Lessons Learned from the Electric Brain:

Michael S. Okun, M.D.

Adelaide Lackner Professor of Neurology
Acknowledgements

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Potential Conflicts of Interest

NPF Medical Director
NPF Ask the Doctor
Book Royalty- Demos/Manson/Humana/Cambridge

CME
Prime, Vanderbilt, Peerview, Journal Watch, Delaware Media
PeerView
Lessons from Electrical Stimulation

• Why DBS? Mechanisms of Action
• Screening and Selecting Candidates (Interdisciplinary Team)
• Targets and Targeting
• Plasticity: Lessons from different disorders
• The Importance of Microlesional Effects
• DBS Failures
• Smarter DBS (Scheduled and Responsive DBS)
Acknowledgements
Circuit Disorders
“Loops”
• Analogy - flipping on a light switch

• Can throw medication bottles away and live “chemically free”
Mechanisms by which stimulation of the ventral contact (red cylinder) but not the dorsal contact (yellow cylinder) could induce a hypomanic state

Mallet L et al. PNAS 2007;104:10661-10666
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Your brain controls everything

We can control your brain
Why in the world would we pump electricity deep into your brain?
We Don’t Know How it Works?

McIntyre, 2005
Insertion site in sub-thalamic nucleus (STN)

GFAP - astrocytes
Cyquant - all cell nuclei
Iba1 - microglia

Shain, Smith, Okun
Figure 4.5. Scanning electron microscopy (SEM) examination of a portion of the DBS lead. (A) Photograph of the electrodes and end of lead. The white boxes the region in B. (B) Montage of SEM images illustrating electrode and lead surfaces. Higher magnification images were collected at the indicated sites (lettered boxes). (C) Example of the cells observed attached to the electrode. (D) Red blood cells and other attached cells near the edge of the electrode. (E) Profile of a cell attached to the body of the lead. These regions were completely coated with material and cells. Magnifications of each panel are indicated by the corresponding scale bar.
Mechanism of Action
Mechanism of Action

• Myelinated axons, neuronal cell bodies and dendrites all have different electrical properties (chronaxies)
Mechanism of Action

• Myelinated axons, neuronal cell bodies and dendrites all have different electrical properties (chronaxies)

• It is likely that the standard stimulation parameters of DBS will predominantly affect axons, rather than the cell bodies or dendrites
Mechanisms of Action
Mechanisms of Action

- DBS will have excitatory and inhibitory activity on a complex neural network
Mechanisms of Action

• DBS will have excitatory and inhibitory activity on a complex neural network

• Inhibitory effects locally
Mechanisms of Action

• DBS will have excitatory and inhibitory activity on a complex neural network

• Inhibitory effects locally

• Retrograde activation of the incoming axons (jamming)
Mechanisms of Action

• DBS will have excitatory and inhibitory activity on a complex neural network

• Inhibitory effects locally

• Retrograde activation of the incoming axons (jamming)

• Neurotransmitter depletion in the outgoing axons (synaptic fatigue)
Mechanisms of Action

• DBS will have excitatory and inhibitory activity on a complex neural network

• **Inhibitory effects locally**

• Retrograde activation of the incoming axons (jamming)

• Neurotransmitter depletion in the outgoing axons (synaptic fatigue)

• **Excitatory effects distally**
Mechanism of Action
Mechanism of Action

- The activity in the axon and the neuronal cell body can be decoupled
Mechanism of Action

- The activity in the axon and the neuronal cell body can be decoupled
- Hyper-polarization of the neuronal cell body and a depolarization of the axon
Mechanism of Action
Mechanism of Action

- Tremor suppression, anxiety reduction, or mood improvement, may occur within seconds following stimulation
Mechanism of Action

• Tremor suppression, anxiety reduction, or mood improvement, may occur within seconds following stimulation

• Likely a rapid and global alteration in neural networks activity and function
Mechanism of Action

• Tremor suppression, anxiety reduction, or mood improvement, may occur within seconds following stimulation

• Likely a rapid and global alteration in neural networks activity and function

• More regular, and probably normalized firing rates and patterns
One human astrocyte interacts with 2 million synapses

Maybe HFS triggers a propagating Ca2+ wave that leads to glial activation and concomitant neurotransmitter release, and subsequent neuromodulation (excitation/inhibition)
Okun, 2012
Deep Brain Stimulation Results in Local Glutamate and Adenosine Release: Investigation Into the Role of Astrocytes
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- Smarter DBS (Scheduled and Responsive DBS)
The number and nature of emergency department encounters in patients with deep brain stimulators

Andrew S. Resnick · Kelly D. Foote · Ramon L. Rodriguez · Irene A. Malaty · Joel L. Moll · Donna L. Carden · Nolte E. Krock · Matthew M. Medley · Adam Burdick · Ihtsham U. Haq · Michael S. Okun

“Bionic Age”
215 Patients in Cohort
25.6% Presented to ER
23% DBS Related

Table 3  Breakdown of complications in DBS patients presenting to the emergency department

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total ED visits by patients</th>
<th>Headache</th>
<th>Mental Status</th>
<th>Local Infection</th>
<th>Infection with Hardware Removal</th>
<th>Non-DBS Fever related infection</th>
<th>Pain</th>
<th>Full</th>
<th>Fracture</th>
<th>MI</th>
<th>Hallucinations</th>
<th>Syncope</th>
<th>Swelling</th>
<th>Panic Attack</th>
<th>Tube (e.g., PEG)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>51</td>
<td>5 (9.8%)</td>
<td>10 (19.6%)</td>
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<tr>
<td>Essential tremor</td>
<td>11</td>
<td>1 (9.1%)</td>
<td>2 (18.2%)</td>
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<td>2 (18.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td>23</td>
<td>12 (52.1%)</td>
<td>1 (4.4%)</td>
<td>3 (13%)</td>
<td>1 (4.4%)</td>
<td>1 (4.4%)</td>
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<td>0 (0%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (MS, OCD, other tremors)</td>
<td>1</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<td>0 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>19 (22.1%)</td>
<td>13 (15.1%)</td>
<td>12 (13.9%)</td>
<td>3 (3.5%)</td>
<td>8 (9.3%)</td>
<td>1 (1.2%)</td>
<td>9 (10.5%)</td>
<td>4 (4.6%)</td>
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This chart represents the complications experienced by patients as they arrived at the ED, including non-DBS related infections (e.g., cellulitis, extremity, but not device related).
**What** operation should be performed?
Brain target(s), unilateral vs. bilateral, simultaneous vs. staged

**When** to operate?
How early is too early to intervene?

**Who** should be operated?
Disease duration, age, symptom profiles and the use of the interdisciplinary screening team

**Why** to operate?
The argument for tailoring
Consider Your DBS Candidates in Three Groups
What about Tremors, Tourette, OCD, Dystonia, Depression, Ataxia, HD?
Figure 1. University of Florida (FL, USA) interdisciplinary work-up and discussion for a patient referred for deep brain stimulation surgery.

