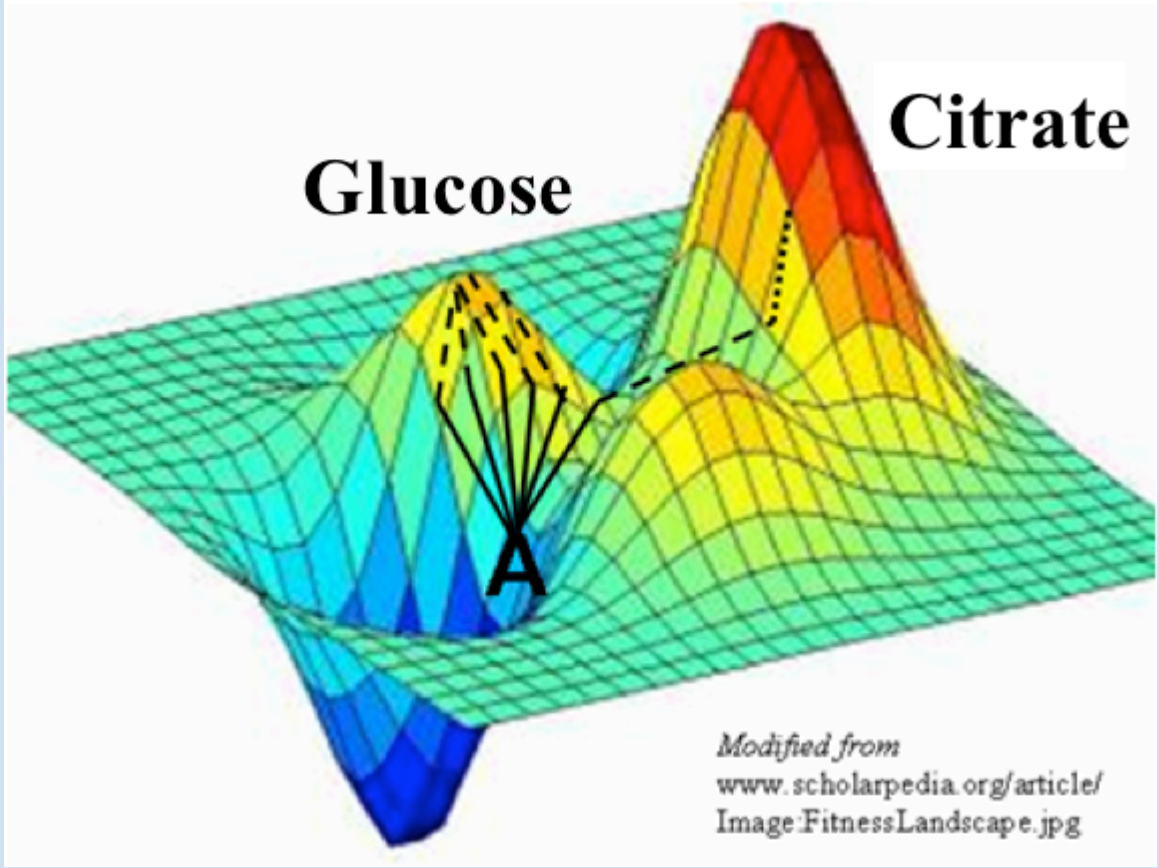
Walter Frank Raphael Weldon

William Bateson

Forthcoming by Greg Radick. Scholarly edition of W. F. R. Weldon's Theory of Inheritance (1904-1905), coedited with Annie Jamieson.

Plate I.

