An Update on DBS Mechanisms and Technological Advances in Movement Disorders

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Disclosures

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7. National Organization for Rare Disorders
• 1930s, caudate nucleus extirpation
• Accidental ligation of anterior choroidal artery
• Introduction of stereotactic techniques targeting specific subcortical structures with millimeter based precision.
Historical aspect

• Thalamotomy and pallidotomy surgeries became established

• Introduction of levodopa therapy for treatment of Parkinson’s disease

• In 1987, high-frequency electrical stimulation to ventral intermediate (VIM) nucleus of thalamus for tremors in Parkinson’s disease.
Outline

• Historical Overview
• DBS Procedure
• DBS Results
• DBS Mechanisms
• Complications
• DBS technology
FDA position on DBS

- Essential Tremor: 1997
- Parkinson’s disease: 2002
- Dystonia: 2003
- Obsessive-compulsive disorder: 2009
- Trials are underway for depression, Tourette's syndrome, Alzheimer’s disease and chronic pain
DBS Procedure

• Selection of candidates
• Interdisciplinary evaluation
  – Neurology,
  – Neurosurgery,
  – Psychiatry,
  – Neuropsychology,
  – Speech pathology,
  – Physical therapy and
  – Occupational therapy
• Identification of target, use of imaging
Standard DBS surgery
Frameless DBS
Microelectrode recording
DBS Results
Parkinson’s disease

**Cardinal features**
- Resting tremor,
- Rigidity,
- Bradykinesia and
- Gait disturbance/postural instability

**Additional features**
- Decreased blinking,
- Masked facies,
- Micrographia,
- Flexed posture and Freezing
DBS for Parkinson’s Disease

Video 1

Video 2
Clinical efficacy in Parkinson’s disease

• Evidence from randomized controlled studies.

• 3 major trials (VA multicenter study, Quality of Life Study in Germany and UK PD Surge Trial).

• Strong evidence showing superior outcome for DBS compared with best medical management for treatment of motor fluctuations
Results

N Engl J Med 2001
Subthalamic Nucleus vs Globus Pallidus Interna Deep Brain Stimulation, the Rematch
Will Pallidal Deep Brain Stimulation Make a Triumphant Return?

Michael S. Okun, MD; Kelly D. Foote, MD
Globus pallidus interna or Subthalamic nucleus?

• VA study randomly assigned either to pallidal stimulation (152 patients) or subthalamic stimulation (147 patients).
  – Primary outcome: At 24 months, significant change in motor function.
  – Concerns: Benefits from globus pallidus interna could potentially diminish over time, however equivalent benefits seen at 36 months follow-up thus challenging previous notion.

• Netherlands study showed similar equivalent improvements.
  – Outcome: Composite of cognition, mood, and behavioral effects
COMPARE DBS study randomized Parkinson’s disease patients into unilateral STN and unilateral GPi.

48% of patients remained satisfied with unilateral surgery at 3.5 years.

Odds of remaining unilateral, significantly higher with GPi DBS.

Quality of life analysis revealed greater benefits for unilateral GPi DBS.
Early DBS or Late DBS

- Average disease duration 10 or more years, rarely DBS offered prior to 5 years
- Randomized 251 Parkinson’s disease patients with early motor complications, patients either provided neurostimulation plus medical therapy or medical therapy alone.
- Average duration of disease of 7.5 years, Motor fluctuations duration less than 2 years, average age 50s
Neurostimulation for Parkinson’s Disease with Early Motor Complications

Dystonia is a movement disorder characterized by sustained or intermittent involuntary muscle contractions causing abnormal twisting movements or postures of the affected body part(s).
Clinical efficacy in Dystonia

**Pallidal Deep-Brain Stimulation in Primary Generalized or Segmental Dystonia**

Andreas Kupsch, M.D., Reiner Benecke, M.D., Jörg Müller, M.D., Thomas Trottenberg, M.D., Gerd-Helge Schneider, M.D., Werner Poewe, M.D., Wilhelm Eisner, M.D., Alexander Wolters, M.D., Jan-Uwe Müller, M.D., Günther Deuschl, M.D., Marcus O. Pinsker, M.D., Inger Marie Skogseid, M.D., Geir Ketil Roeste, M.D., Juliane Vollmer-Haase, M.D., Angela Brentrup, M.D., Martin Krause, M.D., Volker Tronnier, M.D., Alfonso Schnitzler, M.D., Jürgen Voges, M.D., Guido Nikkhah, M.D., Ph.D., Jan Vesper, M.D., Markus Naumann, M.D., and Jens Volkmar, M.D., for the Deep-Brain Stimulation for Dystonia Study Group®

