# *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**

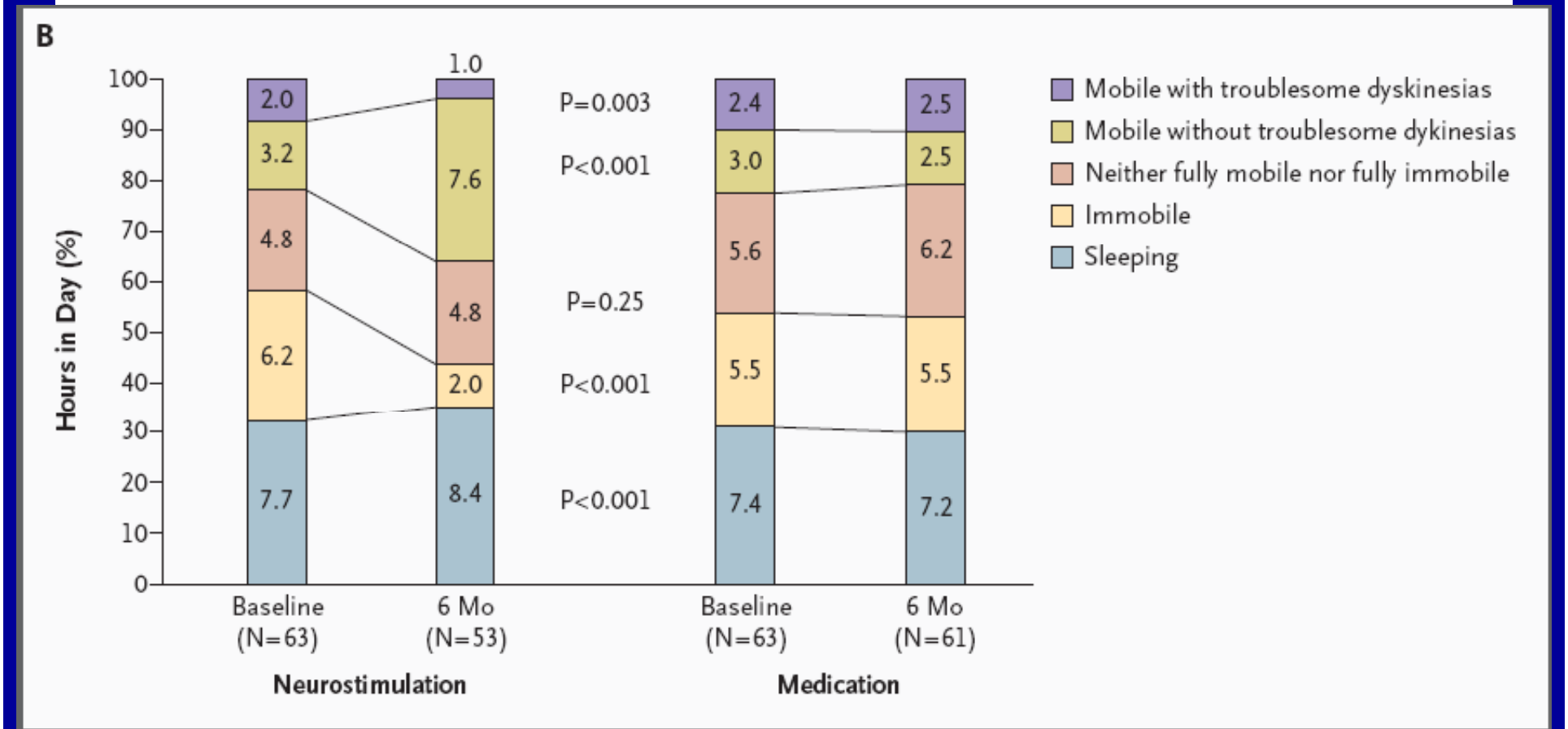
# *Bilateral STN DBS in PD*

- **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**

ORIGINAL ARTICLE

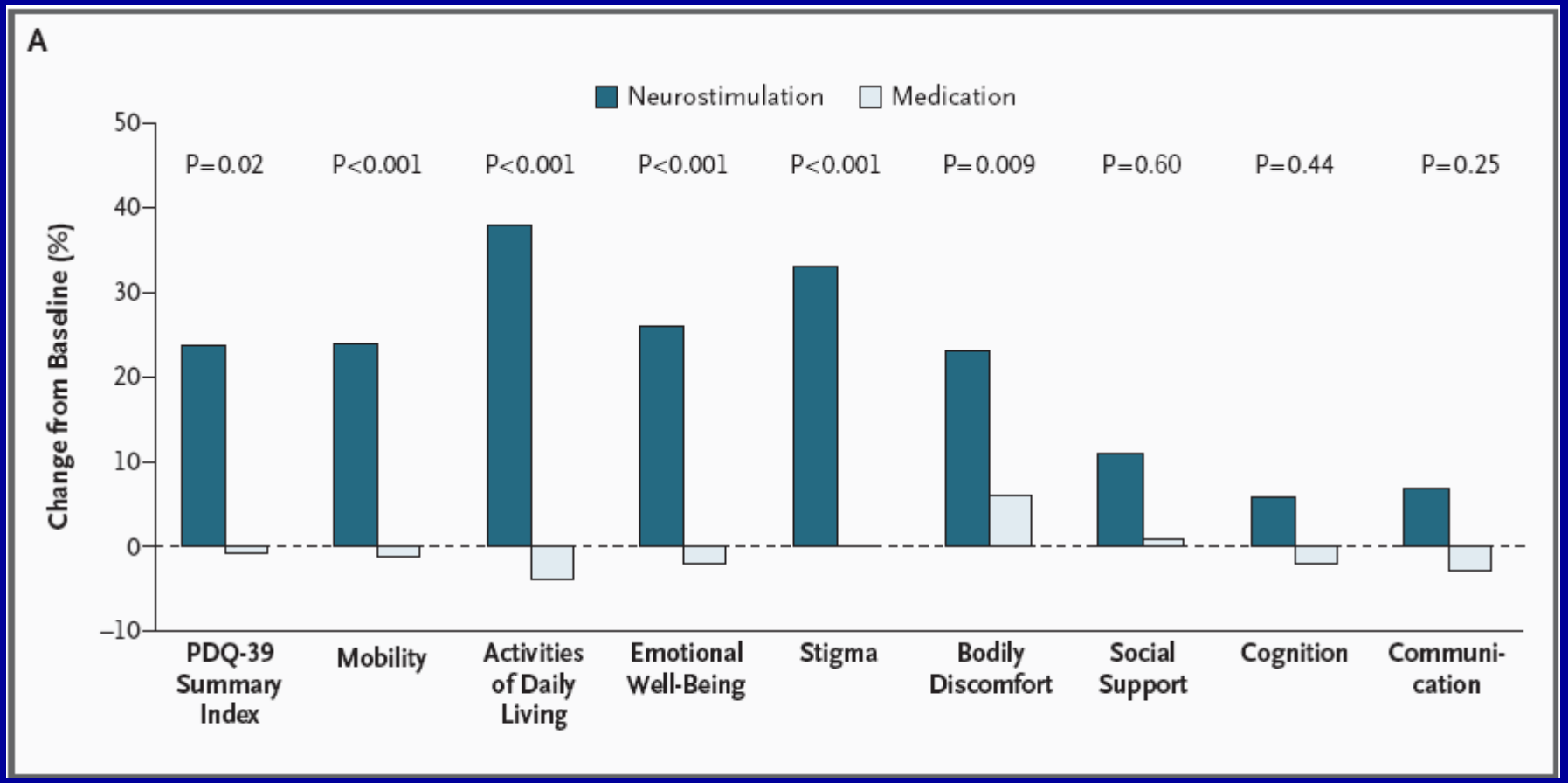
