Interventional Neuropsychiatry: Moving Beyond Neural Cubism

Nolan Williams, MD
Instructor
Department of Psychiatry
Stanford University
Classic Neuropsychiatrist: Trained as Both a Neurologist and a Psychiatrist

Theodor Meynert  Joseph Babinski  Jean-Martin Charcot
Pioneers of Interventional Neuropsychiatry

Helen Mayberg MD
Neurologist, developer of SCC DBS for depression, started career studying PD & HD depression.

Mark George MD
Neurologist-Psychiatrist, developer of rTMS and VNS for TRD, started career studying TS and OCD.

Benjamin Greenberg MD
Neurologist-Psychiatrist, developer of VCVS DBS for OCD, started career studying motor physiology in OCD.

Not a coincidence that all are neurologists, channeling the classic neuropsychiatrist.
Beyond Neural Cubism: Promoting a Multidimensional View of Brain Disorders by Enhancing the Integration of Neurology and Psychiatry in Education

Joseph J. Taylor, Nolan R. Williams, MD, and Mark S. George, MD

2014
Neuropsychiatry and Neural Cubism
Sheldon Benjamin, MD

"Make everything as simple as possible, but not simpler." - Albert Einstein
The Merger of Neurology and Psychiatry Has Already Started at the Level of the Circuit
Proficiency in:
- Electroencephalography: with focus on learning principles of quantitative EEG
- Structural Brain Imaging: MRI, CT
- Functional Brain Imaging: fMRI, PET, SPECT
- Transcranial Magnetic Stimulation: repetitive and paired pulse
- Transcranial Direct Current Stimulation
- Electroconvulsive Therapy and Focal Electrically Administered Seizure Therapy
- Vagus Nerve Stimulation
- Deep Brain Stimulation, psychiatric clearance, intraoperative testing, and programming
Interventional Psychiatry: Why Now?

We must recollect that all of our provisional ideas in psychology will presumably one day be based on an organic substructure.

Sigmund Freud, “On Narcissism”

To the Editor: Despite decades of research, current pharmacotherapies and psychotherapies remain ineffective or intolerable for many patients with psychiatric disorders. These treatment-resistant and treatment-intolerant patients, particularly those with depression, are often referred for neuromodulatory interventions such as transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and deep brain stimulation (DBS). However, unlike cardiology, radiology, and neurology, the field of psychiatry

Formalized training in interventional psychiatry will enable practitioners to adapt to an ever-evolving understanding of brain circuitry and to better modulate its function. Traditional training curricula offer informal, inconsistent, and limited training opportunities in neurotechnologies such as neuromodulation and diagnostic modalities, but the number of proponent for increased exposure to these advances is growing. Clinical neuroscientists, psychiatric interventionalists, and various certifying bodies of accreditation have already begun to collaborate on improvements to the existing education model. Many realize that only formal expansion of interventional psychiatric training through dedicated residency tracks and fellowships will ensure the safe and timely growth of this ever-promising area of psychiatry.

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Table 1. Interventional Psychiatry Tools

<table>
<thead>
<tr>
<th>Interventional Method</th>
<th>Development</th>
<th>FDA-Approved Uses</th>
<th>Currently Being Investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroconvulsive therapy</td>
<td>In use for over 70 years, but with significant recent advances in delivery</td>
<td>Grandfathered in. APA guidelines indicate MDD, bipolar disorder, schizophrenia,</td>
<td>Newer pulse types to further limit cognitive side effects. Use in Parkinson’s disease</td>
</tr>
<tr>
<td>Transcranial magnetic stimulation</td>
<td>Modern version developed in 1985. Multiple newer delivery mechanisms being evaluated</td>
<td>Schizoaffective disorder, and catatonia. Acute, treatment-resistant unipolar MDD</td>
<td>Pain management, psychosis, mania, poststroke recovery</td>
</tr>
<tr>
<td>Vagus nerve stimulation</td>
<td>In use for epilepsy since 1997, for treatment-resistant depression since 2005</td>
<td>Partial-onset epilepsy, chronic course of treatment-resistant depression</td>
<td>Less invasive means currently being evaluated</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
<td>In use for Parkinson’s disease, essential tremor, and dystonia since 2002</td>
<td>Essential tremor, Parkinson’s disease, dystonia, humanitarian device exemption for OCD</td>
<td>Research into use in MDD and Tourette’s disorder</td>
</tr>
</tbody>
</table>

Abbreviations: APA = American Psychiatric Association, FDA = US Food and Drug Administration, MDD = major depressive disorder, OCD = obsessive-compulsive disorder.
It All Started in an Elevator in London 20 Years Ago

Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression

Mark S. George,1,2 Eric M. Wassermann,3 Wendol A. Williams,4 Ann Callahan,1 Terence A. Ketter,1 Peter Basser,5 Mark Hallett5 and Robert M. Post1
Neuropsychiatric Disorders are Disorders of Distributed Neural Networks

Neurology:
- Parkinson’s Disease
- Tourette’s syndrome

Psychiatry:
- Obsessive-Compulsive Disorder
- Depression
- BPAD
All Neuropsychiatric Disorders
Have an Emerging Circuit Diagram Like This One
Neurologic and Psychiatric Disorders Utilize Overlapping Circuits
Interventional Tools
Invasive Interventional Neuropsychiatry

DBS

EpCS
Deep Brain Stimulation (DBS)
The Motor System is a Model System
The Motor System is a Model System
DBS Implantation
Intraoperative Testing
Programming DBS
Deep brain stimulation (DBS) at the interface of neurology and psychiatry

Nolan R. Williams\textsuperscript{1,2} and Michael S. Okun\textsuperscript{3,4,5}

\textsuperscript{1}Department of Psychiatry and \textsuperscript{2}Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina, USA. \textsuperscript{3}Department of Neurology, \textsuperscript{4}Department of Neurosurgery, and \textsuperscript{5}Department of Psychiatry, University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, Florida, USA.
Rule: All Interventional Psychiatry Tools Were Developed in Neurological Disorders First (with the exception of ECT)
NON-INVASIVE MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX

SIR,—This note describes a novel method of directly stimulating the human motor cortex by a contactless and non-invasive technique using a pulsed magnetic field. Merton et al have drawn attention to the electrical stimulation of human brain and spinal cord using external electrodes on the skin. Interesting results have been reported on the cortical threshold in Parkinson’s disease, on pyramidal conduction velocity in multiple sclerosis, and on pelvic neuropathy related to faecal incontinence.

Proceedings of the Meeting of the American Society for Stereotactic and Functional Neurosurgery, Montreal 1987

Combined (Thalamotomy and Stimulation) Stereotactic Surgery of the VIM Thalamic Nucleus for Bilateral Parkinson Disease

A.L. Benabid, P. Pollak, A. Louveau, S. Henry, J. de Rougemont

Lancet, 1985
Rule: No Node in a Given Network is Pure

<table>
<thead>
<tr>
<th>Parkinson's disease</th>
<th>Tourette Syndrome</th>
<th>Obsessive-Compulsive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>VIM</td>
<td>CM-pf</td>
</tr>
<tr>
<td>GPI</td>
<td>PL</td>
<td>PL &amp; AM</td>
</tr>
<tr>
<td>STN</td>
<td>DL</td>
<td>DL</td>
</tr>
<tr>
<td>Reward</td>
<td>VC/VS</td>
<td>VC/VS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VC/VS</td>
</tr>
</tbody>
</table>
Rule: Target Node Dictates Intervention

EpCS
- Cortical Target Node
- Has been performed for depression, BPAD, stroke rehab, and aphasia.

DBS
- Subcortical Target Node
- Has been performed for depression, BPAD, tremor, Parkinson’s disease, and dystonia among others.

Both interventions are intended to change activity in the targeted node and thereby changing the activity in the distributed neural network.
Rule: Stimulating a Single Node has Distributed Effects Through The Network

OCD

Depression

Parkinson’s

Tourette

WJR 6th Anniversary Special Issues (8): fMRI

Role of functional imaging in the development and refinement of invasive neuromodulation for psychiatric disorders

2014

Nolan R Williams, Joseph J Taylor, Kayla Lamb, Colleen A Hanlon, E Baron Short, Mark S George
Rule: While Multiple Nodes Can “Work”, Each Node May Work Better on Specific Domains

Subthalamic Nucleus Versus Globus Pallidus Internus Deep Brain Stimulation: Translating the Rematch Into Clinical Practice

Nolan R. Williams, MD, Kelly D. Foote, MD, Michael S. Okun, MD
Stimulating one node with DBS for treatment may act as a probe for a second disorder/disease.

= Interaction was observed.

= Observed Interaction resulted in new trial (indication) for target.

BLUE = Neurology and RED = Psychiatry
Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus

V Vandewalle, Chr van der Linden, H J Groenewegen, J Caemaert

Gilles de la Tourette syndrome (GTS) is characterised by motor and vocal tics. The disorder is usually self-limiting but may persist into adulthood. The standard treatment is pharmacological. Stereotactic surgery has rarely been done for GTS. Hassler and Dieckmann made bilateral coagulations of the median and rostral intralaminar thalamic nuclei and the inner part of the ventral oral thalamic nucleus in three patients with a partial belief of tics. We decided to operate on a patient with GTS intractable to medical treatment with stereotactic high-frequency stimulation of the thalamic nuclei targeted by Hassler.

Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder

Bart Nuttin, Paul Cosyns, Hilde Demeulemeester, Jan Gybels, Björn Meyerson

Chronic electrical stimulation instead of bilateral capsulotomy was done in four selected patients with long-standing treatment-resistant obsessive-compulsive disorder. In three of them beneficial effects were observed. Stereotactic interventions creating bilateral lesions in specific regions of the brain may be beneficial for some patients with long-standing treatment-resistant obsessive-compulsive disorder (OCD). Such lesions are irreversible; we explored the possibility of replacing this approach by chronic electrical stimulation via implanted electrodes.
Tourette Circuit

Conceptual Diagram

MD
Thalamus

1999

“Neurology Target”=1

“Psychiatry Target”=0
Tourette DBS
OCD Circuit
Conceptual Diagram

ALIC

1999

“Neurology Target” = 0

“Psychiatry Target” = 1
OCD Circuit

Milad & Rauch 2012
**Successful treatment of tics with bilateral internal pallidum (GPI) stimulation in a 27-year-old male patient with Gilles de la Tourette’s syndrome (GTS)**

C. van der Linden, H. Colle, V. Vandewalle, G. Alessi, D. Rijckaert, L. De Waele (Ghent, Belgium; Maastricht, The Netherlands)

Objective: To compare the effect of chronic GPI to medial thalamus (MT) stimulation on motor and phonic tics in an adult patient with GTS refractory to pharmacological anti-tic treatment.

Background: Previously, we reported on the beneficial effect of chronic MT stimulation in GTS. Thus far, other targets have not been explored. We choose the GPI, as the main motor output center of the basal ganglia, to compare the effect of chronic GPI stimulation to MT stimulation on phonic and motor tics in one patient with GTS.

Methods: This 27-year-old man with a diagnosis of GTS according to the criteria of the Tourette syndrome Classification Group suffered from phonic and motor tics since the age of 7. The patient continued to have severe facial, shoulder and phonic tics into adulthood without benefit from anti-tic medication. Apart from mild depression, there was no other comorbidity. The neurological and neuropsychological examinations were normal. We used stereotactic surgery with MRCT scan fusion for determining the targets. Four electrodes were placed, one in each MT and each GPI. Propofol Target Controlled Infusion anesthesia was used to control the level of consciousness in order to test the effect of test stimulation peri-operatively. A period of 7 days of test stimulation with external stimulators was chosen to compare the effect of MT and GPI stimulation.

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**Review**

The nucleus accumbens: a target for deep brain stimulation in obsessive–compulsive- and anxiety-disorders

Volker Sturm a,*, Doris Lenartz a, Athanasios Koulousakis a, Harald Treuer a, Karl Herholz c, Johannes Christian Klein c, Joachim Klosterkötter b

a Department of Stereotactic and Functional Neurosurgery, University of Cologne, Köln 50924, Germany
b Department of Psychiatry, University of Cologne, Cologne, Germany
c Department of Neurology and Max Planck-Institute for Neurological Research, Cologne, Germany

Received 17 April 2003; received in revised form 20 September 2003; accepted 20 September 2003
OCD Circuit

Conceptual Diagram

2003 NAc 2003

ALIC 1999

“Neurology Target” = 0
“Psychiatry Target” = 2
Intraoperative Assessment

Haq, 2011
Nucleus Accumbens OR Testing
In this prospective double blind randomised “N of 1” study, a patient with a severe form of Tourette’s syndrome was treated with bilateral high frequency stimulation of the centromedian-parafascicular complex (Ce-Pf) of the thalamus, the internal part of the globus pallidus (Gpi), or both. Stimulation of either target improved tic severity by 70%, markedly ameliorated coprolalia, and eliminated self injuries. Severe forms of Tourette’s syndrome may benefit from stimulation of neuronal circuits within the basal ganglia, thus confirming the role of the dysfunction of limbic striato-pallido-thalamo-cortical systems in this disorder.

Novel target selected from past experience + animal models.
Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette syndrome

ROBERT J. MACIUNAS, M.D., M.P.H.,† BRIAN N. MADDUX, M.D., PH.D.,‡ DAVID E. RILEY, M.D.,† CHRISTINA M. WHITNEY, R.N.C.S., D.N.Sc.,† MIKE R. SCHOPEN, PH.D.,† PAULA J. OGORCKI, PH.D.,‡ JEFFREY M. ALBERT, PH.D.,§ AND DEBORAH J. GOULD, M.D.¶

Departments of †Neurosurgery and ‡Neurology, Neurological Institute, University Hospitals Case Medical Center; †Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland; and ‡Northeast Ohio Health Services, Beachwood, Ohio

Deep Brain Stimulation of the Antero-Medial Globus Pallidus Interna for Tourette Syndrome

