Mechanism of Action
of Deep Brain Stimulation
In Parkinson Disease

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Conflict of Interest Statement

No drug company pays me any money

NIH, American Parkinson Disease Association (APDA), Greater St. Louis Chapter of the APDA, McDonnell Center for Higher Brain Function, Barnes-Jewish Hospital Foundation
**Bilateral STN DBS in PD**

- STN DBS is effective and safe in advanced PD patients with disabling motor fluctuations:
  - Improves UPDRS scores
  - Improves motor fluctuations:
    - Decreases OFF time
    - Improves dyskinesia
  - Decreases daily dose of levodopa and other PD medications
  - (Improves sleep)
  - (Weight gain)
  - Improves quality of life measures
A Randomized Trial of Deep-Brain Stimulation for Parkinson’s Disease

Deuschl at al NEJM, vol 355;pp 896-908, August 31, 2006
Quality of Life in STN DBS

Deuschl at al NEJM, vol 355;pp 896-908, August 31, 2006
Why Do We Need to Learn About the Mechanism of Action of DBS?

◆ If we know how it works, we may be able to make it work better:
  
  - To optimize motor benefit (“sweet spot”)
  - To minimize adverse effects (cognitive, psychiatric, visual …)
  - To look for tentative new DBS targets for other disorders (dystonia, tics, depression, obsessive-compulsive disorders, seizure…)}
A. Normal Basal Ganglia Circuitry

B. PD Basal Ganglia Circuitry
Basal Ganglia Circuitry After Subthalamic Lesion
What Are We Stimulating And/Or Inhibiting?

- Likely stimulating axons
- With monopolar stimulation: (Holsheimer 2000)
  - Nearby axons may be blocked (by high currents)
  - Distant axons are unlikely affected by stimulation
  - Intermediately located axons may be activated (“shell of activation”)
**STN Efferent & Afferent Projections**

- Frontal Cortex
- Parafascicular Nucleus of Thalamus
- Substantia Nigra (pars compacta)
- Pedunculopontine nucleus
- External Globus Pallidus
- Internal Globus Pallidus
- Substantia Nigra (pars reticulata)
Neurophysiology of STN DBS in Animals & Humans

- In MPTP monkeys: (Hashimoto 2003, Kita 2005)
  - GPe and GPi: Increased firing

- In PD patients:
  - Following 500 msec: ½ of STN cells were inhibited (Filali 2004)
  - Following 20 seconds: all STN cells were inhibited (Welter 2004)
Net Effects of DBS on Basal Ganglia Circuitry and Cortical Targets

If STN is **inhibited** by DBS
- Cortical targets activated

If STN is **stimulated** by DBS
- Cortical targets suppressed

DBS

- STN
- Thalamus
- GPi/SNpr
Bilateral STN DBS Reduces Blood Flow to the Cortex (measured by $H_2O^{15}$ PET)

Increase

Decrease

STN output is increased

cortical targets

thalamus

STN

GPi/SNpr

Hershey et al, 2003
Unilateral STN DBS Improves Rigidity Bilaterally

(N=24)
Unilateral STN DBS Improves Bradykinesia Bilaterally

(N=25)
Effect of Unilateral STN DBS on Gait

(N=44)
Effect of Unilateral STN DBS on Motor Function & Working Memory

- Working memory:
  - ability to maintain, monitor and use internal information to guide behavior
  - essential for carrying more complex executive functions, affected in PD
  - measured using Spatial Delayed Response (SDR) test

- Mean UPDRS and Spatial Delayed Response (SDR) responses to Left DBS vs Right DBS did not differ

- On the more affected side of the brain (compared to the less affected side):
  - contralateral UPDRS improvement was greater
  - SDR performance was more impaired (p=0.008)

- Variability among patients
What Accounts For The Variability in Motor Benefit From STN DBS?

- Disease duration at surgery?
- Age at surgery?
- Disease severity?
- Stimulation parameters?
- Brain atrophy?
- Ability to generate dyskinesia?
- Location of electrode?
Sites of Neurodegeneration in Parkinson Disease

- Substantia nigra pars compacta
- Substantia innominata
- Amygdala
- Ventral tegmental area
- Locus ceruleus
- Raphe nuclei
- Dorsal motor nucleus of vagus nerve
- Intermediolateral column/Sympathetic ganglia

Functional Sections of the STN

**Dorsolateral:** Sensori-motor (SM)
- Afferents from motor and supplementary motor cortex, thalamus, GPe
- Efferents to putamen, GPe/GPi