OT: Occupational therapy; PT: Physical therapy; SCID: Severe combined immunodeficiency; TRS: Tremor rating scale; UDRS/BFMDRS: Unified Dystonia Rating Scale and Burke-Fahn Marsden Dystonia Rating Scale; UPDRS: Unified Parkinson’s Disease Rating Scale.
There is an Appropriate Time for Medications vs. DBS

Enough Is Enough

Moving on to Deep Brain Stimulation in Patients With Fluctuating Parkinson Disease

The increasing use of deep brain stimulation (DBS) therapy for the treatment of Parkinson disease (PD) during the past 2 decades has captured the attention of both the medical and lay communities and has resulted in appropriately increased scrutiny of the procedure and its outcomes. We have been awed and inspired by patients with moderate to advanced PD who have emerged from surgery markedly less disabled—literally transformed before our eyes. Unfortunately, we have also been challenged by patients who have undergone the surgery with results falling short of expectations, a group now referred to as DBS failures. However, the field has thoughtfully responded and examined the characteristics that seem to make a patient with PD a favorable or unfavorable surgical candidate. We now know that DBS surgery, as it is currently performed, may be appropriate for only 10% to 20% of the population with PD. We have learned that only symptoms that preoperatively respond to levodopa tend to respond to DBS and that DBS has, above all, been proven to be a powerful therapy for on-off fluctuators and those with disabling...
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Don’t ask what target...
Don’t ask what target... 
Ask why
Cognition and Mood in Parkinson’s Disease in Subthalamic Nucleus versus Globus Pallidus Interna Deep Brain Stimulation: The COMPARE Trial

Michael S. Okun, MD, Hubert H. Fernandez, MD, Samuel S. Wu, PhD, Lindsey Kirsch-Darrow, MS, Dawn Bowers, PhD, Frank Bova, PhD, Michele Suetter, BS, Charles E. Jacobson IV, BS, Xinpeng Wang, PhD, Clifford W. Gordon, Jr., BS, Pam Zeilman, ARNP, Janet Romrell, PA-C, Pam Martin, RN, Herbert Ward, MD, Ramon L. Rodriguez, MD, and Kelly D. Foote, MD

Pallidal versus Subthalamic Deep-Brain Stimulation for Parkinson’s Disease


Unilateral

Saturday, October 6, 12
Cognition and Mood in Parkinson’s Disease in Subthalamic Nucleus versus Globus Pallidus Interna Deep Brain Stimulation: The COMPARE Trial

Michael S. Okun, MD, Hubert H. Fernandez, MD, Samuel S. Wu, PhD, Lindsey Kirsch-Darrow, MS, Dawn Bowers, PhD, Frank Bova, PhD, Michele Suelter, BS, Charles E. Jacobson IV, BS, Xinpeng Wang, PhD, Clifford W. Gordon, Jr., BS, Pam Zeilman, ARNP, Janet Romrell, PA-C, Pam Martin, RN, Herbert Ward, MD, Ramon L. Rodriguez, MD, and Kelly D. Foote, MD
DV\textsubscript{s}:
1) Total volume of tissue activated (VTA)
2) VTA inside STN
3) VTA outside STN
4) Proportion volume overlap with STN (PVO-STN)
For both the STN and GPi groups:

Patients rated themselves as more “confused” \((p=0.04)\), less “energetic” \((p=0.01)\), less “happy” \((p=0.03)\), and more “sad” \((p=0.05)\)…when stimulation was delivered \textit{ventral} to the \textit{optimal} stimulation site.

In addition, patients were less “energetic” at \textit{dorsal DBS} \((p=0.02)\) and “off” DBS \((p=0.01)\) when compared with the optimal DBS setting.

In addition, patients who received stimulation on the \textit{left side} were significantly less “tired” than those who received stimulation on the right \((p=0.01)\).
Correlation analysis revealed that stimulation dorsal to and outside of the STN, as well as ventrally within the STN was negatively related to verbal fluency performance.

Mikos. et.al.

**STN Outcomes Change When Shifting Stimulation**

GPI Did Not

Negative fluency change values indicate lower than predicted scores obtained with stimulation relative to OFF stimulation, and positive values indicate higher than predicted scores.

**Title:** Stimulation region within the globus pallidus does not affect verbal fluency performance.

**Authors:** Jenna Dietz¹, Angela M. Noecker², Cameron C. McIntyre², Dawn Bowers¹,³, Kelly D. Foote³, Michael S. Okun³
It matters where the stimulation is delivered
Randomized DBS trials should not to be interpreted as yes or no.

Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus.

Laura B. Zahodne · Michael S. Okun · Kelly D. Foote · Hubert H. Fernandez · Ramon L. Rodriguez · Samuel S. Wu · Lindsey Kirsch-Darrow · Charles E. Jacobson IV · Christian Rosado · Dawn Bowers
STN had more balance issues than GPI
STN=GPi Motor Responses
STN more cognitive issues
**STN- more medication reduction**
GPi better flexibility in medication adjustment
DDS and ICD- target unknown
• 28 patients met diagnostic criteria for ICD or DDS
• No change in DDS diagnosis after unilateral or bilateral stimulation
• 2 new cases DDS
• ICD resolved in 2 of 7
• Post-operatively ICD developed in 17 patients
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Before Surgery

After Surgery

Saturday, October 6, 12
GFAP = magenta
lba1 = cyan
Cell nuclei = yellow
SOX2
Stem/Progenitors
Human 3rd Ventricle
Red is RBC Artifact

Cellular Changes in Human PD DBS Brains
Vedam-Mai, et. al.
Neurogenic Hippocampal Targets of Deep Brain Stimulation

Juan M. Encinas,1 Clement Hamani,2 Andres M. Lozano,2 and Grigori Enikolopov1*

1Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724
2Division of Neurosurgery, Toronto Western Hospital, Toronto, Ontario, M5T 2S8 Canada
Vagus Nerve Stimulation and Tinnitus
Lessons from Electrical Stimulation

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- DBS Failures
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Surgical Effect?