Perminder S. Sachdev1,2*, Adith Mohan1,2, Elisabeth Cannon1, John D. Crawford2, Paul Silberstein3, Raymond Cook3, Terrence Coyne4,5, Peter A. Silburn4,5

1 Neuropsychiatric Institute, Prince of Wales Hospital, Randwick, NSW, Australia, 2 Centre for Healthy Brain Ageing, School of Psychiatry, The University of New South Wales, Sydney, Australia, 3 North Shore Private Hospital, St. Leonards, Sydney, NSW, Australia, 4 Centre for Clinical Research, University of Queensland, Herston, QLD, Australia, 5 St. Andrew’s War Memorial Hospital, Spring Hill, QLD, Australia
Anteromedial GPi as OCD Target along with TS target

### Outcome related to Tourette’s syndrome tics

<table>
<thead>
<tr>
<th>Patient</th>
<th>YGTSS component</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Motor</td>
<td>23/25</td>
<td>4/25</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Vocal</td>
<td>13/25</td>
<td>0/25</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Impairment</td>
<td>50/50</td>
<td>10/10</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>Motor</td>
<td>25/25</td>
<td>0/25</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Vocal</td>
<td>21/25</td>
<td>6/25</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>Impairment</td>
<td>50/50</td>
<td>0/50</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>Motor</td>
<td>23/25</td>
<td>4/25</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Vocal</td>
<td>21/25</td>
<td>4/25</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>Impairment</td>
<td>40/50</td>
<td>0/50</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>Motor</td>
<td>24/25</td>
<td>5/25</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>Vocal</td>
<td>25/25</td>
<td>0/25</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Impairment</td>
<td>50/50</td>
<td>0/25</td>
<td>100%</td>
</tr>
</tbody>
</table>

YGTSS = Yale Global Tic Severity Scale.

### Outcome relating to obsessive-compulsive disorder symptoms

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-op OCI Freq</th>
<th>Post-op OCI Freq</th>
<th>Pre-op OCI Distress</th>
<th>Post-op OCI Distress</th>
<th>Improved Freq (%)</th>
<th>Improved Distress (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>0</td>
<td>26</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>12</td>
<td>75</td>
<td>11</td>
<td>85.4</td>
<td>85.3</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>1</td>
<td>55</td>
<td>2</td>
<td>97.7</td>
<td>96.4</td>
</tr>
</tbody>
</table>

Freq = frequency, OCI = Obsessive Compulsive Inventory.
CASE REPORT

Obsessive–Compulsive Disorder following Bilateral Globus Pallidus Infarction

P. Rodrigo Escalona, John C. Adair, Brian B. Roberts, and David A. Graeber

Key Words: Obsessive–compulsive disorder, depression, basal ganglia, stroke, anxiety

Biol Psychiatry 1997;42:410–412

Brain (1989), 112, 699–725

OBSESSIVE-COMPULSIVE AND OTHER BEHAVIOURAL CHANGES WITH BILATERAL BASAL GANGLIA LESIONS

A NEUROPSYCHOLOGICAL, MAGNETIC RESONANCE IMAGING AND POSITRON TOMOGRAPHY STUDY

by D. Laplane, M. Levasseur, B. Pillon, B. Dubois, M. Baulac, B. Mazoyer, S. Tran Dinh, G. Sette, F. Danze and J. C. Baron
CM nucleus as OCD Target along with TS target

Thalamic deep brain stimulation for treatment-refractory Tourette syndrome
Two-year outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>YGTSS baseline</th>
<th>YGTSS 24 mo</th>
<th>YBOCS baseline</th>
<th>YBOCS 24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
<td>36</td>
<td>32</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>52</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>97</td>
<td>44</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>17</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>46</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>89</td>
<td>33</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>91</td>
<td>48</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>91</td>
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<td>36</td>
<td>21</td>
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<td>9</td>
<td>66</td>
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<td>10</td>
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<td>30</td>
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<td>11</td>
<td>69</td>
<td>40</td>
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<td>12</td>
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<tr>
<td>12</td>
<td>42</td>
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<td>13</td>
<td>82</td>
<td>45</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>14</td>
<td>78</td>
<td>45</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>15</td>
<td>63</td>
<td>42</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Mean (SD): YGTSS 76.5 (15.1) 36.6 (10.8) YBOCS 20.9 (9.8) 14.4 (8.5)

p Value: 0.001 0.009

Porta 2009
Increased Thalamic Gamma Band Activity Correlates with Symptom Relief following Deep Brain Stimulation in Humans with Tourette’s Syndrome

Nicholas Maling1,9, Rowshanak Hashemiyoont2, Kelly D. Foote3,4, Michael S. Okun4,5, Justin C. Sanchez2,6,7,85