**Bilateral Deep-Brain Stimulation of the Globus Pallidus in Primary Generalized Dystonia**

Marie Vidalhuet, M.D., Ph.D., Laurent Vercueil, M.D., Jean-Luc Houeto, M.D., Ph.D., Pierre Krystkowiak, M.D., Alim-Louis Benabid, M.D., Ph.D., Philippe Cornu, M.D., Christelle Lagrange, Ph.D., Sophie Tézenas du Montcel, M.D., Ph.D., Didier Dormont, M.D., Ph.D., Sylvie Grand, M.D., Ph.D., Serge Blond, M.D., Olivier Detante, M.D., Bernard Pillon, Ph.D., Claire Ardouin, Ph.D., Yves Agid, M.D., Ph.D., Alain Destée, M.D., and Pierre Pollak, M.D., Ph.D., for the French Stimulation du Pallidum Interne dans la Dystonie (SPIODY) Study Group®
Essential tremor is most common movement disorder.

Key features:
- Postural tremor of arms
- Kinetic tremor of arms during voluntary tasks
- In severe cases can spread to other body parts or occur at rest.

Significant physical impairment and markedly decreased quality of life.
• 25-50% have medication-refractory essential tremor
• DBS when significant impairment in quality of life (i.e., unable to independently feed or go to toilet)
Worsening essential tremor following deep brain stimulation: disease progression versus tolerance

Christopher G. Favilla, David Ullman, Aparna Wagle Shukla, Kelly D. Foote, Charles E. Jacobson IV and Michael S. Okun
Unilateral thalamic deep brain stimulation in essential tremor demonstrates long-term ipsilateral effects

Zhongxing Peng-Chen a,b, Takashi Morishita c, David Vaillancourt d, Chris Favilla a, Kelly D. Foote c, Michael S. Okun a, Aparna Wagle Shukla a,*
Obsessive Compulsive Disorder

Acute Stimulation

Video 5

10% refractory to medications and psychotherapy

61.5% of treatment resistant OCD patients achieved >35% reduction in YBOCS (responder criteria) at long term follow-up
DBS mechanisms
Problems with rate model

Original Albin-Delong model of direct and indirect pathways

- STN stimulation useful
- Why pallidotomy and pallidal stimulation helpful in dyskinesia
- Thalamotomy alleviates parkinsonian symptoms
Firing pattern

- Microelectrode single unit (neuron) studies demonstrate a tendency for discharge in STN and GPi to occur in three modes, irregular, bursting, and oscillatory.

- Oscillatory mode shows strong tendency for synchronization between neurons.

- Projections from GPe as well as GPi could further amplify tendency of other neuronal pools to fire in a synchronous and oscillatory fashion by virtue of their widespread connections to other thalamic subnuclei and cortical regions.
Oscillatory basal ganglia-cortical interactions.

Coupling between globus pallidus interna and electroencephalogram (EEG) in region of supplementary motor cortex in a Parkinson’s disease (PD) patient off medication (red) and after reinstitution of levodopa (blue, GP).

Off medication, coupling (coherence) between GP and cortex is dominated by activity 10 Hz and at 20 to 30 Hz. After levodopa, strong coupling at 60 Hz appears. Arrows show dominating direction of connectivity in each frequency band. STN, subthalamic nuclei; Gpi, GP interna.

Lower frequency oscillations facilitate slow idling rhythms in motor areas of cortex, whereas synchronization at higher frequency restores dynamic task related cortical ensemble activity in gamma band.
Basic mechanisms

- **Depolarization block**: A depolarizing block means that membrane is so depolarized that spikes become smaller and smaller and finally can no longer be evoked, owing to inactivation of voltage-gated Na current.

- **Synaptic inhibition**: by stimulation of inhibitory afferents to target nucleus.

- **Synaptic failure**: by induced neurotransmitter depletion.

Evidence for Inhibition or functional lesion

Large myelinated axons: Neural elements most easily stimulated by electrical current.

Electrical stimulation affects multiple regions of neuron: dendrite, soma, axon hillock, and axon.
Evidence for Excitation

- MPTP-lesioned primates stimulation of STN at 136 and 157 Hz actually drove neurons in GPi, so firing was time-locked to STN stimuli.

- Similarly with GPi stimulation reduction in firing rates in VL thalamus secondary to excitation of inhibitory pallidothalamic GABAergic projections.

- Findings confirmed with concentrations of neurotransmitters downstream from implanted STN electrodes.
Effective current density decreases along radial distance from a DBS electrode.