# A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease

**Deuschl at al NEJM, vol 355;pp 896-908, August 31, 2006**



# *Quality of Life in STN DBS*

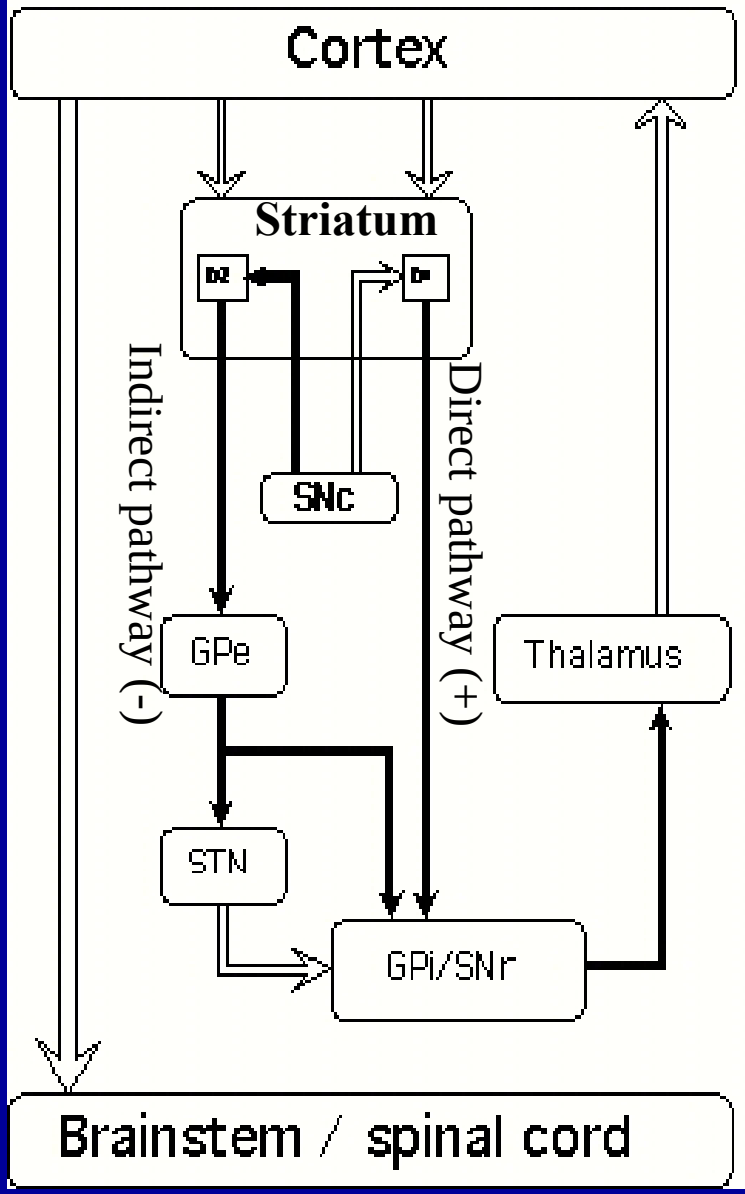
**Deuschl at al NEJM, vol 355;pp 896-908, August 31, 2006**