Akin, Morishita, Rhoton, Okun-
National DBS Brain Bank
Stimulation Effect

McIntyre and Noecker, Cleveland Clinic
Subthalamic deep brain stimulation with a constant-current device in Parkinson’s disease: an open-label randomised controlled trial

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Management of Referred Deep Brain Stimulation Failures

A Retrospective Analysis From 2 Movement Disorders Centers

Michael S. Okun, MD; Michele Tagliati, MD; Michael Pourfar, MD; Hubert H. Fernandez, MD; Ramon L. Rodriguez, MD; Ronald L. Alterman, MD; Kelly D. Foote, MD
Figure 2. Examples of preventable “deep brain stimulation failures” (n=events) in this study. Improvements in triage, screening, operative procedure, and follow-up programming and medication changes may have eliminated the issues identified in the 41 patients in this study.
When There are Problems: Troubleshoot
Even Expert Centers Can Miss-
Targets are Very Small

Reoperation for Suboptimal Outcomes after Deep Brain Stimulation Surgery

OBJECTIVE: To examine a case series of reoperations for deep brain stimulation (DBS) leads in which clinical scenario revealed suboptimal outcomes from a previous operation. Suboptimally placed DBS leads are not a potential predictor for unsatisfactory results after surgery for Parkinson’s disease (PD), essential tremor (ET), or dystonia. In a previous study of patients who experienced suboptimal results, 19 of 41 patients had misplaced leads. Similarly, another report commented that lead placement beyond a 2-10.3 mm window resulted in inadequate clinical benefit, and, in 1 patient, revision improved outcomes. The goal of the current study was to perform an unblinded retrospective chart review of 1295 patients with unsatisfactory outcomes who presented for reoperation.

METHODS: Patients who had DBS lead replacements after reoperation were assessed with the use of a retrospective review of an institutional review board-approved treatment database. Data points included age, disease duration, diagnosis, motor outcomes (Unified Parkinson’s Disease Rating Scale III in PD, the Tremor Rating Scale in ET, and the Unified Dystonia Rating Scale in dystonia), quality of life (Hoehn and Yahr’s Disease Questionnaire-39 in PD), and the Clinician Global Impression Scale. Data from before and after reoperation were examined to determine the estimated impact of repeat surgery.

RESULTS: There were 11 patients with PD, 7 with ET, and 4 with dystonia. The average age of the PD group was 52 years; the disease duration was 10 years, and the average vector distance of the location of the active (DBS) contact was adjusted 5.6 mm, 5.8 patients (54%) with PD had preoperative of medication on DBS ratings scores. The average improvement across this group of patients was 24.3%. The Parkin’s Disease Questionnaire-39 improved in the area of mobility 22.1 (14.6-29.5), activities of daily living (14.2-28.2), stigma (17.1-21.6), and dyskinesia decreases in 2.0 (1.2-2.8). The average age of the ET group was 66 years, with the disease duration was 9 years, and the average adjusted distance was 6.1 mm. Five ET patients (83.3%) in the cohort had a prereplacement on DBS Tremor Rating Scale and a postreplacement on DBS Tremor Rating Scale with the average improvement of 49.6%. The average age of the dystonia group was 39 years, the average disease duration was 7 years, and the average adjusted lead distance was 6.7 mm. Three patients (75%) with dystonia had prereplacement on DBS Unified Dystonia Rating Scale and postreplacement on DBS Unified Dystonia Rating Scale scores. Across these 3 diseases (2 PD, 1 dystonia), the improvement was 12.8%. Clinician Global Impression scale scores (0, very much improved; 1, much improved; 2,-minimally improved; 3: no change; 4, minimally worsened; 5, much worsened) after replacement revealed the following results in patients with PD: 1.7 patients (2.3 patients; 5.1 patients), with ET (1), and patients with dystonia (1). Patients 2.2 patients; 3, 1 patients; and with dystonia (1.1 patients; 2, 1 patients; 3, 1 patients). The latency from original lead placement to reoperation (replacement/revision) overall was 29.5 months (range 2-104 mos), however, 10 patients referred from outside institutions (n = 11 patients). The latency was an average of 10 months (range 2-80 mos). The most common clinical history was failure to achieve a perceived outcome; however, history of an asymmetric benefit was present in 4 (14.2%) of 22 patients, and lead migration was present in 1 (1.3%) of 22 patients.

CONCLUSION: There are many potential causes of suboptimal benefit after DBS. Temporal identification of suboptimal lead placements followed by reoperation and lead placement in a subset of patients may improve outcomes.

KEYWORDS: Complications, Deep brain stimulation, Dystonia, Essential tremor, Lead, Parkinson’s disease, Replacement, Reoperation.
Take a Picture After the Operation
There are Complications Even at the Expert Centers
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Tolerance, Disease Progression and a Smarter Approach

Worsening essential tremor following deep brain stimulation: disease progression versus tolerance

Christopher G. Favilla,¹ David Ullman,¹ Aparna Wagle Shukla,¹ Kelly D. Foote,² Charles E. Jacobson IV¹ and Michael S. Okun¹,²
Figure 2  Secondary tremor progression. (A) A total of six patients experienced secondary tremor progression (progression of tremor rating scale off score), but demonstrated sustained benefit of stimulation. (A) Represents the mean values of these six subjects. (B) Only one patient experienced secondary tremor progression with diminished benefit of stimulation at 36 months (decrease in difference between tremor score on stimulation and off stimulation).
31 year old woman from Davenport, Iowa
“I was living with Obsessive Compulsive Disorder for 13 years which became increasingly worse after my daughter was born. Eventually I was unable to leave my home for over a year because I felt the outside was contaminated. My days were spent showering, cleaning and nights were consumed with obsessive dreams of being contaminated. My life was over”
Obsessed with germs and contamination
Rob Stein wrote in July 2004

“Today, her obsessive thoughts have quieted.”
Deep Brain Stimulation for Intractable Obsessive Compulsive Disorder: Pilot Study Using a Blinded, Staggered-Onset Design

Wayne K. C. and Nathan A. Ward,
Will There be “Smart DBS?”

Scheduled and Responsive Approaches

Using Neurophysiology in “Real Time”
Assessed for Eligibility  
(n=9)

Excluded  
(n=4)
Did not meet inclusion criteria  
(n=1)
Refused to participate  
(n=1)
Other reasons  
(n=2)

Randomized  
(n=5)

Allocated to DBS Activation at Day 30  
(n=2)
Received allocated intervention  
(n=2)

Allocated to DBS Activation at Day 60  
(n=3)
Received allocated intervention  
(n=3)

Monthly for 6 months
Lost to Followup  
(n=0)
Discontinued Intervention  
(n=0)

Monthly for 6 months
Lost to Followup  
(n=0)
Discontinued Intervention  
(n=0)