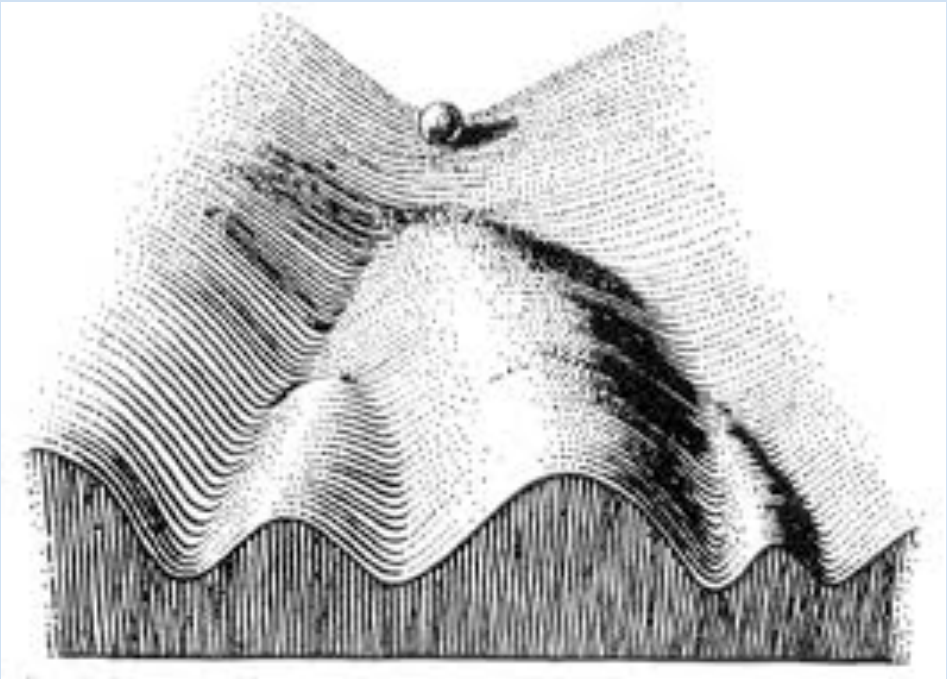
Weldon, W. F. R. 1902. Mendel's laws of alternative inheritance in peas. *Biometrika*, 1:228-254.



E. coli adapting to low glucose conditions, in the context of media containing citrate. "Finally, novel functions often emerge in rudimentary forms that must be refined to exploit the ecological opportunities. This three-step process — in which potentiation makes a trait possible, actualization makes the trait manifest, and refinement makes it effective — is probably typical of many new functions." - Lemski

Genomic analysis of a key innovation in an experimental Escherichia coli population.
Blount ZD, Barrick JE, Davidson CJ, Lenski RE.
Nature. 2012 Sep 19. doi: 10.1038/nature11514

Waddington claimed that canals form in the landscape during evolution, and that this is useful for understanding the unique qualities of biological robustness.



The canalisation metaphor suggests that phenotypes are very robust to small perturbations, for which development does not exit the canal, and rapidly returns back down, with little effect on the final outcome of development. But perturbations whose magnitude exceeds a certain threshold will break out of the canal, moving the developmental process into uncharted territory. Strong robustness up to a limit, with little robustness beyond, is a pattern that could increase evolvability in a fluctuating environment.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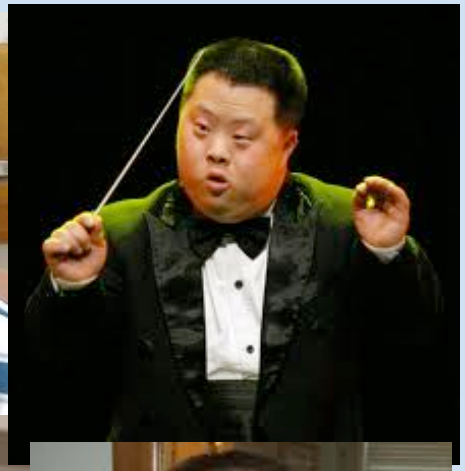
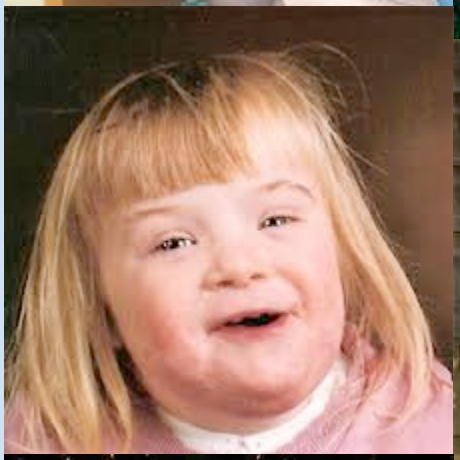
Down Syndrome

