Functional Neurosurgery: Movement Disorder Surgery

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Movement Disorder Surgery

- New results of an OHSU Study
  - Thalamotomy v. DBS for Tremor
- Latest results of the VA/NIH trial for DBS Parkinson’s Disease
- New data on the physiology of DBS
- The future
  - DBS
  - Movement disorder surgery
Movement Disorder Surgery

- **1950’s**: Pallidotomy
- **1960’s**: Pallidotomy replaced by Thalamotomy
- **1970’s**: The Levodopa era
- **1980’s**: Thalamic stimulation for tremor
- **1990’s**: Pallidotomy/thalamotomy rediscovered
- **2000’s**: STN and GPi stimulation
- **2010’s and beyond**:
  - Diffusion catheters for trophic factors?
  - Transplantation of engineered cells?
  - Gene therapy?
Treatment of Parkinson’s Disease

• Symptomatic
  – Therapies to help the symptoms of PD
    • Medicine
    • Surgery

• Neuroprotective
  – Therapies to slow progression
  – Therapies to delay onset

• Neurorestorative
  – Therapies to restore lost dopamine cells
Treatment of Parkinson’s Disease

• Symptomatic
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• Neuroprotective
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  – Therapies to restore lost dopamine cells
Movement Disorder Surgery

- Vim
- GPI
- STN

- Ablative
- Neuromodulation
Movement Disorder Surgery

- Vim Thalamotomy
- PV Pallidotomy (GPI)
- Vim Stimulation
- GPi Stimulation
- STN Stimulation

OHSU Neurological Surgery
Movement Disorder Surgery

- **DBS**
  - Less adverse effects (?)
  - Reversible / adjustable
  - Equipment maintenance
  - Expensive

- **Lesion**
  - Easier
  - Not bilateral (?)
  - Less expensive
Movement Disorder Surgery

Vim  G Pi  STN

Ablative  Neuromodulation

OHSU Neurological Surgery
Thalamotomy Target Location

VIM

OHSU Neurological Surgery
Thalamotomy

OHSU Neurological Surgery
Thalamotomy
Thalamotomy
Movement Disorder Surgery

Vim  GPI  STN

Ablative  Neuromodulation

OHSU Neurological Surgery
Pallidotomy
Movement Disorder Surgery

- Vim
- GPI
- STN

- Ablative
- Neuromodulation

OHSU Neurological Surgery
Movement Disorder Surgery

Vim

GPI

STN

Ablative

Neuromodulation
Movement Disorder Surgery

Vim → GPI → STN

Ablative Neuromodulation

OHSU Neurological Surgery
DBS Implantation
Activa® Parkinson’s Control System
Vim DBS
First DBS*

*Outside France
Thalamic DBS
OHSU Study: Thalamotomy v. DBS

• 20 patients with Essential Tremor (ET)
• Matched demographics
• Rigorous testing
• Randomly assigned to
  – Deep brain stimulation (Vim)
  – Thalamotomy (Vim)
• Follow-up with repeat testing
<table>
<thead>
<tr>
<th>Event</th>
<th>Thalamotomy (N= 10)</th>
<th>DBS (n= 10)</th>
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<tbody>
<tr>
<td>Surgical:</td>
<td></td>
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<tr>
<td>Repeat thalamotomy (poor tremor control post fall)</td>
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<tr>
<td>Replace burr hole cover screw</td>
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<tr>
<td>Transient:</td>
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<td>weakness</td>
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<tr>
<td>balance disturbance</td>
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<td>speech difficulties</td>
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<tr>
<td>hematoma</td>
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<td>1</td>
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<tr>
<td>metallic taste in mouth</td>
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</tbody>
</table>
Clinical scales show no difference in function after 6 months of TH or DBS.
Contralateral tremor power is reduced by DBS and TH; Peak frequency is not.
On the ipsilateral hand, neither tremor power nor peak frequency are affected by DBS or TH.
CV determined from analysis of the middle third keystrikes
Contralateral simple repetitive (SS) finger movements are improved by both DBS and TH

$P_{0.06} (\text{DBS v TH}) = 0.03$
Timing variability of contralateral alternate finger tapping tends to improve more with DBS.