Analyzed  
(n=5)
1) Safety analysis (n=5)
2) Immediate (n=2) vs Delayed Activation (n=3) for differences at Days 60 and 90
3) Pre-op vs. 6 months (n=5)
4) Continuous vs. scheduled vs. off experiment at 6 months (n=5)
<table>
<thead>
<tr>
<th>Implant Number</th>
<th>Sex</th>
<th>Age</th>
<th>Disease Duration</th>
<th>Common Tics</th>
<th>Behavioral Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1</td>
<td>F</td>
<td>34</td>
<td>26</td>
<td>Head jerks, limb-jerking, slapping/hitting self and hitting nearby objects, abdominal-lensing, coprolalia</td>
<td>OCD moderate and chronic</td>
</tr>
<tr>
<td>TS2</td>
<td>M</td>
<td>37</td>
<td>34</td>
<td>Eye-rolling, rotating wrists and shoulders, cracking joints, hitting nearby objects, vomiting</td>
<td>ADHD hyperactive and impulsive, stable and secondary substance dependency, OCD traits</td>
</tr>
<tr>
<td>TS3</td>
<td>M</td>
<td>28</td>
<td>20</td>
<td>Face-scrunching, arm jerks, head twists, bending at the waist, copropraxia, squawking, grunting, sniffing</td>
<td>OCD, moderate and chronic</td>
</tr>
<tr>
<td>TS4</td>
<td>F</td>
<td>39</td>
<td>37</td>
<td>Eye-rolling, jaw cracking, head twists, fingertip tapping, hits with elbow, copropraxia, growling, coprolalia</td>
<td>OCD mild to moderate and chronic, PTSD mild and chronic (resolved at time of DBS)</td>
</tr>
<tr>
<td>TS5</td>
<td>F</td>
<td>36</td>
<td>27</td>
<td>Fingertip waving, grimacing, eye-rolling, echolalia, yelling, growling</td>
<td>OCD current moderate and chronic, PTSD (past resolved), MDD (past resolved)</td>
</tr>
</tbody>
</table>

Components from this table have been reproduced with permission from Okun (Archives of Neurology Express, 2012) and have been published with the original NIH supported FDA clinical trial (clinicaltrials.gov).
B

Screening
5/9 met inclusion criteria

Surgery
5/5 received bilateral CM DBS implant

6 Months of Follow-up
4/5 completed monthly programming visits for 6 months following surgery.
1/5 had battery failure following month 4

Long Term Assessment
Visits at month 12 and every 6 months thereafter are planned for the duration of study
Tailored DBS
Dual/Multiple Leads
Specific Symptoms
Imaging/How we do it
Improvements Hardware
Scheduled/Responsive Stimulation
Collectively Lead to More Rational Approaches to Programming (neurophysiology)
The Horizon is Moving

Depression

Cluster Headache

Obesity

Coma
Appendix

• Extra Slides and References


"Bionic Age"

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25.6% Presented to ER
23% DBS Related

---

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<th>Hallucinations</th>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Dystonia</td>
<td>23</td>
<td>12 (52.1%)</td>
<td>1 (4.4%)</td>
<td>3 (13%)</td>
<td>1 (4.4%)</td>
<td>1 (4.4%)</td>
<td>1 (4.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (4.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Other (MS, OCD, other tremor)</td>
<td>1</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>19 (22.1%)</td>
<td>13 (15.1%)</td>
<td>12 (13.9%)</td>
<td>3 (3.5%)</td>
<td>8 (9.3%)</td>
<td>1 (1.2%)</td>
<td>9 (10.5%)</td>
<td>4 (4.6%)</td>
<td>8 (9.3%)</td>
<td>1 (1.2%)</td>
<td>2 (2.3%)</td>
<td>2 (2.3%)</td>
<td>4 (4.6%)</td>
<td>100%</td>
</tr>
</tbody>
</table>

This chart represents the complications experienced by patients as they arrived at the ED, including non-DBS related infections (e.g. cellulitis, extremitis, but not device related).
There are important questions facing the DBS field
Why Tailor DBS?

• Important patient relevant issues may impact outcome
• Motor
• Mood/Cognition
• Quality of Life
Why should we consider tailoring therapies?

We have the tools to make a difference:

1- surgical approaches,
2- imaging,
3- physiology,
4- clinical outcomes,
5- field modeling,
6- combinations
Question #1
Lesion Effects or Stimulation Induced
Does it matter where we deliver stimulation?
Cognition and Mood in Parkinson’s Disease in Subthalmic Nucleus versus Globus Pallidus Interna Deep Brain Stimulation: The COMPARE Trial

Michael S. Okun, MD, Hubert H. Fernandez, MD, Samuel S. Wu, PhD, Lindsey Kirsch-Darrow, MS, Dawn Bowers, PhD, Frank Bova, PhD, Michele Suetler, BS, Charles E. Jacobson IV, BS, Xiping Wang, PhD, Clifford W. Gordon, Jr., BS, Pam Zeilman, ARNP, Janet Romrell, PA-C, Pam Martin, RN, Herbert Ward, MD, Ramon L. Rodriguez, MD, and Kelly D. Foote, MD
62 Parkinson Subjects

Baseline Pre-operative Evaluations

Randomized

STN DBS n=26

GPI DBS n=26

STN DBS n=22

GPI DBS n=23

DBS and Medication Optimization Period

Maintenance Period (Minimum 30 days)

Planned 2 Day Admission at 6 months

OFF DBS

OPTIMAL DBS

DORSAL DBS

VENTRAL DBS

Screen Failures n=10

n=5 Chose not to have DBS

n=3 Met inclusion criteria but failed interdisciplinary evaluation

n=2 Failed inclusion/exclusion criterion

Failed to Complete n=7

STN n=4

n=2 Unable to tolerate protocol

n=1 Pneumonia/Death

n=1 Symptomatic hemorrhage

GPI n=3

n=2 Discomfort off medication

n=1 Symptomatic hemorrhage
Stimulation? Patient-specific models of DBS

DVs:
1) Total volume of tissue activated (VTA)
2) VTA inside STN
3) VTA outside STN
4) Proportion volume overlap with STN (PVO-STN)
For both the STN and GPi groups: Patients rated themselves as more “confused” ($p=0.04$), less “energetic” ($p=0.01$), less “happy” ($p=0.03$), and more “sad” ($p=0.05$) when stimulation was delivered ventral to the optimal stimulation site.

In addition, patients were less “energetic” at dorsal DBS ($p=0.02$) and “off” DBS ($p=0.01$) when compared with the optimal DBS setting.