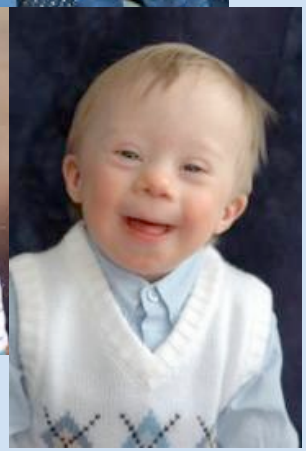


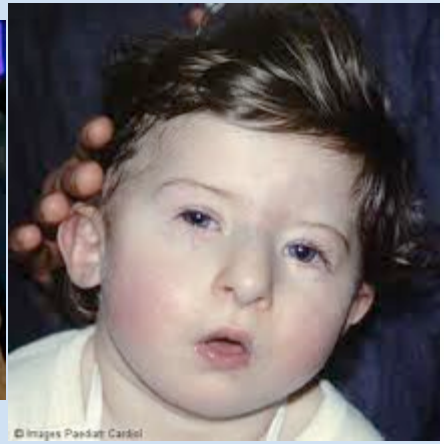


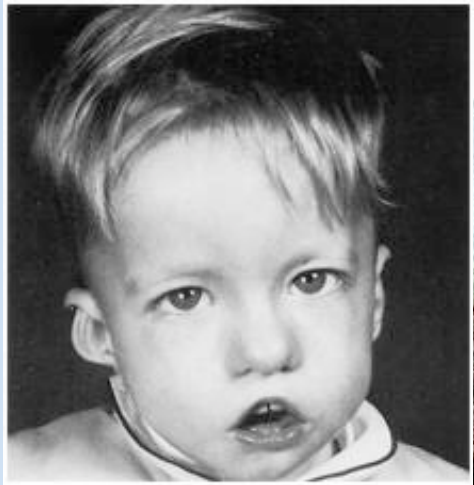






Velocardiofacial (22q11.2) Syndrome



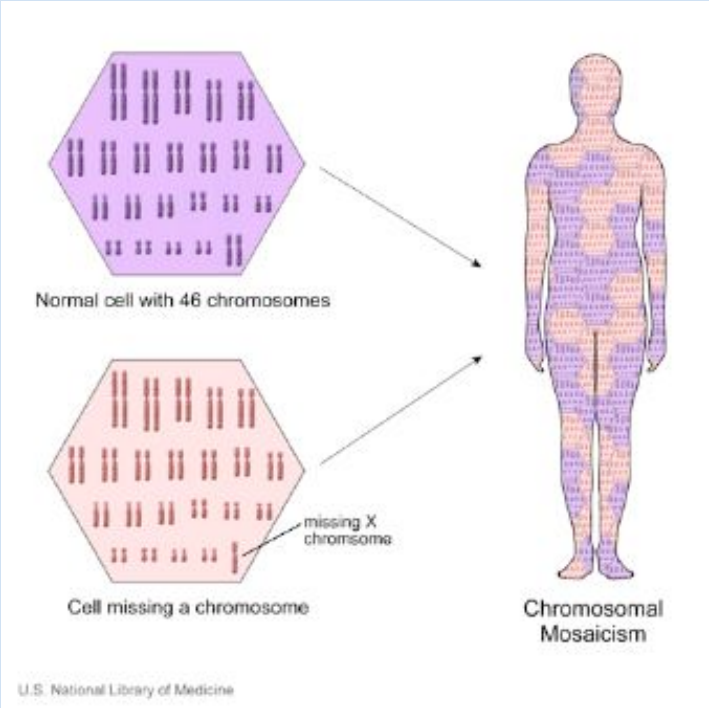


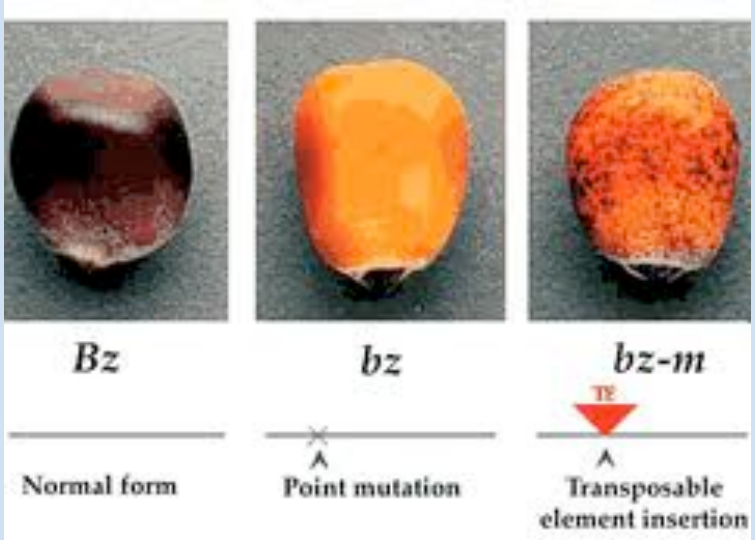
Take Home Message

Genotype ≠ Phenotype

Environment matters!
Ancestry matters!
Genomic background matters!
Longitudinal course matters!

We can only begin to really understand this if we utilize the power of intense networking via internet-enabled archiving and distribution of data.