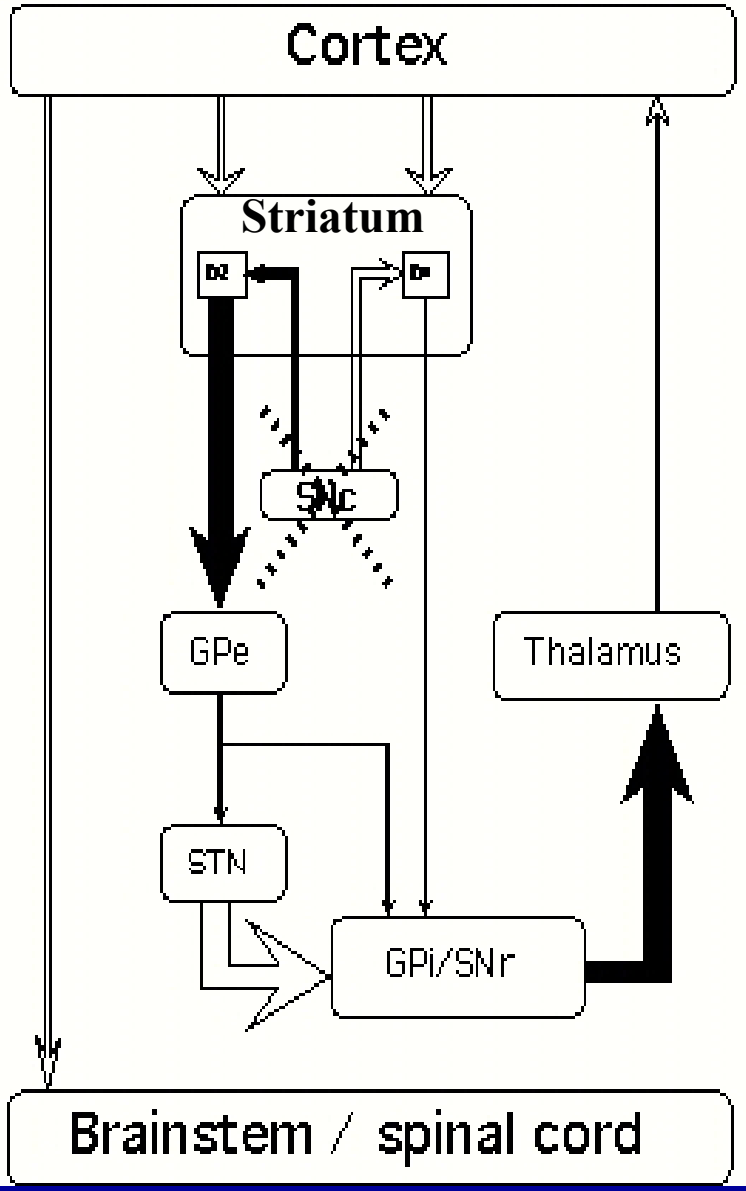
# *Why Do We Need to Learn About the Mechanism of Action of DBS?*