1 Department of Neuroscience, University of Florida, Gainesville, Florida, United States of America, 2 Department of Biomedical Engineering, University of Miami, Coral Gables, Florida, United States of America, 3 Department of Neurosurgery, University of Florida, Gainesville, Florida, United States of America, 4 Center for Movement Disorders & Neurorestoration, University of Florida, Gainesville, Florida, United States of America, 5 Department of Neurology, University of Florida, Gainesville, Florida, United States of America, 6 Neuroscience Program, University of Miami, Miami, Florida, United States of America, 7 Miami Project to Cure Paralysis, University of Miami, Miami, Florida, United States of America

Best Responders

<table>
<thead>
<tr>
<th>Subject</th>
<th>Correlation Coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1</td>
<td>-0.317</td>
<td>0.270</td>
</tr>
<tr>
<td>TS2</td>
<td>-0.950</td>
<td>0.004</td>
</tr>
<tr>
<td>TS3</td>
<td>-0.704</td>
<td>0.049</td>
</tr>
<tr>
<td>TS4</td>
<td>-0.855</td>
<td>0.032</td>
</tr>
<tr>
<td>TS5</td>
<td>-0.399</td>
<td>0.217</td>
</tr>
</tbody>
</table>

- Gamma Power  
- YGTSS

Graphic representations showing normalized gamma power over months after surgery for TS 1, TS 2, and TS 5, with correlation coefficient and p-values provided.

Zabek M, Sobsyl M, Koziarz H, Dzierzecki S.

Abstract

We describe the effects of unilateral right-sided nucleus accumbens (NA) stimulation in a patient with intractable Gilles de la Tourette syndrome (GTS) with associated compulsions and self-injurious behaviour. Pharmacological and behavioural therapies had completely failed to control the patient's tics and compulsions. The electrode (Model 3389 Medtronic, Minneapolis, MN) was implanted in the right NA. At 28-month follow-up, deep brain stimulation (DBS) of the right NA effectively alleviated tics and compulsions with patient's self-injurious behaviour. We suggest that this approach can be an effective treatment option for GTS with intractable motor and vocal tics with associated compulsions with self-injurious behaviour.

PMID: 19235110 [PubMed - indexed for MEDLINE]
Deep Brain Stimulation for Refractory Obsessive–Compulsive Disorder

James L. Abelson, George C. Curtis, Oren Sagher, Ronald C. Albucher, Mark Harrigan, Stephan F. Taylor, Brian Martis, and Bruno Giordani

Background: Neurosurgery (anterior capsulotomy) has been beneficial to many patients with debilitating, refractory obsessive–compulsive disorder (OCD), but the irreversibility of the procedure is an important limitation to its use. Nondestructive, electrical stimulation (deep brain stimulation; DBS) has proven an effective alternative to ablative surgery for neurological indications, suggesting potential utility in place of capsulotomy for OCD.

Methods: The effects of DBS for OCD were examined in four patients in a short-term, blinded, on–off design and long-term, open follow-up. The patients had incapacitating illness, refractory to standard treatments. Hardware developed for movement disorder treatment was surgically implanted, with leads placed bilaterally in the anterior limbs of their internal capsules. Patients received stimulation in a randomized “on–off” sequence of four 3-week blocks. Ongoing, open stimulation was continued in consenting patients after the controlled trial.

Results: Patients tolerated DBS well. Dramatic benefits to mood, anxiety, and OCD symptoms were seen in one patient during blinded study and open, long-term follow-up. A second patient showed moderate benefit during open follow-up.

Conclusions: It appears that DBS has potential value for treating refractory psychiatric disorders, but additional development work is needed before the procedure is utilized outside of carefully controlled research protocols.
Archival Reports

Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Treatment-Resistant Depression 2008


Deep Brain Stimulation to Reward Circuitry Alleviates Anhedonia in Refractory Major Depression 2009

Thomas E Schlaepfer*, 1, 2, Michael X Cohen3, 4, Caroline Frick1, Markus Kosel1, Daniela Brodesser1, Nikolai Axmacher3, Alexius Young Joe5, Martina Kreft1, Doris Lenartz6 and Volker Sturm6

1 Department of Psychiatry and Psychotherapy, University Hospital, Bonn, Germany; 2 Departments of Psychiatry and Mental Health, The Johns Hopkins University, Baltimore, MD, USA; 3 Department of Epileptology, University Hospital, Bonn, Germany; 4 Department of Psychology, University of California, Davis, CA, USA; 5 Department of Nuclear Medicine, University Hospital, Bonn, Germany; 6 Department of Functional Neurensurgery, University Hospital, Cologne, Germany
Deep Brain Stimulation for Treatment-Resistant Depression