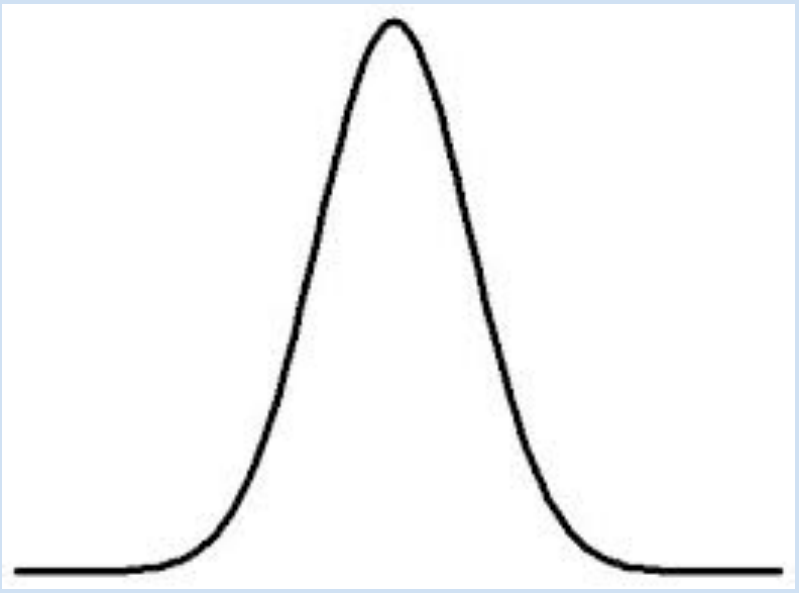


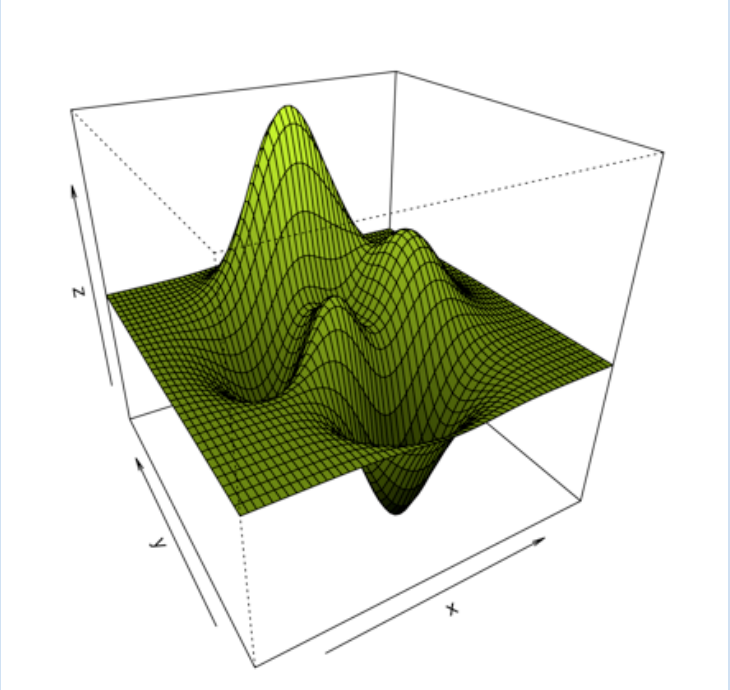


Source: http://www.thenakedscientists.com/HTML/features/article/jamilcolumn1.htm/

Expression Issues

- We do not really know the expression of pretty much ALL mutations in **humans**, as we have not systematically sequenced or karyotyped any genetic alteration in **Thousands to Millions** of **randomly** selected people, nor categorized into ethnic classes, i.e. clans.