- **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

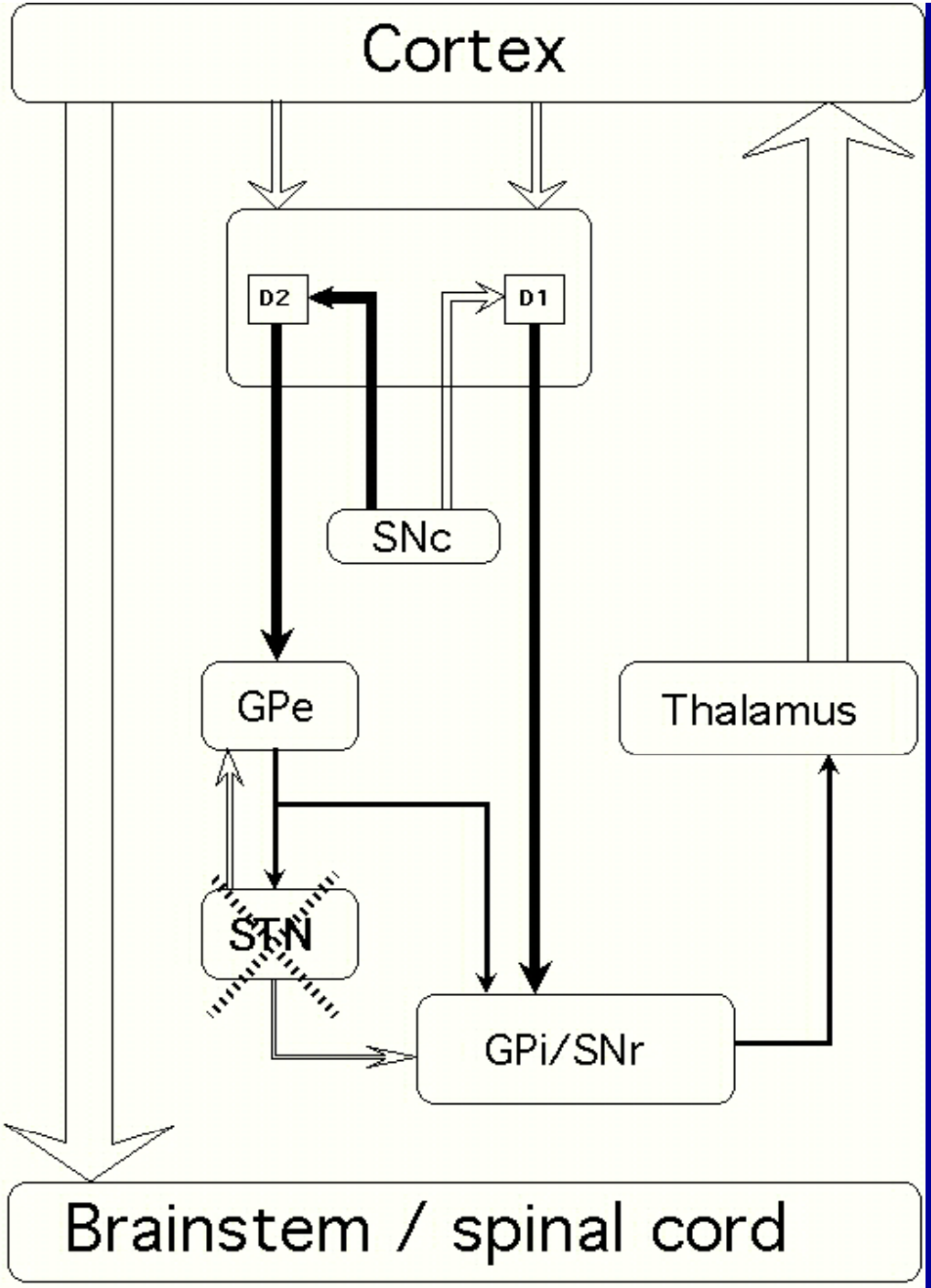
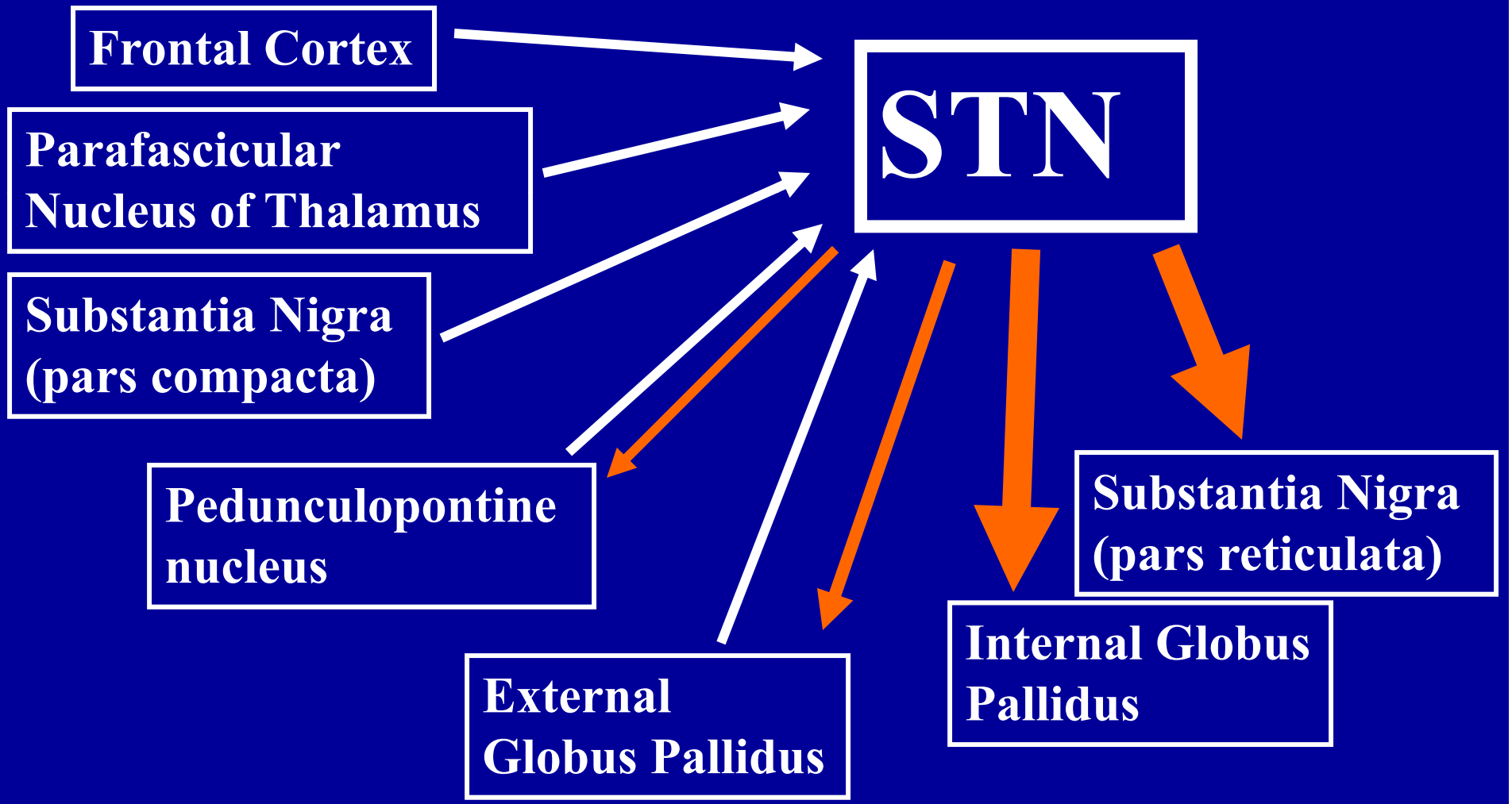