In addition, patients who received stimulation on the left side were significantly less “tired” than those who received stimulation on the right ($p=0.01$).
It matters where the stimulation is delivered
What domains should we measure for DBS outcomes?
DBS Outcome

- **Motor Improvement**  
  Weaver, et al., 2005; Boucai, et al., 2004
  - UPDRS-III reduction: 40%-Gpi & 54%-STN
  - Anti-PD medications reduction with STN surgery

- **Cognitive Decline**  
  Parsons et al., 2006; Tir et al., 2007
  - Verbal fluency
  - Reports on other abilities vary

- **Mood changes**  
  Takeshita, et al., 2005; Appleby, et al., 2007
  - On average, small reduction in depression
  - Subset of patients with increased depression, suicidality, mania, hypomania
Hold Your Horses: Impulsivity, Deep Brain Stimulation, and Medication in Parkinsonism

Michael J. Frank, Johan Samanta, Ahmed A. Moustafa, Scott J. Sherman

Deep brain stimulation (DBS) of the subthalamic nucleus markedly improves the motor symptoms of Parkinson’s disease, but causes cognitive side effects such as impulsivity. We showed that DBS selectively interferes with the normal ability to slow down when faced with decision conflict. While on DBS, patients actually sped up their decisions under high-conflict conditions. This form of impulsivity was not affected by dopaminergic medication status. Instead, medication impaired patients’ ability to learn from negative decision outcomes. These findings implicate independent mechanisms leading to impulsivity in treated Parkinson’s patients and were predicted by a single neurocomputational model of the basal ganglia.

Original Article

Stimulation of the subthalamic nucleus and impulsivity: Release your horses†

Benedicte Ballanger, PhD 1 2, Thilo van Eimeren, MD 1 2, Elena Moro, MD, PhD 3, Andres M. Lozano, MD, PhD 1 4, Clement Hamani, MD 1 4, Philippe Boulinguez, PhD 5, Giovanna Pellecchia, PhD 2, Sylvain Houle, MD, PhD 2, Yu Yan Poon, RN 3, Anthony E. Lang, MD 1 3, Antonio P. Strafella, MD, PhD 1 2 3 *

1 Division of Brain, Imaging and Behaviour-Systems Neuroscience, Toronto Western Research Institute, University Health Network, University of Toronto, Toronto, Ontario, Canada
2 PET Imaging Centre, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada
3 Movement Disorders Center, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada
4 Department of Neurosurgery, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada
5 Center for Cognitive Neuroscience, Claude Bernard University, Lyon, France

†Correspondence to Antonio P. Strafella (antonio.strafella@uhnres.utoronto.ca or antonio.strafella@camhpet.ca)
Delayed Dopamine Withdrawal
Apathy
Depression
Anxiety
* Dopamine Denervation
Sorting out Verbal Fluency Deficits Resulting from Deep Brain Stimulation for Parkinson Disease
Reliable Change Index (RCI)

Theoretical Findings Before & After DBS

Decline in DBS group due to?
- Small amount of decline in most Ss?
- Large decline in subset of Ss?

Reliable Change Index (RCI)
- Computes confidence interval around expected post-test changes derived from control group
- Takes into account imprecision of measurement; practice effects
- Derive statistical significance of individual changes

FORMULA
RCI = ±1.645 * SE_{DIFF}
SE_{DIFF} = \sqrt{(SE_{M}(Time 1)^2 + SE_{M}(Time 2)^2)}
Surgical Effect?

Akin, Morishita, Rhoton, Okun-
National DBS Brain Bank
Stimulation Effect

McIntyre and Noecker, Cleveland Clinic
Pre-post (surgery) comparison

Letter Fluency

Animal Fluency

Group \times Testing Session Interaction:

- **Letter Fluency**
  - Group X Testing Session Interaction:
    - F(1, 50)=4.836, p=0.033, $\eta^2=0.088$, power=0.578

- **Animal Fluency**
  - Group X Testing Session Interaction:
    - F(1, 50)=3.742, p=0.059, $\eta^2=0.070$, power=0.475
**ON/OFF (stimulation) comparison**

**Letter Fluency**

Group Effect:

\[ F(1, 50) = 10.0, \ p = 0.003, \ \eta^2 = 0.167, \ \text{power} = 0.873 \]

Remain significant when controlling for disease duration.

---

**Semantic Fluency**

Group Effect:

\[ F(1, 49) = 4.619, \ p = 0.037, \ \eta^2 = 0.086, \ \text{power} = 0.558 \]

Zahodne et al.
Patient-specific models of DBS for 2 patients.

**Thalamus**
- STN
- VTA

**DV's:**
- Total VTA
- VTA inside STN
- VTA outside STN
- Proportion volume overlap w/STN (PVO-STN)

**Contact Areas:**
- Dorsal contact
- Optimal contact
- Ventral contact

Saturday, October 6, 12
Correlation analysis revealed that stimulation dorsal to and outside of the STN, as well as ventrally within the STN was negatively related to verbal fluency performance.

Negative fluency change values indicate lower than predicted scores obtained with stimulation relative to OFF stimulation, and positive values indicate higher than predicted scores.

Mikos, NeuroImage, 2009
Question #6

Are we missing important outcomes of DBS?
Do PD Patient’s Get Angry Post-DBS?

Aggressive behavior induced by intraoperative stimulation in the triangle of Sano

B.P. Bejjani, MD; J.L. Houeto, MD; M. Hariz, MD, PhD; J. Yelnik, MD; V. Mesnage, MD; A.M. Bonnet, MD; B. Pidoux, MD; D. Dormont, MD; P. Cornu, MD; and Y. Agid, MD, PhD

Explosive-aggressive behavior related to bilateral subthalamic stimulation

M. Sensi\textsuperscript{a,b,*}, R. Eleopra\textsuperscript{a}, M.A. Cavallo\textsuperscript{a}, E. Sette\textsuperscript{a}, P. Milani\textsuperscript{a}, R. Quatrale\textsuperscript{a}, J.G. Capone\textsuperscript{a}, V. Tognoli\textsuperscript{a}, M.R. Tola\textsuperscript{a}, E. Granieri\textsuperscript{a}, P.G. Data\textsuperscript{b}

Burdick, et. al.
Do patient's get angrier following STN, GPI, and thalamic deep brain stimulation

Adam P. Burdick a, Kelly D. Foote a, Samuel Wu e, Dawn Bowers c, Pam Zeilman b, Charles E. Jacobson b, Herbert E. Ward d, Michael S. Okun a,b,⁎

a University of Florida Movement Disorders Center, Department of Neurosurgery, Gainesville, FL, USA
b University of Florida Movement Disorders Center, Department of Neurology, Gainesville, FL, USA
c University of Florida, Movement Disorders Center, Department of Clinical and Health Psychology, Gainesville, FL, USA
d University of Florida, Movement Disorders Center, Department of Psychiatry, Gainesville, FL, USA
⁎ University of Florida, Department of Epidemiology and Health Policy Research, FL, USA
• **N = 322 operations**
  • **STN = 195**
  • **Vim = 71**
  • **GPi = 56**

• **Parkinson’s Disease**
  • **STN (subthalamic nucleus) and GPi (globus pallidus interna)**
Only the VAMS Angry Score Was Different Between Groups
STN and GPi Angrier