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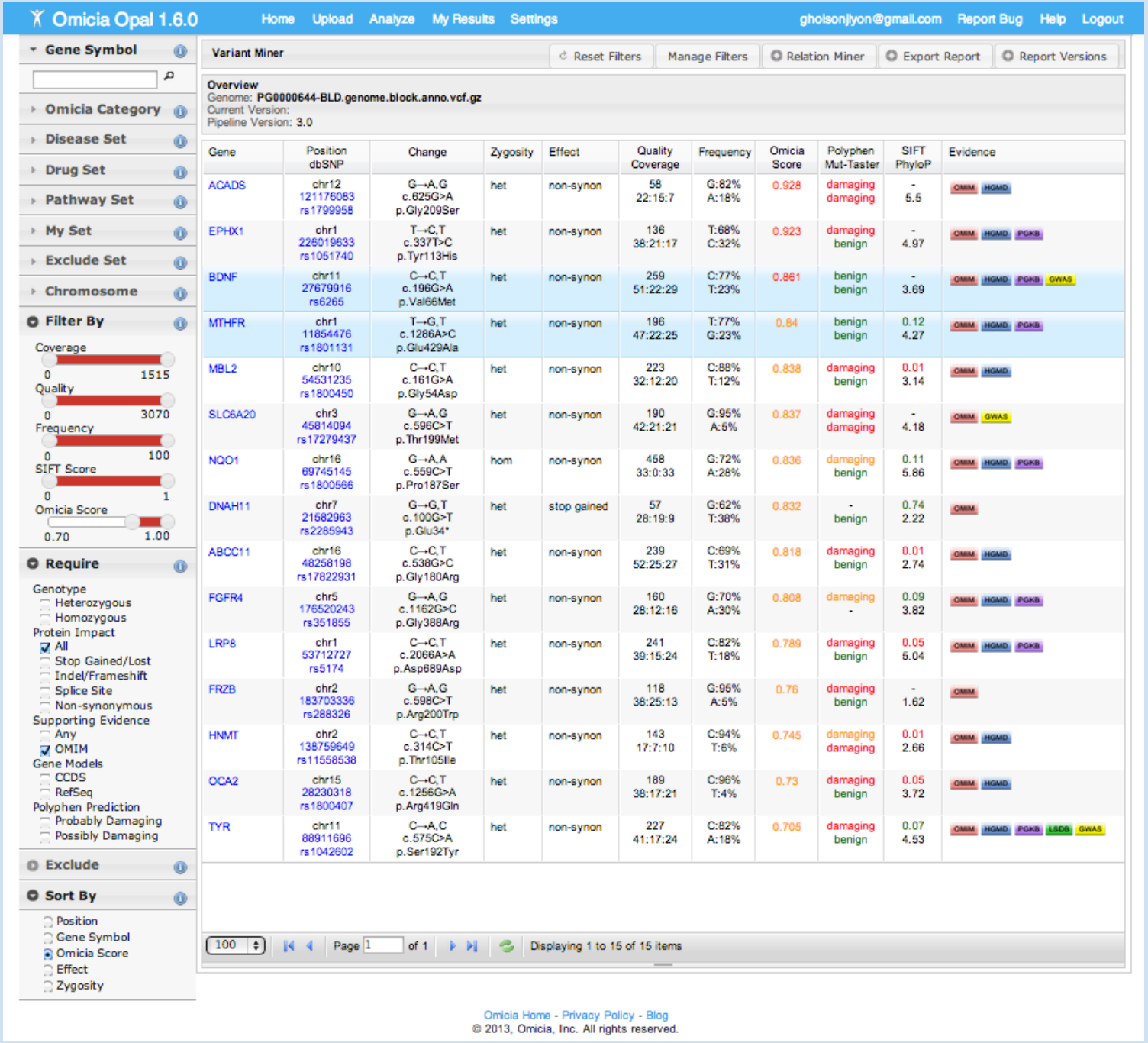
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Help
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Drug Set
Pathway Set
My Set
Exclude Set
Chromosome
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Coverage
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3070
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100
SIFT Score
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Omicia Score
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1.00
Require
Genotype
Heterozygous
Homozygous
Protein Impact
All
Stop Gained/Lost
Indel/Frameshift
Splice Site
Non-synonymous
Supporting Evidence
Any
OMIM
Gene Models
CCDS
RefSeq
Polyphen Prediction
Probably Damaging
Possibly Damaging
Exclude
Sort By
Position
Gene Symbol
Omicia Score
Effect
Zygosity
Variant Miner
Reset Filters
Manage Filters
Relation Miner
Export Report
Report Versions
Overview
Genome: PG0000644-BLD.genome.block.anno.vcf.gz
Current Version:
Pipeline Version: 3.0
Gene
Position dbSNP
Change
Zygosity
Effect
Quality Coverage
Frequency
Omicia Score
Polyphen Mut-Taster
SIFT PhyloP
Evidence
ACADS chr12 121176083 rs1799958 G→A,G c.625G>A p.Gly209Ser het non-synon 58 22:15:7 G:82% A:18% 0.928 damaging damaging - 5.5 OMIM HGMD
EPHX1 chr1 226019633 rs1051740 T→C,T c.337T>C p.Tyr113His het non-synon 136 38:21:17 T:68% C:32% 0.923 damaging benign - 4.97 OMIM HGMD PGKB
BDNF chr11 27679916 rs6265 C→C,T c.196G>A p.Val66Met het non-synon 259 51:22:29 C:77% T:23% 0.861 benign benign - 3.69 OMIM HGMD PGKB GWAS