Figure 5a

# *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*

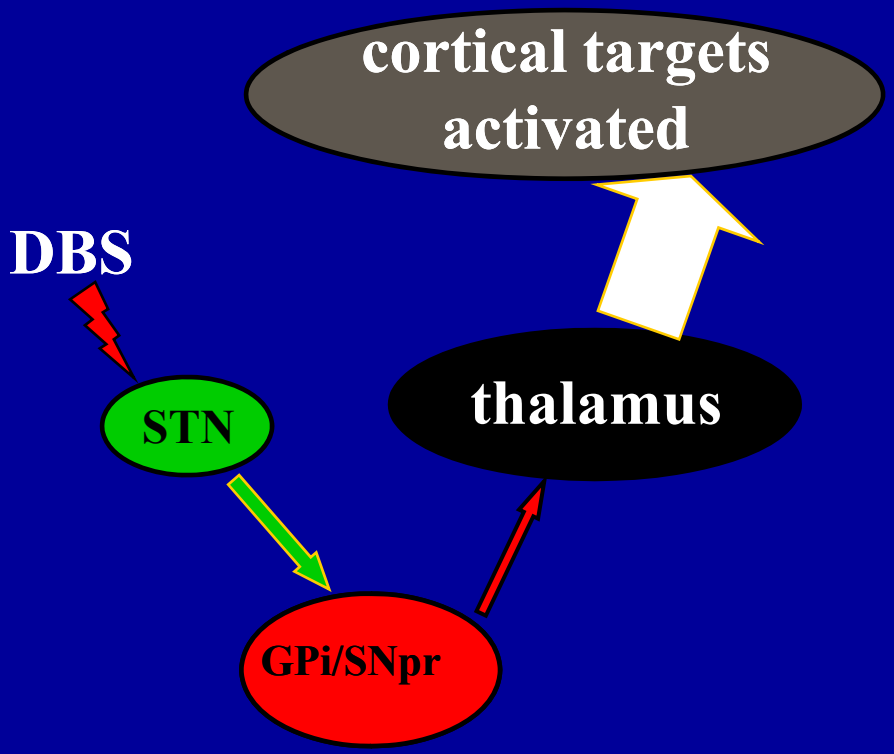


# *Neurophysiology of STN DBS in Animals & Humans*

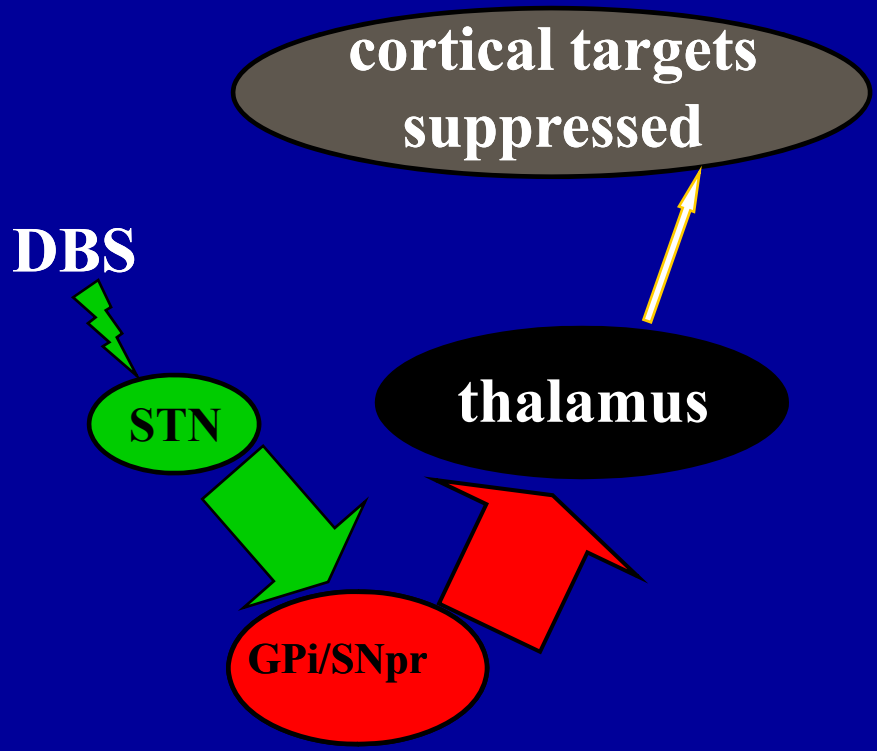
- **In MPTP monkeys:** **(Hashimoto 2003, Kita 2005)**
  - **GPe and GPi: Increased firing**
- **In PD patients:**
  - **Following 500 msec: ½ of STN cells were inhibited (Filali 2004)**
  - **Following 20 seconds: all STN cells were inhibited (Welter 2004)**