- Close to DBS electrode Area of higher current density stimulation above level of somatic activation -> depolarization block of somatic elements.

- Axons fire at 1:1 ratio between stimulus and axonal spike -> synaptic failure of synapses downstream at frequencies greater than 100 Hz.

Network changes occur over multiple time scales.

**Immediate effect of DBS:** Removal of abnormal synchronization

**Chronic effects:** Anatomical reorganization (e.g., synaptic plasticity)
Insights from transcranial magnetic stimulation
Transcranial Magnetic Stimulation (TMS)

- TMS is a painless, non-invasive way to stimulate human brain.
- TMS works by passing a large, brief current through a wire coil placed on the scalp.
1. TMS pulses applied to the motor cortex, 2. Motor cortex interneurons that mediate SICI and ICF, 3. Sensory cortex neurons that mediate sensorimotor integration such as SAI and LAI, 4. Corticospinal output neurons that generate motor evoked potentials are activated transsynaptically by the TMS pulse, 5. Sensory stimuli from the periphery are projected to sensory cortex by the thalamus, 6. Motor evoked potentials recording from the first dorsal interosseus muscle, 7. Median nerve stimulation at the periphery that forms the conditioning stimulus.

First column shows motor cortex inhibition (SICI and ICF) and sensorimotor integration (SAI and LAI)
Second column shows sensorimotor plasticity obtained with paired associative stimulation protocol (PAS). Traces show average motor evoked potential recordings with test pulse alone (TS) or preceded by median nerve stimulation delivered at interstimulus interval (ISI) of 20ms (MNS 20) and 200 ms (MNS 200) or when preceded by a conditioned stimulus (CS) delivered to the motor cortex at an interstimulus interval of 2ms (CS2) and 10ms (CS10) For the PAS protocol, 90 pairs of median stimulation preceding the TMS pulse by 25ms are delivered.
Short Latency Afferent Inhibition and Facilitation in Patients With Writer’s Cramp

Kirk R. Kessler, MD,* Diane Ruge, MD, Tihomir V. Ilić, MD, and Ulf Ziemann, MD

Motor Cortex Laboratory, Department of Neurology, J.W. Goethe University, Frankfurt/Main, Germany

Subthalamic nucleus stimulation modulates afferent inhibition in Parkinson disease

A. Sailer, MD; D.I. Cunic, PhD; G.O. Paradiso, MD, PhD; C.A. Gunraj, MHS; A. Wagle-Shukla, MD; E. Moro, MD, PhD; A.M. Lozano, MD, PhD, FRCSC; A.E. Lang, MD, FRCSC; and R. Chen, MB, BChir, MSc, FRCPC

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RESEARCH PAPER

Long-term subthalamic nucleus stimulation improves sensorimotor integration and proprioception

Aparna Wagle Shukla,1 Elena Moro,2,3 Carolyn Gunraj,4 Andres Lozano,5 Mojgan Hodaie,5 Anthony Lang,2,3 Robert Chen2,3,4
Pathophysiologic insight into STN DBS in dystonia: Role of TMS
Increased Motor cortex excitability

Impaired interaction of sensory and motor system

Exaggerated sensorimotor plasticity

Short interval intracortical inhibitory (SICI): reduced
Intracortical facilitation (ICF): increased

Short latency afferent inhibition (SAI): increased
Long latency afferent inhibition (LAI): not known
SAI and LAI when sensory load is increased: not known

Paired associative stimulation (PAS): response is increased
To determine effects of subthalamic nucleus (STN) DBS surgery on sensorimotor integration (SAI and LAI), and sensorimotor plasticity in patients with predominantly primary cervical dystonia.

Hypothesis: STN DBS restores sensorimotor integration and abnormal sensorimotor plasticity. A multilevel modulatory effects are underlying factors for clinical improvements.
Clinical cohorts

- Controls
- Primary cervical dystonia
- Primary cervical dystonia and STN DBS

OFF STIM
ON STIM
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Disease duration in yrs</th>
<th>Distribution of dystonia</th>
<th>Medications</th>
<th>Duration after DBS in yrs</th>
<th>TWSTRS score</th>
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<td>F</td>
<td>12</td>
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There was an increased functioning of SAI circuit (20ms) in dystonia subjects (p=0.03). An increase in SAI indicated an active compensation for an impaired surround inhibition. However during dual peripheral nerve stimulation when there was an increase in the sensory load, dystonia subjects seemed to lose this compensatory ability. Compared to controls, SAI was reduced (p=0.04).