MTHFR chr1 11854476 rs1801131 T→G,T c.1286A>C p.Glu429Ala het non-synon 196 47:22:25 T:77% G:23% 0.84 benign benign 0.12 4.27 OMIM HGMD PGKB
MBL2 chr10 54531235 rs1800450 C→C,T c.161G>A p.Gly54Asp het non-synon 223 32:12:20 C:88% T:12% 0.838 damaging benign 0.01 3.14 OMIM HGMD
SLC6A20 chr3 45814094 rs17279437 G→A,G c.596C>T p.Thr199Met het non-synon 190 42:21:21 G:95% A:5% 0.837 damaging damaging - 4.18 OMIM GWAS
NQO1 chr16 69745145 rs1800566 G→A,A c.559C>T p.Pro187Ser hom non-synon 458 33:0:33 G:72% A:28% 0.836 damaging benign 0.11 5.86 OMIM HGMD PGKB
DNAH11 chr7 21582963 rs2285943 G→G,T c.100G>T p.Glu34* het stop gained 57 28:19:9 G:62% T:38% 0.832 - benign 0.74 2.22 OMIM
ABCC11 chr16 48258198 rs17822931 C→C,T c.538G>C p.Gly180Arg het non-synon 239 52:25:27 C:69% T:31% 0.818 damaging benign 0.01 2.74 OMIM HGMD
FGFR4 chr5 176520243 rs351855 G→A,G c.1162G>C p.Gly388Arg het non-synon 160 28:12:16 G:70% A:30% 0.808 damaging - 0.09 3.82 OMIM HGMD PGKB
LRP8 chr1 53712727 rs5174 C→C,T c.2066A>A p.Asp689Asp het non-synon 241 39:15:24 C:82% T:18% 0.789 damaging benign 0.05 5.04 OMIM HGMD PGKB
FRZB chr2 183703336 rs288326 G→A,G c.598C>T p.Arg200Trp het non-synon 118 38:25:13 G:95% A:5% 0.76 damaging benign - 1.62 OMIM
HNMT chr2 138759649 rs11558538 C→C,T c.314C>T p.Thr105Ile het non-synon 143 17:7:10 C:94% T:6% 0.745 damaging damaging 0.01 2.66 OMIM HGMD
OCA2 chr15 28230318 rs1800407 C→C,T c.1256G>A p.Arg419Gln het non-synon 189 38:17:21 C:96% T:4% 0.73 damaging benign 0.05 3.72 OMIM HGMD
TYR chr11 88911696 rs1042602 C→A,C c.575C>A p.Ser192Tyr het non-synon 227 41:17:24 C:82% A:18% 0.705 damaging benign 0.07 4.53 OMIM HGMD PGKB LSDB GWAS
100
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Gene Symbol