# *Net Effects of DBS on Basal Ganglia Circuitry and Cortical Targets*

**If STN is <u>inhibited</u> by DBS**

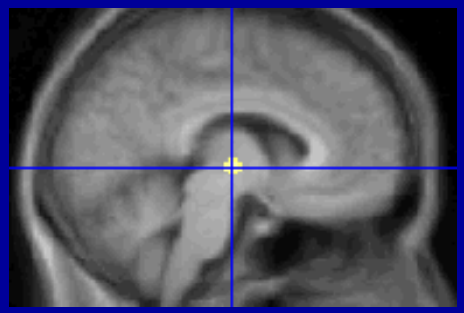


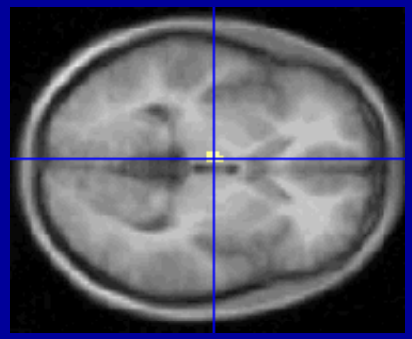

**If STN is <u>stimulated</u> by DBS**

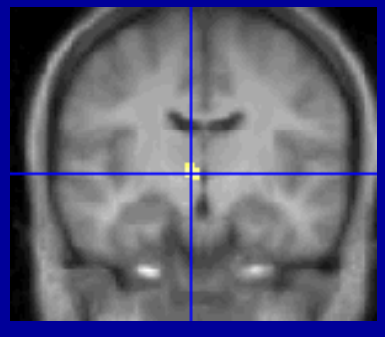


# *Bilateral STN DBS Reduces Blood Flow to the Cortex (measured by $H_2O^{15}$ PET)*

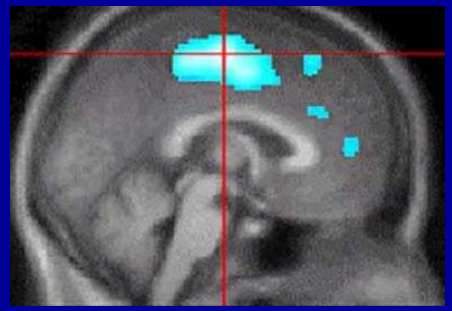