With STN DBS, there was a further increase in functioning of the SAI circuit regardless of the sensory load. These changes were significant for SAI 20 (p=0.04 single stim, p=0.05 dual stim). There were no major differences seen between on and off stimulation conditions.
LAI

LAI was reduced at 150ms (p=0.054) and 200ms (p=0.041) in dystonia subjects only with dual stimulation. This abnormality was seen to be corrected with STN DBS surgery in dual stim conditions (p=0.03, 150 ms and p=0.001, 200 ms). When STN DBS was turned ON, there was further increase in LAI at 200ms dual stimulation.
Maximum PAS response was seen to be increased in dystonia patients compared to controls (p=0.056), this increased response was corrected when STN DBS was turned ON (p=0.04).
Conclusion

• There is an increased SAI in dystonia. An increased SAI probably compensates for excessive muscle activity however this compensation is lost in presence of dual sensory load. STN DBS increases functioning of SAI circuit (20ms) regardless of sensory load. STN DBS enhances the functioning of compensatory circuits. STN DBS corrects abnormal PAS plasticity response suggesting there is a reorganization of neural response with chronic DBS.
GPI: Effectively-Placed Bilateral Leads

- Medtronic 3387 GDS leads shown in both hemispheres

GPI: Medial Observed Effects

- Left hemisphere, 3387 lead, unipolar contact 0
- Stimulation spread into posterior limb of internal capsule
Complications related to Cognition and Mood

Cognition and Mood in Parkinson Disease in STN versus GPi DBS: The COMPARE Trial


Movement Disorders Center, University of Florida, McKnight Brain Institute, College of Medicine

Methods—Fifty-two subjects with moderate-to-advanced PD were randomized to either unilateral STN or GPi DBS. Right or alternatively left sided stimulation was chosen to address the side of the body with the most bothersome symptoms. The co-primary outcome measures were the change in the 8 subscales of the Visual Analog Mood Scale (VAMS), and the change in the 2 versions of verbal fluency (i.e. semantic and letter), at 7 months post-DBS in the optimal setting compared to the pre-DBS state. In addition, at 7 months post-DBS, after subjects underwent initial evaluation off medications and on optimized DBS therapy, they were tested in four randomized and counterbalanced conditions (optimal DBS, ventral DBS, dorsal DBS, and off DBS) while remaining off medication. Secondary outcome measures then compared the differences in the VAMS items and verbal fluency subscales within the 4 DBS conditions at 7 months, and the change in the VAMS items and verbal fluency subscales from the pre-DBS state to the other 3 DBS conditions (ventral, dorsal and off) at 7 months.

Results—Forty-five subjects (23 GPi and 22 STN) completed the protocol. The study revealed no significant difference between STN and GPi DBS in the change of co-primary mood and cognitive outcomes from pre- to post-DBS in the optimal setting (Hotelling's $T^2$ test: $p=0.16$ and 0.08 respectively). When comparing the 4 DBS conditions at 7 months, subjects in both targets were less “happy”, less “energetic” and more “confused” when stimulated ventrally to the optimal stimulation site. When comparing the other 3 DBS conditions (ventral, dorsal and off DBS) to the pre-DBS state, the STN group showed a larger deterioration of letter verbal fluency scores than the GPi group, especially in the off DBS state. A 12-point mean improvement in the UPDRS motor subscale was seen post DBS, but there was no significant difference between targets.
Complications related to Speech and swallowing

- STN and VIM DBS: 4-17%
- Current spread into internal capsule as an important factor or contacts abutting zona incerta and prelemniscal radiation
DBS technology

- Constant Current Stimulator
- Lead design
- Neurostimulator
- Closed loop system
At 1 year, motor scores on UPDRS scale during OFF medication, ON stimulation condition improved by 39%, and ON time improved by 4 h compared with baseline.
Current Steering - Navigate Along the Axis of the Lead

Initial stimulation outside target area

Real time adjustment allows final stimulation field to be completely confined to target

16 Independent Current Sources for Customizable Stimulation: Fine control of stimulation position and shape
Collect real time, local field potentials (LFPs) time synchronized with clinical behavior. Collect from both CM region and from pre-motor and motor cortex in order to study thalamocortical interactions in human Tourette's syndrome.

Closed loop responsive stimulation

- Medtronic Activa PC+S device and cortical ECOG strips placed over pre-motor and motor cerebral cortex.
- Capabilities to record local field potentials (LFPs) and detect specific electrographic patterns.
- Device allows physiology to be recorded even after internalization of hardware for programming.
It’s not the building, it’s the people:

The UF Center for Movement Disorders and Neurorestoration

Thank You