Helen S. Mayberg,1,2,* Andres M. Lozano,3,* Valerie Voon,4 Heather E. McNeely,5 David Seminowicz,6 Clement Hamani,3 Jason M. Schwalb,3 and Sidney H. Kennedy4

electrical stimulation of the subgenual cingulate white matter can effectively reverse symptoms in otherwise treatment-resistant depression.
Modified Mayberg Target

Riva-Posse 2014
Mood Disorders

Conceptual Diagram

2005

2008

2009

"Neurology Target" = 0

"Psychiatry Target" = 3
Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a phase 1 pilot trial

Nir Lipsman, D Blake Woodside, Peter Giacobbe, Clement Hamani, Jacqueline C Carter, Sarah Jane Norwood, Kalam Sutandar, Randy Staab, Gavin Elias, Christopher H Lyman, Gwenn S Smith, Andres M Lozano

### YBOCS

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Compulsions, Parkinson’s disease, and stimulation

Luc Mallet, Valérie Mesnage, Jean-Luc Houeto, Antoine Pelissolo, Jérôme Yelnik, Cécile Behar, Marcella Gargiulo, Marie-Laure Welter, Anne-Marie Bonnet, Bernard Pillon, Philippe Cornu, Didier Dormont, Bernard Pidoux, Jean-François Allilaire, Yves Agid

Pathophysiological models suggest that obsessive compulsive disorder (OCD) might be associated with dysfunctions in cortico-striato-pallido-thalamo-cortical neuronal circuits. We implanted subthalamic electrodes to alleviate parkinsonian symptoms in two patients who had Parkinson’s disease and a history of severe OCD. Parkinsonian disability improved postoperatively in both patients, and 2 weeks after the procedure, their compulsions had disappeared and obsessive symptoms improved (58% improvement for patient 1 on the Yale-Brown obsessive compulsive scale, 64% for patient 2). The improvements in these two patients suggest that high-frequency stimulation could improve function in the subcortical-limbic circuitry in patients with severe OCD.

Effect of subthalamic nucleus stimulation on obsessive–compulsive disorder in a patient with Parkinson disease

Case report

Denys Fontaine, M.D., Vianney Mattei, M.D., Michel Borg, M.D., Daniel von Langsdorff, M.D., Marie-Noelle Magnie, M.D., Ph.D., Stéphane Chanalet, M.D., Philippe Robert, M.D., and Philippe Paqu
Subthalamic Nucleus Stimulation in Severe Obsessive–Compulsive Disorder

Luc Mallet, M.D., Ph.D., Mircea Polosan, M.D., Nematollah Jaafari, M.D., Nicolas Baup, M.D., Marie-Laure Welter, M.D., Ph.D., Denys Fontaine, M.D., Ph.D., Sophie Tezenas du Montcel, M.D., Ph.D., Jérôme Yelnik, M.D., Isabelle Chéreau, M.D., Christophe Arbus, M.D., Sylvie Raoul, M.D., Ph.D., Bruno Aouizerate, M.D., Ph.D., Philippe Damier, M.D., Ph.D., Stephan Chabardès, M.D., Ph.D., Virginie Czerniecki, Ph.D., Claire Ardouin, Ph.D., Marie-Odile Krebs, M.D., Ph.D., Eric Bardinet, Ph.D., Patrick Chaynes, M.D., Ph.D., Pierre Burbaud, M.D., Ph.D., Philippe Cornu, M.D., Philippe Derost, M.D., Thierry Bougerol, M.D., Ph.D., Benoît Bataille, M.D., Vianney Mattei, M.D., Didier Dormont, M.D., Ph.D., Bertrand Devaux, M.D., Marc Vérin, M.D., Ph.D., Jean-Luc Houeto, M.D., Ph.D., Pierre Pollak, M.D., Ph.D., Alim-Louis Benabid, M.D., Ph.D., Yves Agid, M.D., Ph.D., Paul Krack, M.D., Ph.D., Bruno Millet, M.D., Ph.D., and Antoine Pelissolo, M.D., Ph.D., for the STOC Study Group*
Deep Brain Stimulation of the Nucleus Accumbens Has Positive Effects on Parkinson's Disease-Related Apathy (P7.050)

Nolan Williams1, Baron Short2, Emily Williams3, Alexandra Jeffery3, Suzanne Kerns4, Gregory Sahlem4, Colleen Hanlon5, Gonzalo Revuelta6, Istvan Takacs6 and Mark George7

Background: Deep brain stimulation (DBS) is a technique that consists of an implanted lead that provides neural-network modulation within a brain circuit(s) of interest. DBS was first utilized in movement disorders such as Parkinson's disease (PD) then later psychiatric disorders such as obsessive-compulsive disorder (OCD). There are several DBS targets for the motor symptoms of PD including the sensorimotor subthalamic nucleus (STN). OCD is characterized by a combination of intrusive thoughts along repetitive behaviors and has several DBS targets including the ventral capsule/ventral striatum (VC/VS).
VCVS Stimulation
Parkinson’s Circuit

Conceptual Diagram

VCVS

STN

“Neurology Target” = 3

“Psychiatry Target” = 1
STN DBS Stimulation
Mood can be turned down...
...by incidentally inhibiting a node in the mood regulation network.