**Ventrolateral:** Associative (AS)
- Afferents from prefrontal cortex
- Efferents to caudate, putamen, GPi/SNpr

**Ventromedial:** Limbic (Li)
- Afferents from GPM/GPV, caudate, putamen, thalamus, medial frontal, orbitofrontal and anterior cingulate cortex
- Efferents to caudate, GPe/GPi, SNpr
- Is just dorsal of white matter tracts connecting the amygdala and hypothalamus

Coronal view of the STN (Parent & Hazrati 1995)
Is the Subthalamic Nucleus Hypointense on T2-Weighted Images? A Correlation Study Using MR Imaging and Stereotactic Atlas Data


Didier Dormont, Kenneth G. Ricciardi, Dominique Tandé, Karine Parain, Carole Menuel, Damien Galanaud, Soledad Navarro, Philippe Cornu, Yves Agid, and Jérôme Yelnik
Active Contact Localization

AC-18.6 mm
The Uncertainty of The Zona Incerta

J. Mitrofanis / Neuroscience 130 (2005) 1–15

Overall incertal connections
Post-Operative CT

(Tom Videen, PhD) Tip of electrode
Intra-Operative MRI: Intensity Inverted
Overlap MRI/CT Images Using AIR* (Roger Woods, UCLA)

*Automated Image Registration*
Overlap Coronal MRI on Whole Brain
Co-registered MRI/CT
Overlap Active Contacts on Coronal MRI
Active Contact Localization
Unilateral Dorsal vs Ventral STN DBS

- No difference in motor function:
  - Bradykinesia UPDRS and hand rotation velocity
  - Rigidity UPDRS and impedance (rigidity analyzer)
  - Gait

- Ventral STN DBS caused definite impairment of response inhibition (Go-No-Go)
Sami Harik

- Mentor
- Best Friend
- Best Squash partner!
Active Contact Localization
Active Contact Localization
Volume of Activation

Cameron McIntyre
Cleveland Clinic, Dept of Biochemical Engineering
Spatial Delayed Response Task

Cue

Delay

Response
STN DBS May Affect Higher Cognitive Function

Spatial Delayed Response  Response Inhibition

Hershey at al, 2004
Spatial working memory (rated by SDR performance):
- *improved* on DBS when the active contact was located *out* of the STN.
- *worsened* when the active contact was located *in* the STN.

Hershey et al., 2006
Unilateral STN DBS Improves Bradykinesia Bilaterally

(N=38)  
(N=25)
Unilateral STN DBS Improves Rigidity Bilaterally

$r_S = 0.67$, $p < 0.0003$

(N=42)  (N=24)
Levodopa-Equivalents Reduction at 6 Months After STN DBS

![Bar chart showing mean levodopa equivalents in milligrams before and after surgery. The chart indicates a significant reduction in levodopa equivalents from pre-surgery to follow-up, with a p-value of less than 0.001.](image)

* p < 0.001
# Effect of STN DBS on UPDRS Motor Scores

<table>
<thead>
<tr>
<th></th>
<th>6-Month Follow-Up OFF Stimulation UPDRS Score</th>
<th>6-Month Follow-Up ON Stimulation UPDRS Score</th>
<th>Average Percent Change*</th>
<th>Significance of Change (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (0-108)</strong></td>
<td>43.4 ± 16.1</td>
<td><strong>22.8 ± 11.6</strong></td>
<td>47%</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td><strong>Tremor</strong> <strong>(0- 28)</strong></td>
<td>7.3 ± 0.8</td>
<td>0.7 ± 0.2</td>
<td>74%</td>
<td>≤ 0.001</td>
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<tr>
<td><strong>Rigidity</strong> <strong>(0-20)</strong></td>
<td>9.0 ± 4.3</td>
<td>4.1 ± 3.2</td>
<td>58%</td>
<td>≤ 0.001</td>
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<tr>
<td><strong>Bradykinesia</strong> <strong>(0-36)</strong></td>
<td>17.9 ± 6.9</td>
<td><strong>11.0 ± 6.1</strong></td>
<td>37%</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td><strong>Speech</strong> <strong>(0-4)</strong></td>
<td>1.5 ± 0.6</td>
<td>1.3 ± 0.7</td>
<td>13%</td>
<td>= 0.002</td>
</tr>
<tr>
<td><strong>Postural Instability</strong> <strong>(0-4)</strong></td>
<td>1.8 ± 1.2</td>
<td><strong>1.1 ± 1.1</strong></td>
<td>35%</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td><strong>Gait</strong> <strong>(0-4)</strong></td>
<td>2.1 ± 0.9</td>
<td>1.2 ± 0.9</td>
<td>44%</td>
<td>≤ 0.001</td>
</tr>
<tr>
<td><strong>Axial</strong> <strong>(0-16)</strong></td>
<td>7.5 ± 3.8</td>
<td>4.3 ± 3.1</td>
<td>42%</td>
<td>≤ 0.001</td>
</tr>
</tbody>
</table>
### Demographic Profile