<table>
<thead>
<tr>
<th>Change (Post - Baseline)</th>
<th>All Surgeries</th>
<th>GPI</th>
<th>STN</th>
<th>Vim</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI Score</td>
<td>-3.57 (6.61)</td>
<td>-3.8 (5.97)</td>
<td>-4 (7.37)</td>
<td>-2.25 (4.86)</td>
<td>0.134</td>
</tr>
<tr>
<td>VAM Afraid</td>
<td>-4.41 (18.42)</td>
<td>-3.34 (16.59)</td>
<td>-4.61 (20.76)</td>
<td>-4.92 (11.54)</td>
<td>0.498</td>
</tr>
<tr>
<td>VAM Confused</td>
<td>0.46 (12.95)</td>
<td>2.11 (12.97)</td>
<td>0.18 (14.21)</td>
<td>-0.37 (8.01)</td>
<td>0.326</td>
</tr>
<tr>
<td>VAM Sad</td>
<td>-1.29 (15.31)</td>
<td>-0.13 (11.81)</td>
<td>-0.2 (14.82)</td>
<td>-5.81 (18.97)</td>
<td>0.851</td>
</tr>
<tr>
<td>VAM Angry</td>
<td>3.14 (13.26)</td>
<td>2.38 (9.53)</td>
<td>4.82 (14.52)</td>
<td>-1.17 (11.51)</td>
<td>0.012</td>
</tr>
<tr>
<td>VAM Energetic</td>
<td>2.05 (14.9)</td>
<td>3.19 (13.9)</td>
<td>1.98 (14.27)</td>
<td>1.12 (17.71)</td>
<td>0.519</td>
</tr>
<tr>
<td>VAM Tired</td>
<td>-4.76 (14.22)</td>
<td>-4.94 (12.99)</td>
<td>-5.91 (14.49)</td>
<td>-1.12 (14.26)</td>
<td>0.065</td>
</tr>
<tr>
<td>VAM Happy</td>
<td>5.56 (15.53)</td>
<td>7.51 (14.93)</td>
<td>4.61 (15.6)</td>
<td>6.42 (15.99)</td>
<td>0.460</td>
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<tr>
<td>VAM Tense</td>
<td>-10.16 (18.37)</td>
<td>-12.89 (19.35)</td>
<td>-8.63 (18.48)</td>
<td>-12 (16.8)</td>
<td>0.365</td>
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</table>
Table 3. Estimates of Parameters

<table>
<thead>
<tr>
<th>Dependent</th>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>VAM Anger Change</td>
<td>Surgery Side</td>
<td>Left</td>
<td>-1.89</td>
<td>1.98</td>
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<td></td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Handedness</td>
<td>Left</td>
<td>4.60</td>
<td>3.47</td>
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<tr>
<td></td>
<td>Right</td>
<td></td>
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<tr>
<td></td>
<td>Gender</td>
<td>F</td>
<td>-1.68</td>
<td>2.18</td>
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<tr>
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<td>M</td>
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<td></td>
<td>Ethnicity</td>
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<td>0.73</td>
<td>9.95</td>
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<td>1</td>
<td>-2.39</td>
<td>14.58</td>
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<td></td>
<td></td>
<td>2</td>
<td>0.38</td>
<td>10.33</td>
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<tr>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Target</td>
<td>GPI</td>
<td>8.21</td>
<td>3.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STN</td>
<td>11.67</td>
<td>3.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vim</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Education (Years)</td>
<td></td>
<td>0.05</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>Years With Symptoms</td>
<td></td>
<td>0.24</td>
<td>0.11</td>
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<tr>
<td></td>
<td>Age at Surgery</td>
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<td>-0.07</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>MMSE</td>
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<td>-0.44</td>
<td>0.74</td>
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<td></td>
<td>DRS Total Raw</td>
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<td>-0.27</td>
<td>0.19</td>
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<tr>
<td></td>
<td>Baseline Medical Off Motor Score</td>
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<td>-0.08</td>
<td>0.10</td>
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<tr>
<td></td>
<td>Baseline BDI Score</td>
<td></td>
<td>-0.09</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Years with Symptoms - Most Important Variable
p=.002

Microelectrode Recording and Anger (p= 0.014)
Anger score increased 2.29 units per microelectrode pass
Question #7

Should I do Unilateral or Bilateral DBS

- Simultaneous versus Staged
n = 73 UF patients
A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort

Clinical article

HOUTAN A. TABA, B.S.,¹ SAMUEL S. WU, PH.D.,² KELLY D. FOOTE, M.D.,² CHRIS J. HASS, PH.D.,¹ HUBERT H. FERNANDEZ, M.D.,¹ IRENE A. MALATY, M.D.,¹ RAMON L. RODRIGUEZ, M.D.,¹ YUNFENG DAI, M.S.,³ PAMELA R. ZEILMAN, A.R.N.P.,¹ CHARLES E. JACOBSON IV, B.S.,¹ AND MICHAEL S. OKUN, M.D.¹

Departments of ¹Neurology and ²Neurosurgery, University of Florida Movement Disorders Center; and ³Division of Biostatistics, College of Medicine, University of Florida, Gainesville, Florida
• Twenty-one patients out of the 44 (47%) in the cohort remained unilateral (3.5 years)

• **Second lead**- Higher baseline UPDRS III motor and ipsilateral UPDRS III scores,

• **Second lead**- Lower asymmetric index

• The odds of proceeding to bilateral DBS was 5.2 times higher for STN than for GPi
Question #8
What Factors should I consider in Simultaneous versus Staged DBS?

Age

Post-op confusion/AE’s

Safety issues

Tolerability issues

Brain shift issues

How accurately can you place two leads in one OR sitting
Question #9

How do I Think Through Tailoring DBS?
<table>
<thead>
<tr>
<th>Criterion</th>
<th>STN</th>
<th>GPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td></td>
<td></td>
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<tr>
<td>Bradykinesia</td>
<td></td>
<td></td>
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<tr>
<td>Gait/Postural Instability</td>
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<tr>
<td>Dyskinesia</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
<td></td>
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<tr>
<td>Surgical Morbidity</td>
<td></td>
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<tr>
<td>Medication Reduction</td>
<td></td>
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<tr>
<td>Battery Consumption</td>
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</table>
Choose a Target and Uni/Bilateral

Table 1. Pre-operative Target Selection Issue Important to Maximizing Benefit

<table>
<thead>
<tr>
<th>Pre-operative Symptom/Issue/Indication</th>
<th>Bilateral STN DBS</th>
<th>Bilateral GPI DBS</th>
<th>Unilateral STN DBS</th>
<th>Unilateral GPI DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral Tremor</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Bilateral Rigidity</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Bilateral Bradykinesia</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Unilateral Tremor</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Unilateral Rigidity</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Unilateral Bradykinesia</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Unilateral Dyskinesia</td>
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<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Unilateral Dyskinesia</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Bilateral Dyskinesia</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Bilateral Dyskinesia</td>
<td>✗</td>
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<td>Levodopa Responsive Gait Issue</td>
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<td>Levodopa Responsive Balance Issue</td>
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<tr>
<td>Need for Medication Reduction</td>
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<td>Need for Potential Medication Increase</td>
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<tr>
<td>Desires Quality of Life Improvement</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Patient Desires Only One Sided Operation</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Highly Asymmetric Motor Symptoms</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Legend:
- Reasonable option
- * Potentially More Desirable Option
- - Undesirable Option
- ? Suspected Possibly Better but Need More Data