Omicia Category

Aging
Cardiovascular
Drugs and Pharmacology
Endocrinological and Metabolic
Gastrointestinal
Blood and Lymphatic
Immune and Joints
Infectious Disease
Kidney and Urinary Tract
Neonatal
Neurological
Nutrition
Cancer
Other
Psychiatric
Respiratory
Sight
Hearing, Smell and Taste

Disease Set

Drug Set

Pathway Set

My Set

Exclude Set

Chromosome

Filter By

Require

Genotype
- Heterozygous
- Homozygous

Protein Impact
- All
- Stop Gained/Lost
- Indel/Frameshift
- Splice Site
- Non-synonymous

Supporting Evidence
- Any
- OMIM

Gene Models
- CCDS
- RefSeq

Polyphen Prediction
- Probably Damaging
- Possibly Damaging

Exclude

Sort By
- Position
- Gene Symbol
- Omicia Score
- Effect
- Zygosity

Variant Miner | Reset Filters | Manage Filters | Relation Miner | Export Report | Report Versions

Overview
Genome: **PG0000644-BLD.genome.block.anno.vcf.gz**
Current Version:
Pipeline Version: 3.0

Gene	Position dbSNP	Change	Zygosity	Effect	Quality Coverage	Frequency	Omicia Score	Polyphen Mut-Taster	SIFT PhyloP	Evidence
NQO1	chr16 69745145 rs1800566	G→A,A c.559C>T p.Pro187Ser	hom	non-synon	458 33:0:33	G:72% A:28%	0.836	damaging benign	0.11 5.86	OMIM HGMD PGKB
DPYD	chr1 98348885 rs1801265	G→A,A c.85C>T p.Arg29Cys	hom	non-synon	317 20:0:20	G:23% A:77%	0.708	- -	0.18 2.55	HGMD PGKB
ABCA1	chr9 107562804 rs2230808	T→C,C c.4760A>G p.Lys1587Arg	hom	non-synon	536 38:0:38	T:41% C:59%	0.7	benign benign	1 4.87	HGMD
NAT2	chr8 18258103 rs1799930	G→A,G c.590G>A p.Arg197Gln	het	non-synon	220 37:16:21	G:76% A:24%	0.653	damaging benign	0.08 3.11	OMIM HGMD PGKB
ABCA1	chr9 107589255 rs2066718	C→C,T c.2311G>A p.Val771Met	het	non-synon	195 40:19:21	C:94% T:6%	0.562	benign damaging	1 1.4	HGMD