**Increase**

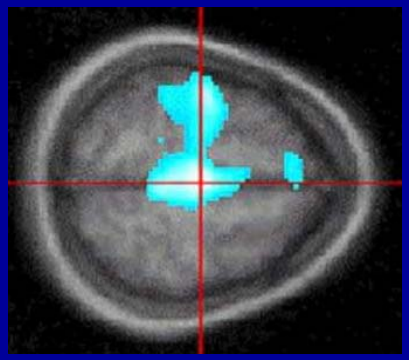


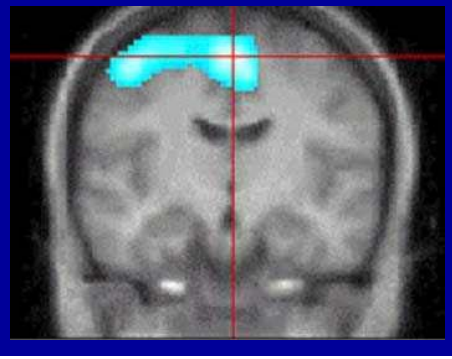




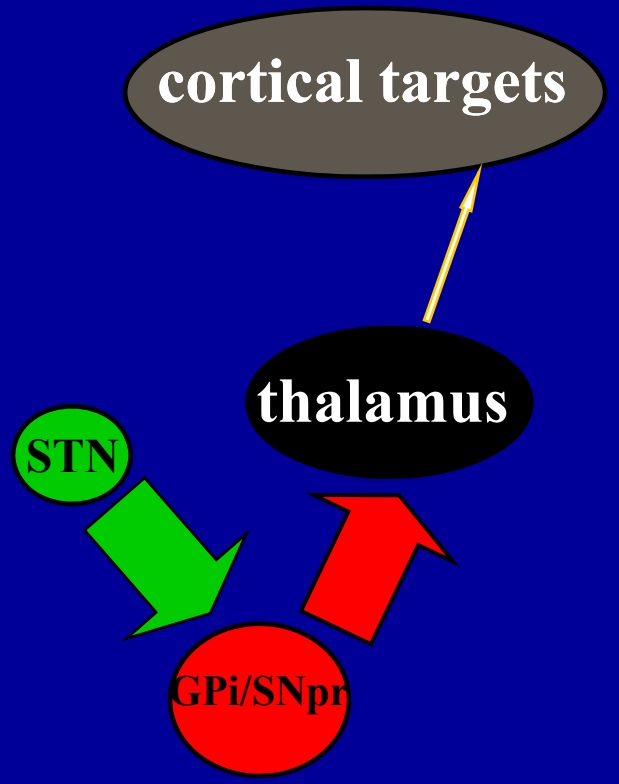
**Decrease**





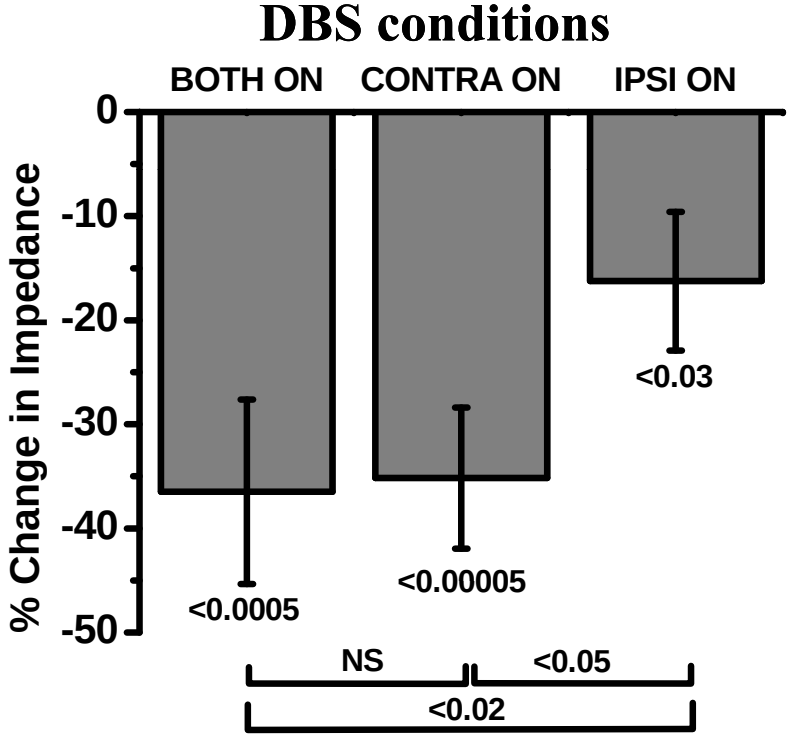


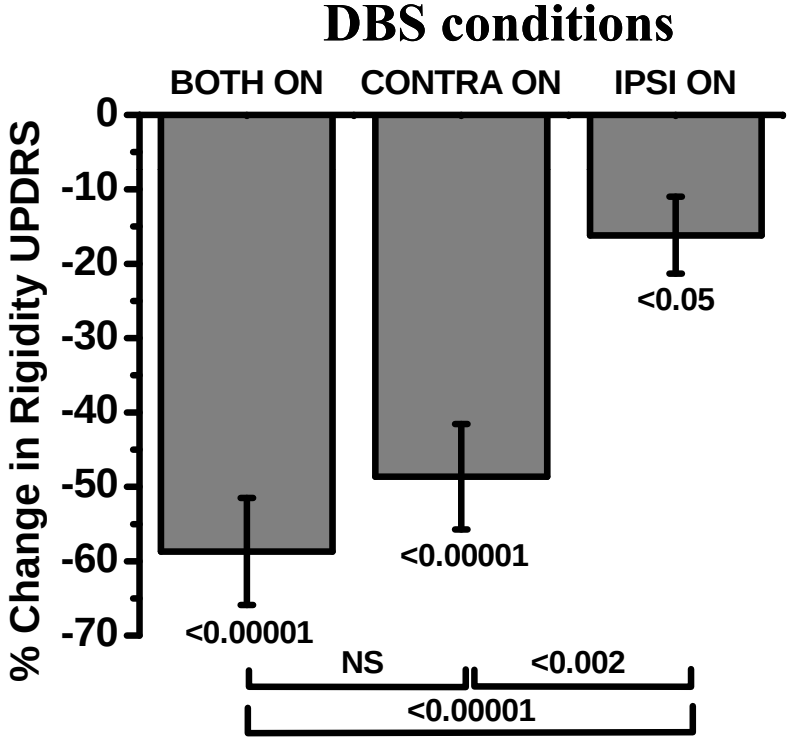
**STN output is increased**




**Hershey et al, 2003**

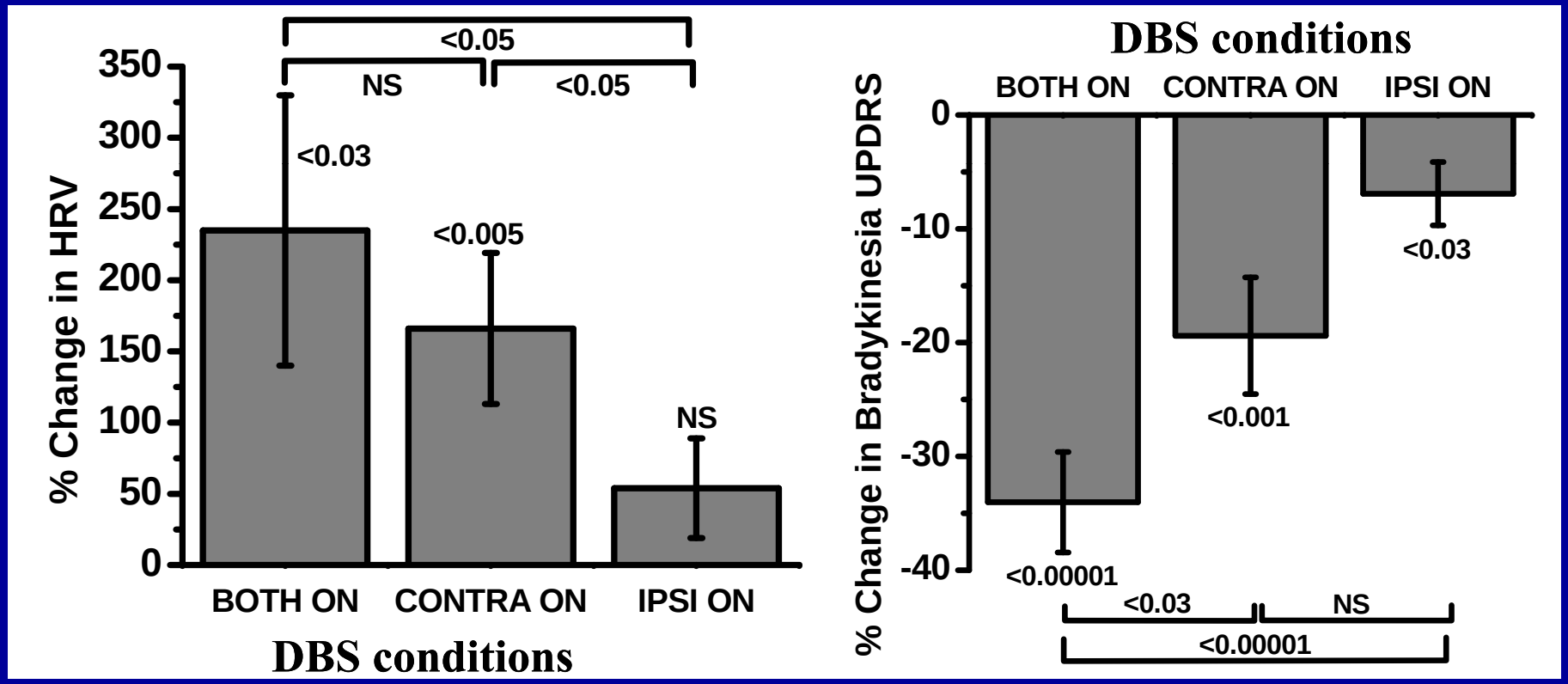
# *Unilateral STN DBS Improves Rigidity Bilaterally*