To Maximize Benefit
Choose a Target and Unilateral/Bilateral

Table 2. Pre-operative Target Selection Issue Important to Minimizing Risk

<table>
<thead>
<tr>
<th>Pre-operative Symptom/Issue/Indication</th>
<th>Bilateral STN DBS</th>
<th>Bilateral GPI DBS</th>
<th>Unilateral STN DBS</th>
<th>Unilateral GPI DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worried About Hypophonia</td>
<td>-</td>
<td>-</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Worried About Verbal Fluency</td>
<td>-</td>
<td>-</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Worried About Dysarthria</td>
<td>-</td>
<td>-</td>
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<td>*</td>
</tr>
<tr>
<td>Swallowing/Aspiration Issue</td>
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<tr>
<td>Levodopa Unresponsive Gait Issue</td>
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<tr>
<td>Levodopa Unresponsive Balance Issue</td>
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<tr>
<td>Cognitive Issue</td>
<td>-</td>
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<td>*</td>
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<tr>
<td>Mood Issue/Disorder</td>
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<tr>
<td>Dopamine Dysregulation</td>
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<tr>
<td>Impulse Control Disorder</td>
<td>*</td>
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<tr>
<td>Age Greater than 69 years</td>
<td>*</td>
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<tr>
<td>Significant Medical Comorbidity</td>
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<tr>
<td>Desires Less Weight Gain</td>
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<td>*</td>
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<tr>
<td>Desires Less Frequent Battery Changes</td>
<td>-</td>
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</tbody>
</table>

Legend:
- Reasonable option
* Potentially More Desirable Option
- Undesirable Option
? Suspected Possibly Better but Need More Data

To Minimize Risk
Question #10

What about tailoring for other indications and other targets beyond simple PD?
What about the future of STN DBS for Dystonia?
Subthalamic nucleus stimulation for primary dystonia and tardive dystonia

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1 Center for Functional Neurosurgery, Shanghai Jiao Tong University Ruijin Hospital, Shanghai, P.R. China
2 Division of Neurosurgery, University of California, Los Angeles, USA

The Subthalamic Nucleus in Primary Dystonia: Single-Unit Discharge Characteristics

Lauren E. Schrock, Jill L. Ostrem, Robert S. Turner, Shoichi A. Shimamoto and Philip A. Starr

1 Department of Neurology and 2 Department of Neurological Surgery, University of California, San Francisco; 3 Parkinson's Disease Research, Education, and Clinical Center, San Francisco Veterans Affairs Medical Center, San Francisco, California; and 4 Department of Neurobiology and Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, Pennsylvania

Submitted 22 June 2009; accepted in final form 15 October 2009
Are we approaching a clinical trial comparing STN vs. GPi for dystonia?

Potential Questions for the Therapy?

- More immediate effect?
- Charge densities less?
- Equal or better efficacy?
- Body Region- cervical, segmental, generalized
- Bursting/Oscillatory STN Patterns
What are the emerging targets for Tourette DBS?
Research Review

Surgery in Tourette Syndrome

Yasin Temel, MD,* and Veerle Visser-Vandewalle, MD

Department of Neurosurgery, Academic Hospital Maastricht, Maastricht, The Netherlands
What are the outcomes we should measure in Tourette DBS?

May not be enough to suppress motor and vocal tics

May be better to begin tracking non-motor features

Broaden focus to reintegration into society

*TSA International Database
COMMUNICATION

Toward closed-loop optimization of deep brain stimulation for Parkinson’s disease: concepts and lessons from a computational model

Xiao-jiang Feng1,*, Brian Greenwald1, Herschel Rabitz2, Eric Shea-Brown3,4 and Robert Kosut1

1 Department of Chemistry, Princeton University, Princeton, NJ 08544, USA
2 Courant Institute of Mathematical Sciences and Center for Neural Science, New York University, USA
3 SC Solutions, Sunnyvale, CA 94085, USA
E-mail: habitat@princeton.edu

* Bergey, GB, et.al., Implementation of an external responsive neurostimulator system (eRNS) in patients with intractable epilepsy undergoing intracranial seizure monitoring. Epilepsia Vol 43, Suppl 7, 2002
Parkinson Disease: Beta Bands for Intraoperative Placement and Post-operative Programming?

STN LFPs from one PD patient, as filtered by simulated RNS sensing hardware, are shown at top. Halfwaves detected by simulated RNS detection hardware are indicated by black vertical lines, at bottom. The abnormal beta-band oscillation is detectable before stimulation (at left, 17 qualifying half-waves per second) and its attenuation is detectable after stimulation (at right, 4.6 qualifying half-waves per second) by the RNS™ neurostimulator system. (Figures prepared with the assistance of a device engineer, Brett Wingeier)

Bronte-Stewart, Wingeier, Exp Neurology 2009
Tourette?

NIMH R34-PI Okun, Sanchez, Foote
What about using multiple DBS leads?
Horizon

Tailored DBS
Dual/Multiple Leads
Specific Symptoms
Imaging/How we do it
Improvements Hardware
Scheduled/Responsive Stimulation
Collectively Lead to More Rational Approaches to Programming (neurophysiology)
The End or the Beginning?
### A. Deep Brain Stimulation (DBS) Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UPDRS Motor</strong></td>
<td>↑40%</td>
<td>↑34%</td>
<td>↑48%</td>
</tr>
<tr>
<td><strong>Verbal Fluency</strong></td>
<td>↑2%</td>
<td>↓21%</td>
<td>↓35%</td>
</tr>
<tr>
<td><strong>Verbal Memory</strong></td>
<td>↓18%</td>
<td>↓5%</td>
<td>↑23%</td>
</tr>
</tbody>
</table>

↑ = improvement  ↓ = decline

#### Key Observations
- Response to DBS can be inconsistent.
- Even in good motor responders to DBS, neuropsychological effects are variable.

#### Questions
- Can we improve motor outcome based on PD subtype?
- Why the variability in outcomes?
B. Computational Modeling of DBS

Insight: The volume of tissue activated (VTA) is a prediction of the spread of stimulation from computational models. The accuracy of the VTA has been established in previous studies (see Approach for details).