<table>
<thead>
<tr>
<th></th>
<th>All operated patients (N=110)</th>
<th>Outcome Analysis Subgroup (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66</td>
<td>41</td>
</tr>
<tr>
<td>Female</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td><strong>Age at onset of symptoms</strong> (in years)</td>
<td>47.9 ± 10.2 (22-69)</td>
<td>48.4 ± 9.8 (28-69)</td>
</tr>
<tr>
<td><strong>Age at time of surgery</strong> (in years)</td>
<td>62.6 ± 8.8 (31-84)</td>
<td>63.0 ± 8.2 (45-78)</td>
</tr>
<tr>
<td><strong>Duration of Parkinson disease at time of surgery</strong> (in years)</td>
<td>14.5 ± 6.3 (4-29)</td>
<td>14.5 ± 6.5 (4-29)</td>
</tr>
<tr>
<td>Leading Author</td>
<td>Year of publication</td>
<td>Number of patients</td>
</tr>
<tr>
<td>------------------------</td>
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<tr>
<td>Limousin</td>
<td>1998</td>
<td>24</td>
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<td>Kumar</td>
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<td>Burchiel</td>
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<td>Pinter</td>
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<td>Bejjani</td>
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<td>Houeto</td>
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<td>Rodriguez-Oroz</td>
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<td>Molinuevo</td>
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<td>DBS for PD Study Group</td>
<td>2001</td>
<td>91</td>
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<td>Lopiano</td>
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<td>Pahwa</td>
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<td>Herzog</td>
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<td>Ford</td>
<td>2004</td>
<td>30</td>
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<tr>
<td>Tabbal</td>
<td>2006</td>
<td>72</td>
</tr>
</tbody>
</table>
First 110 STN DBS Patients at Washington University in St Louis

- Retrospective analysis:
  - First 110 patients assessed at around 6 months post-DBS surgery
  - 47% improvement in UPDRS motor score ON vs OFF DBS (OFF medication)
  - 45% mean reduction in daily levodopa-equivalent dose

- Average weight gain $5.1 \pm 0.7$ kg
  - median 3.7 kg ; range -3.6 kg to +23.9 kg

- Operating room time (from the mounting of the stereotactic frame to its removal):
  - Median 5 hours 25 minutes

- Mild and transient adverse events
STN DBS Studies from 1998 to 2006:
UPDRS & Levodopa-Equivalent % Reduction
STN DBS Studies from 1998 to 2006:
UPDRS vs Levodopa-Equivalent % Reduction
STN DBS Parameters

- **DBS parameter programming**
  - Voltage (volts)
  - Pulse width (μsec)
  - Pulse frequency (Hz)
  - Electric contacts combination

- **Stimulation pattern:**
  - Monopolar in 74%
  - Multipolar in 26%
  - None were set in bipolar pattern

- **Optimal contact:**
  - contact #2 in 58%
  - contact #1 in 34%
  - contact #3 in 27%
**Post-Operative DBS Programming**

- Programming starts 2-4 weeks after electrode implantation
- OFF medication
- Frequency: 130 to 185 Hz
- Pulse width: 60, 90 or 120 μsec
- Voltage: 2.5 to 4 volts
- Contact configuration: usually monopolar or multipolar
- Decrease medication gradually
**STN Spans**

- No significant correlation between the STN span and improvement of UPDRS motor scores
- Average STN span:
  - on the right $4.5 \pm 0.9$ mm (range 2.0 to 6.8 mm)
  - on the left $4.9 \pm 0.8$ mm (range 3.2 to 7.4 mm)
Overlap Atlas on MRI/CT

◆ Fiducials used to stretch the atlas images:
  - Anterior commissure
  - Posterior commissure
  - Optic chiasm
  - Optic tract (in mid-commissural plane)
  - Anterior tip of the putamen (in commissural plane)
  - Red nucleus
  - Brain edge (in commissural plane)

◆ Using reformatted MRI images:
  - Transverse:
    ● 3D windowed sinc (sharpest but artifacts near optic chiasm)
    ● trilinear interpolation
  - Coronal:
    ● nearest neighbor (sharpest but abrupt jumps between planes)
    ● trilinear interpolation