CYP4F2	chr19 15990431 rs2108622	C→C,T c.1297G>A p.Val433Met	het	non-synon	183 30:12:18	C:78% T:22%	0.473	damaging benign	0.01 2.31	HGMD PGKB GWAS
NAT2	chr8 18257854 rs1801280	T→C,T c.341T>C p.Ile114Thr	het	non-synon	191 39:20:19	T:70% C:30%	0.467	benign benign	0.08 0.74	OMIM HGMD PGKB
DPYD	chr1 97981395 rs1801159	T→C,T c.1627A>G p.Ile543Val	het	non-synon	153 24:11:13	T:80% C:20%	0.295	benign benign	1 0.86	HGMD PGKB
OGG1	chr3 9798773 rs1052133	C→C,G c.294C>G p.Ile98Met	het	non-synon	146 30:16:14	C:70% G:30%	0.258	- -	0.01 -0.25	HGMD
OGG1	chr3 9798773 rs1052133	C→C,G c.994C>G p.Pro332Ala	het	non-synon	146 30:16:14	C:70% G:30%	0.258	- -	0.01 -0.25	HGMD
OGG1	chr3 9798773 rs1052133	C→C,G c.977C>G p.Ser326Cys	het	non-synon	146 30:16:14	C:70% G:30%	0.258	- -	0.01 -0.25	HGMD
CYP2C9	chr10 96741053 rs1057910	A→C,C c.1076A>C p.Ile359Leu	hom	non-synon	496 36:0:36	A:96% C:4%	0.189	benign damaging	0.11 -	OMIM HGMD PGKB
ABCA1	chr9 107620867 rs2230806	C→C,T c.656G>A p.Arg219Lys	het	non-synon	131 30:18:12	C:58% T:42%	0.187	benign benign	0.32 0.16	OMIM HGMD PGKB
CYP2B6	chr19 41515263 rs28399497	A→A,G c.785A>G p.Lys262Arg	het	non-synon	54 17:8:9	-	0.178	benign benign	1 0.84	HGMD
NBN	chr8 90990479 rs1805794	C→C,G c.553G>C p.Glu185Gln	het	non-synon	193 30:12:18	C:67% G:33%	0.172	benign benign	1 0.5	HGMD
CYP4F12	chr19 15789140 rs609290	A→G,G c.267+1A>G	hom	splice site	578 44:0:44	A:6% G:94%	0.172	- -	- -0.6	HGMD
CYP3A7	chr7 99306685 rs2257401	C→G,G c.1226G>C p.Arg409Thr	hom	non-synon	331 22:0:22	C:27% G:73%	0.163	benign benign	0.16 0.35	PGKB
CYP4F12	chr19 15789140 rs609290	A→G,G c.269A>G p.Ile90Val	hom	non-synon	578 44:0:44	A:6% G:94%	0.126	- benign	0.7 -0.6	HGMD
CETP	chr16	G→A,G	het	non-synon	203	G:45%	0.088	benign	1	HGMD PGKB

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