Key Observations
- “STN DBS” can refer to a large anatomical region.
- Stimulation may spread outside the intended target area.
- The VTA can accurately predict the spread of activation in individual patients.

Questions
- Can computational models predict effects of DBS when combined with outcome data?
C. Current Application: Probabilistic Stimulation Atlas (PSA)

**Insight:** Patients stimulated in this region experienced a 50% or greater improvement in rigidity compared to DBS OFF (Butson et al, 2011).

**Insight:** Patients stimulated in this cluster experienced an average **decline** of 13% in verbal fluency compared to 1% outside this region (p<.05) despite no significant difference across cohort (see Aim 2 Preliminary Data).

**Insight:** Patients stimulated in this cluster experienced an average **improvement** of 10% in verbal memory compared to a 13% **decline** outside this region (see Aim 2 Preliminary Data).

**Key Observations**
- A PSA can provide new insights: differences in outcome can be correlated with stimulation location even if no significant difference is found across patient cohort.

**Knowledge Gap**
- Are PSA clusters a robust predictor of DBS outcome?
- How do the clusters vary with:
  - Outcome type (motor vs neuropsychiological)?
  - PD subtype (tremor vs akinetic rigid)?
  - Unilateral versus Bilateral DBS?

**Significance**
- The PSA provides a key piece of information necessary to personalize DBS treatment for individual patients.
D. Vision for Future: Personalized DBS From PSA & Patient-Specific Models

**De Novo PD DBS Patient**
- Young onset
- Occupation: attorney
- PD Subtype: akinetic rigid
- Concerns: fluency, verbal memory

**Lead Placement** Patient may receive best overall benefit from more anterior lead placement

**DBS Programming**
Patient may receive best overall benefit from contact 1, 90μsec pulse width, 2.5V, 130 Hz

**Key Observations**
- Outcomes of DBS could be predicted by targeting or avoiding certain regions.
- Such predictions could be made for de novo patients by using the PSA in combination with patient-specific models.
A New Era: Neurologists Needs to be Thinking About Psychiatric Symptoms

Pies, Psychiatric Times, March 4, 2010
Figure 1. University of Florida (FL, USA) interdisciplinary work-up and discussion for a patient referred for deep brain stimulation surgery.

OT: Occupational therapy; PT: Physical therapy; SCID: Severe combined immunodeficiency; TRS: Tremor rating scale; UDRS/BFMDRS: Unified Dystonia Rating Scale and Burke-Fahn Marsden Dystonia Rating Scale; UPDRS: Unified Parkinson’s Disease Rating Scale.
Survey of U.S. neurologists' attitudes towards deep brain stimulation for Parkinson's disease.

Shih LC, Tarsy D.

Department of Neurology, National Parkinson Foundation Center of Excellence, Harvard Medical School, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA. lshih@bidmc.harvard.edu

Abstract

OBJECTIVES: Deep brain stimulation (DBS) for Parkinson's disease (PD) was approved by the Food and Drug Administration in 2002 and has demonstrated clinical benefit in advanced PD. Our aim was to assess attitudes of U.S. neurologists towards the role of DBS in management of advanced PD.

MATERIALS AND METHODS: We sent a 40-item Internet-based survey assessing opinions regarding the role of medical and surgical therapies in managing PD to 7722 neurologists in the American Medical Association Physician MasterFile data base.

RESULTS: The response rate was low (4.2%). In total, 78 of the 298 (26%) responders self-identified as movement disorders specialists. Specialists and non-specialists had differences on a number of medical strategies used to manage PD. There were no statistically significant differences in reasons for or against referring patients for DBS, except for the number of non-specialists who agreed with referring a patient who had a "poor or absent response to levodopa" (71% vs. 16%, p < 0.001). Both groups indicated a need for more information concerning appropriate indications for DBS, adverse effects of surgery, and postoperative programming.

CONCLUSIONS: Movement disorders specialists and non-specialists were in general agreement towards the beneficial role of DBS in management of advanced PD except for whether to refer patients with poor or absent response to levodopa.

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Management of Referred Deep Brain Stimulation Failures

A Retrospective Analysis From 2 Movement Disorders Centers

Michael S. Okun, MD; Michele Tagliati, MD; Michael Pourfar, MD; Hubert H. Fernandez, MD; Ramon L. Rodriguez, MD; Ronald L. Altermann, MD; Kelly D. Foote, MD

Editorial commentary

Avoiding deep brain stimulation failures in Tourette syndrome

Michael S Okun, Hubert H Fernandez, Kelly D Foote, Tanya K Murphy, Wayne K Goodman

Author Affiliations
TSA DBS Registry
An International Database for Deep Brain Stimulation Research in Tourette Syndrome

Latest
DBS Contributor Dr. Takanobu Kaido's article in *Neuromodulation*, 01/14/2011, Deep Brain Stimulation for Tourette Syndrome: A Prospective Pilot Study in Japan
An approach to deep brain stimulation for severe treatment-refractory Tourette syndrome: the UK perspective.

Upcoming Events
June 5-9, 2011
MDS 15th International Congress of Parkinson's Disease and Movement Disorders - Toronto, ON, Canada

Monday June 6, 2011
2210 Parallel Session
Gilles de la Tourette syndrome
15:30-17:30 Chairs: Jonathan Mink, Rochester, NY, USA; Paul Sandor, Toronto, ON, Canada
15:30 The circuitry of behavioral disorders: From animal models to Tourette Syndrome - Yulia Worbe,

Basal Ganglia
Caudate nucleus
Putamen
Globus pallidus
Accumbens nucleus

Registry Progress
- December 29, 2010—Dr. Andreas Hartmann - Hopital Pitie-Salpetriere becomes a Contributor/member of the Data Sharing Committee
- December 24, 2010—Dr. Soledad Navarro - Hopital Pitie-Salpetriere becomes a Contributor/member of the Data Sharing Committee
- December 23, 2010—Dr. Carine Karachi - Hopital Pitie-Salpetriere becomes a Contributor/member of the Data Sharing Committee
- December 15, 2010—Dr. Takanobu Kaido - National Center Hospital of Neurology and Psychiatry in Japan, becomes a Contributor/member of the Data Sharing Committee
- December 15, 2010—Dr. Alberto Priori - University of Milan becomes a Contributor/member of the Data Sharing Committee
- November 10, 2010—TSA DBS Database Conference call on Registry; Dr. Yves Agid - ICM, Hopital Pitie-Salpetriere becomes a Contributor/member of the Data Sharing Committee

Tourette syndrome (TS) is a complex neurodevelopmental disorder that affects children, adolescents and adults worldwide. The condition is characterized clinically by sudden, rapid, recurrent, non-rhythmic movements and sounds called motor and vocal/phonics tics, respectively.

Deep brain stimulation (DBS), which is the electrical...