Contact 0 of the left electrode was located in the central substantia nigra, including part of the pars compacta and pars reticulata.
Mood can be turned up...
...by activating adjacent reward circuitry...

**FIGURE 6.** Conceptual sketch showing findings. The medial, inferior, and anterior EC position in the STN (red dot) leads to activation of limbic STN tributaries to the MFB. The limbic STN uses the STN as a pathway to connect to the reward centers (LH, lateral hypothalamus and AcN, accumbens nucleus). Clinical response to this situation suggests that axonal activation outside the limbic STN, and not neuronal inhibition of the limbic STN, leads to hypomania in STN DBS.
MEDIAL FOREBRAIN BUNDLE STIMULATION AS A PATHOPHYSIOLOGICAL MECHANISM FOR HYPOMANIA IN SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION FOR PARKINSON’S DISEASE

Objective: Hypomania accounts for approximately 4% to 13% of psychotropic adverse events during subthalamic nucleus (STN) deep brain stimulation (DBS) for Parkinson’s disease. Diffusion of current into the inferior and medial “limbic” STN is often reported to be the cause. We suggest a different explanation, in which the coactivation of the medial forebrain bundle (MFB), outside the STN, leads to hypomania during STN DBS.

Methods: Six patients with advanced Parkinson’s disease (ages 54 to 84 years) underwent

Medial Lemniscus=Internal Capsule=Medial Forebrain Bundle:
All white matter fibers which course close to the STN.

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**Priority Communication**

**Rapid Effects of Deep Brain Stimulation for Treatment-Resistant Major Depression**

Thomas E. Schlaepfer, Bettina H. Bewernick, Sarah Kayser, Burkhard Mädler, and Volker A. Coenen

**Background:** Treatment-resistant major depressive disorder is a prevalent and debilitating condition. Deep brain stimulation to different targets has been proposed as a putative treatment.

**Methods:** In this pilot study, we assessed safety and efficacy of deep brain stimulation to the supero-lateral branch of the medial forebrain bundle in seven patients with highly refractory depression. Primary outcome criterion was severity of treatment-resistant major depressive disorder as assessed with the Montgomery-Åsberg Depression Rating Scale. General psychopathologic parameters, social functioning, and tolerance were assessed with standardized scales, the Global Assessment of Functioning scale, quality of life (Short-Form Health Survey Questionnaire), and neuropsychological tests.
Mood Disorders

2009 2008 2009

“Neurology Target”=1

“Psychiatry Target”=3

NAc
Treatment-Resistant Depression

• Depression is a state of extreme sadness or melancholia that affects a person’s activities of daily life as well as social functioning (Williams 2009).

• Treatment-resistant depression (TRD) is a severely disabling disorder with no proven treatment options once standard/approved therapies (medication, psychotherapy, TMS, VNS, ECT) have failed (Williams 2013).
Treatment-Resistant Depression Targets

There are multiple cortical and subcortical targets for treating TRD:

– Cortical:
  • Dorsolateral Prefrontal Cortex
  • Frontopolar Cortex

– Subcortical:
  • Subcallosal Cingulate [FAILED]
  • Medial Forebrain Bundle
  • Ventral Capsule/ Ventral Striatum [FAILED]
A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression

Ideal Depression Implanted Device

• So straightforward that any major medical center can do it (like rTMS).
  – Easy surgical approach that requires non-functional neurosurgeon and trained psychiatrist.
  – Easy programming approach.

• Low risk.
  – Low to no ICH risk.
  – Low risk of hardware failure.
EpCS for TRD
“Most likely deep brain stimulation for depression will be a transitional technology, which will lead to even more refined, but less invasive treatments of the brain.”

Thomas E. Schlaepfer, MD—Scientific American Interview, 2013
EpCS: Two Cortical Stimulation Sites

- The frontopolar (FP-BA 10) and dorsolateral (DL-BA 9/46) prefrontal cortices (PFC) play distinct, yet complementary roles in the integration of emotional and cognitive experiences (Nahas 2010).

- One or both of these two cortical areas appear to be central to the efficacy of deep targets (Williams 2014).

- Our study utilized bilateral dorsolateral prefrontal and the frontopolar cortex as stimulation sites (Nahas 2010).
EpCS: Dorsolateral Prefrontal Cortex

- Established cortical stimulation site for non-invasive brain stimulation (transcranial magnetic stimulation) (George 2010).