Trill

$P_{0.6}$ (DBS vs TH) = 0.12
Accuracy of contralateral finger movements improves with DBS
Timing variability of ipsilateral tapping is improved by DBS
Ipsilateral accuracy errors are unchanged by DBS and TH.
Thalamotomy v. DBS

- TH and DBS both reduce contralateral tremor equally
  - Neither TH or DBS changes ipsilateral tremor frequency
- Early adverse events more common with TH
Thalamotomy v. DBS

- Both TH and DBS affect neural systems involved in temporal processing and sequencing of contralateral finger movements in ET:
  - Regularity of simple, repetitive movements is improved by both TH and DBS, with greater improvement after DBS
  - Regularity and accuracy of more complex sequences that involve non-motor cortical areas are improved by DBS and may be worsened by TH
Thalamotomy v. DBS

- DBS improves regularity of finger movements **ipsilateral** to the stimulated thalamus.
Thalamotomy v. DBS

- Taken together, these results provide evidence that:
  - DBS affects a more widespread neural network than TH
  - That network most reasonably includes ipsi-lesional:
    - motor cortex
    - basal ganglia
    - cerebellar structures.
Movement Disorder Surgery

Vim

GPi

STN

Ablative

Neuromodulation
Physiology of Parkinson’s Disease

Brainstem/spinal cord

Parkinsonism

- facilitation
- inhibition

Putamen

D2

D1

SNc

GPe

STN

GPi/SNr

Cortex

VPL

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The brain system that produces movement is normally in balance.

Inhibition (-)

Facilitation (+)
Parkinson’s Disease puts it out of balance - movement becomes difficult
The system can be rebalanced by shutting down the right parts - movement is improved.
Microelectrode and DBS Electrode
Microelectrode Mapping
Microelectrode Mapping
GPi Microrecording

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GPI DBS
VA/NINDS DBS Study
Study Design

- **Entry criteria**
  - Idiopathic Parkinson’s Disease
  - Hoehn & Yahr ≥ 2 (off meds)
- **Randomized**
  - BMT and DBS
  - Study site
  - Age < 70 or 70+
- **Followed for 6 months**
Study Design

- Investigators blinded to implant site

- PD: H&Y > 2 (- meds)
- DBS
- BMT

- Gpi*
- STN*

*Investigators blinded to implant site
Study Design

- PD H&Y > 2 (- meds)
- DBS
- BMT
- Gpi*
- STN*

*Investigators blinded to implant site
Outcome Measures

- **Primary outcome measure**
  - On-time (w/o troubling dyskinesias)
    - Patient diaries

- **Secondary outcome measures**
  - Hoehn & Yahr
  - Schwab & England
  - UPDRS I-IV
  - PDQ-39
  - SF-36
  - Stand-walk-sit test
Patient Population

- 255 patients
  - Male 82%
  - White 96%
  - Married 69%
  - Age: 63 + 8.8 years
  - Time from PD Dx: 12 + 5.8 years
Results

- On time increased 5.1 hours/day
  - No change in BMT ($p < .001$)
- UPDRS-III improved 35.6% (- meds/+ stim)
  - Improved 4.5% in BMT ($p < .001$)
- PDQ-39 significantly improved with DBS
  - All except social support
  - BMT showed no change in PDQ-39
Patient Motor Diaries

![Graph showing patient hours in various states over time.](image)
Patient Motor Diaries

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Serious Adverse Events

- **DBS** – 40%
  - Falls (21.5%), gait disturbance (20.7%), headache (17.4%), dyskinesias (16.5%)
  - 10% > implant site infection

- **BMT** – 11%
  - Dyskinesias (11.9%), motor dysfunction (11.2%), gait disturbance (9.7%), falls (8.2%)
Serious Adverse Events

- **0-3 months DBS v BMT**
  - Headache, bradykinesia, confusional states, speech disorder, pain, constipation, musculoskeletal pain (all p’s < .05)

- **3-6 months DBS v BMT**
  - Falls (11.6% v 3.7%; p < .029), dystonia (6.6% v 0.7%; p < .015)
Serious Adverse Events

• Deaths
  - 2- metastatic cancer
  - 1- cerebral hemorrhage
Conclusions

• DBS is superior to BMT
  – Improving on-time
  – Motor function
  – Quality of life
• Both older and younger patients
• Both earlier and later stages of PD
Study Design

- Investigators blinded to implant site

- PD
  H&Y > 2 (- meds)

- DBS
- BMT

- Gpi*
- STN*

*Investigators blinded to implant site

OHSU Neurological Surgery
Conclusions

- Results of GPi v STN due out in the next few months
- Publication > 1 year
- Consensus statement will incorporate findings of the VA/NIH trial re: target
How Does DBS Work?