- In TRD, L DLPFC hypoactivity is associated with negative emotional judgment and right DLPFC hyperactivity is linked to attentional modulation (Grimm 2008).

- DLPFC has been demonstrated to be anti-correlated with subcallosal cingulate (SCC) (Fox 2012).
EpCS: Frontopolar Cortex

• The medial prefrontal cortex has been implicated in animal (Covington 2010) and human studies (Downar 2013) as playing a central role in the pathogenesis of depression as well as in its recovery.

• There is a consistent finding of increased resting-state activity in the frontopolar cortex (FPC) in patients with depression (Fitzgerald 2008).

• Effective SCC DBS requires functional connection to the FPC (Riva Posse 2014).
Modified Mayberg Target
Epidural Prefrontal Cortical Stimulation

- We implanted five adults with four stimulation paddles over dura (between dura and skull) covering FP and DLPFC.

- These five individuals had failed an average of 5.8 antidepressants prior to implant with three who had failed VNS and four who had failed or were unable to tolerate ECT.

- All subjects received ongoing clinical assessments at baseline, seven-month (7mo), one-year (1yr), two-year (2yr), and five-year (5yr) time points.
Epidural Prefrontal Cortical Stimulation

- All patients have continued to tolerate the therapy.
- There were five serious adverse events: one paddle infection and four device malfunctions, all resulting in suicidal ideation and/or hospitalization with three involving the battery (2-drain, 1-turned off) and one involving connectors.
- Three of five (60%) subjects continued to be in remission at 5yr.
- One of the non-responders converted to a responder (80%) once a technical error was discovered.
Average HAMD Scores
Results

• There was a statistically significant reduction of the MADRS (p=.05) and CGI (p=0.043) for baseline to 5 years.

• No significant change in cognitive measures (choice reaction test, continuous performance task, MMSE, cognitive failures test).
Sam’s Experience

One of five epidural patients that gave permission to tape/show interview.
Score Card

Mood Disorders
“Neurology Target”=1
“Psychiatry Target”=5

OCD
“Neurology Target”=3
“Psychiatry Target”=3

Tourette
“Neurology Target”=4
“Psychiatry Target”=2

Parkinson’s
“Neurology Target”=3
“Psychiatry Target”=1
EpCS is Qualitatively Different from DBS

- Except for NAc TRD target, DBS has no potential for long-term recording.
- DBS has at least 1% intracranial hemorrhage risk.
- DBS has complex targeting which can result in unintended neural elements to be stimulated (3D).
EpCS is Qualitatively Different from DBS

- EpCS has the potential for long-term recording.
- EpCS inherently has the ability to develop closed loop system.
- EpCS has no intracranial hemorrhage risk.
- EpCS has the potential to test spike timing in multiple ways/sites (L DLPFC—R DLPFC & DLPFC --- FPC).
- The EpCS sites that were chosen are rTMS sites for numerous disorders which are co-morbid with depression.
- EpCS has a simple targeting method (2D).
Psychiatrist Targeting of EpCS with rTMS Targeting Technology
Cautionary Tale:

- Team could not get voltage over 0.5V (very low) with significant side effects.
- CAPS scores barely changed from 105 → 95 in 6 months.
- Patient with very limited benefit and significant side effects along with risk of ICH.
The Third Age of Psychiatry:
*Stigma Cannot Survive at the Level of the Circuit*
Meetings of Psychiatrists, Neurologists, and Neurosurgeons are Already Happening
Music is among all cultures an important part of the live of most people. Music has psychological benefits and may generate strong emotional and physiological responses. Recently, neuroscientists have discovered that music influences the reward circuit of the nucleus accumbens (NAcc), even when no explicit reward is present. In this clinical case study, we describe a 60-year old patient who developed a sudden and distinct musical preference for Johnny Cash following deep brain stimulation (DBS) targeted at the NAcc. This case report substantiates the assumption that the NAcc is involved in musical preference, based on the observation of direct stimulation of the accumbens with DBS. It also shows that accumbens DBS can change musical preference without habituation of its rewarding properties.

**Keywords:** nucleus accumbens, deep brain stimulation, obsessive-compulsive disorder, musical preference, reward system
Emily’s Rule

- I asked my wife Emily what her estimation of my hours dedicated to a patient with an implanted device was relative to the surgeon.
- I said 1:10 and she said 1:30. We averaged this estimation and will say 1:20.
- For every one hour that the neurosurgeon spends with an implanted device patient, I must spend 20 hours.
- We agreed that the only implanted device patients that I should accept are those that I 100% believe in the science.
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Istvan Takacs

Ziad Nahas
References


References


References