- Mechanism is still unknown
- Stimulates axons not somata
- Probably inhibitory
  - Effective at same sites as lesions
    - Thalamotomy, pallidotomy, subthalamotomy
- No evidence of permanent lesion with chronic stimulation
- Recent OHSU data
  - Does not inhibit STN neurons
  - Changes firing pattern (less bursting)
The primary effect of DBS on neural tissues is activation of myelinated axons.

**Typical DBS Parameters:** 140 Hz, 100 \( \mu \)s PW, 2 to 4 V

**Myelinated Axon**

- **Chronaxie**
- **Axon** 30 – 200 \( \mu \)s
- **Cell Body** 1 – 10 ms


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MER During DBS

OHSU Neurological Surgery
Adjustment of Firing Rate During DBS Stimulation

A - Spike not detectable
B - Spike is detectable
C - Amplifier is saturated
D - Filter transient

Firing Rate Adjustment = 1 + \frac{A}{A + B}
Adjusted Firing Rate Histogram

Before Stimulation  Stim  After Stimulation

Averaged Firing Rate (Hz)

Time (s)
Pattern of Neuronal Activity

- Random Firing Pattern: $N = 11$
- Bursting Firing Pattern: $N = 14$
- Tonic Firing Pattern: $N = 6$
STN Neuronal Firing Patterns After DBS

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Conclusions

- DBS does not produce a functional lesion.
- DBS does not produce a long-lasting change in firing rate.
- Changes in firing pattern may be important.
- This data is consistent with the jamming theory of DBS.
DBS Consensus Conference  
NYC  April 2-3, 2009

- **Sponsor:** Parkinson Alliance
- **48 invitees**
  - International
    - Neurologists, Neurosurgeons, Psychiatrists, Psychologists, Speech Pathologists, Neuroscientists
- **Goals**
  - Consensus statement on the current use of DBS in Parkinson’s Disease
  - Publish on the Parkinson Alliance website and journal (Neurology)
The Future of DBS?

- DBS is a "platform" technology
  - Movement disorders
  - Pain
  - Epilepsy
  - Behavioral disorders
  - Other
- The technology of DBS will advance
  - Closed loop systems
The Future of DBS?

- **DBS is palliative**
  - Not protective or restorative
- **DBS is transitional technology**
  - Pain surgery
  - Movement disorder surgery
  - Behavioral disorders
- **DBS is the bridge to the future for Functional Neurosurgery**

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What’s Next?

- Trophic factors
- Gene therapy
- Stem cell therapy
What’s Next?

- Trophic factors
  - ICV GDNF
    - Study stopped due to toxicity
      - Implanted intracerebroventricular. Glial cell line-derived neurotrophic factor. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD.
  - Intra-putaminal GDNF
    - Negative Phase II trial
      - Randomized controlled trial of intraputaminal glial cell line-derived neurotrophic factor infusion in Parkinson disease
What’s Next?

- Gene therapy
  - Adeno-associated virus (AAV) vector
    - AAV-GAD/STN
      - Improvement in human basal ganglia metabolism in an open label phase I study of gene therapy for Parkinson’s Disease
  - AAV-Aromatic L-amino decarboxylase/putamen
    - Aromatic L-Amino Acid Decarboxylase Gene Transfer Therapy for Parkinson’s Disease: Initial Results of an Open-Label, Dose Escalation, Safety and Tolerability Study
  - AAV-neurturin/putamen
    - Phase I Study of Putaminal Gene Transfer with Adeno-Associated Virus Serotype 2 (AAV2)-Neurturin [NTN] (CERE-120) for Parkinson’s Disease: Preliminary Observations.

- All phase I trials, ? efficacy
What's next?

- Stem Cells?
  - Stem cells
- Two negative double-blind trials
  - Fetal dopaminergic cells
- “Engineered” cell lines
  - Cells to produce GDNF?
Movement Disorder Surgery

- DBS is the current state-of-the-art surgical therapy for Parkinson’s Disease
  - Will there be a re-discovery of ablative surgery?
- DBS now proven to be more effective than “Best Medical Therapy”
- No proven difference between GPi and STN DBS (pending)
  - VA/NIH study will answer many of the questions re: DBS
- Future
  - Movement disorder surgery
    - Trophic factors
    - Gene therapy
    - Stem and engineered cell implants
  - DBS as a “platform” technology
    - Behavioral disorders
Thanks!