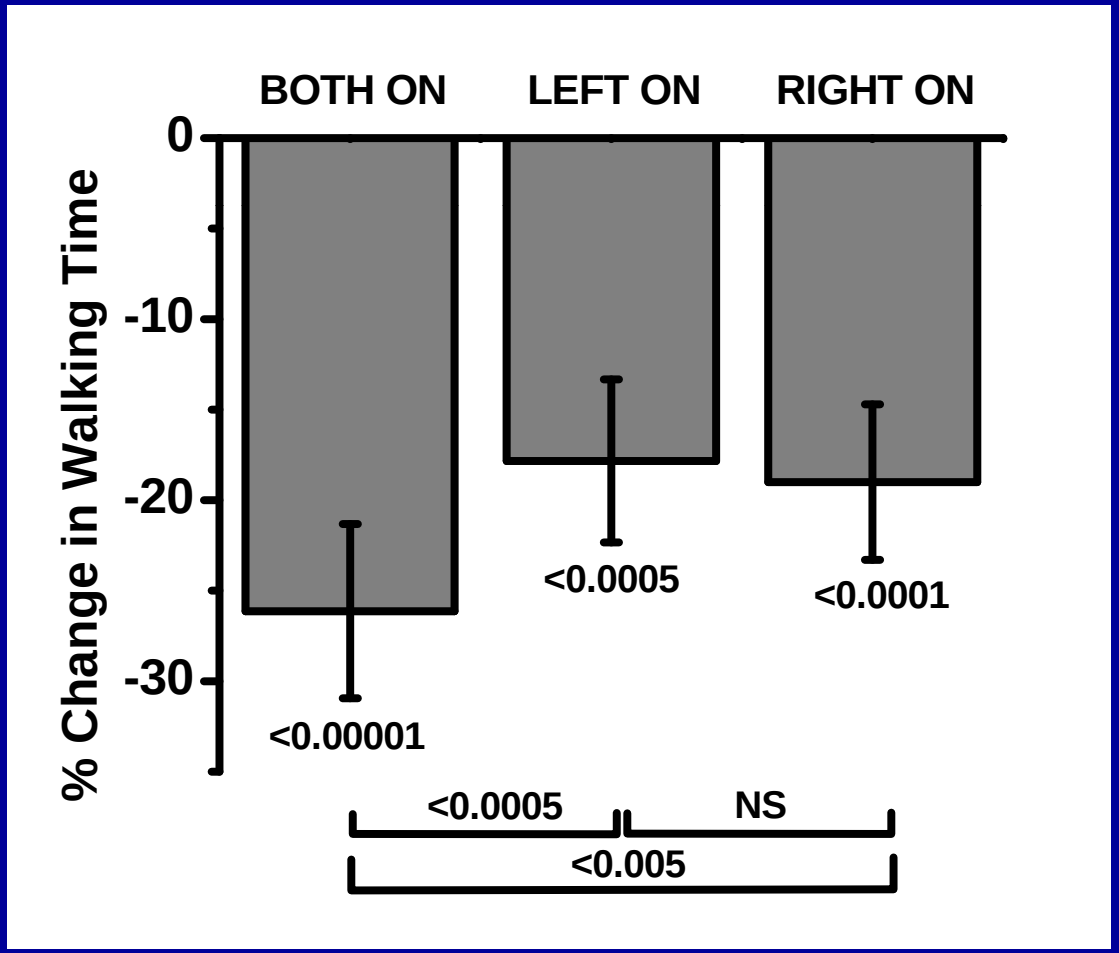

**(N=24)**

# *Unilateral STN DBS Improves Bradykinesia Bilaterally*




(N=25)

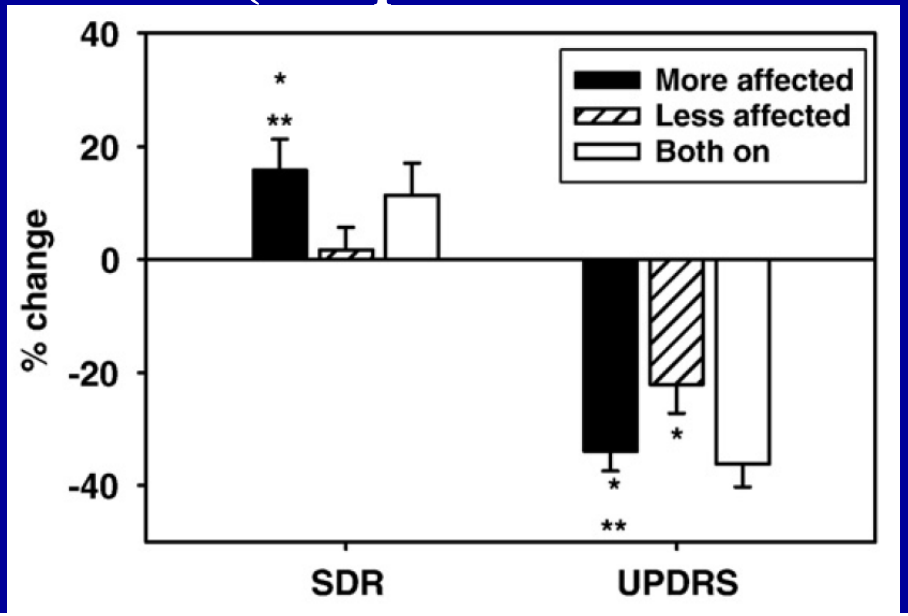
# *Effect of Unilateral STN DBS on Gait*




(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**

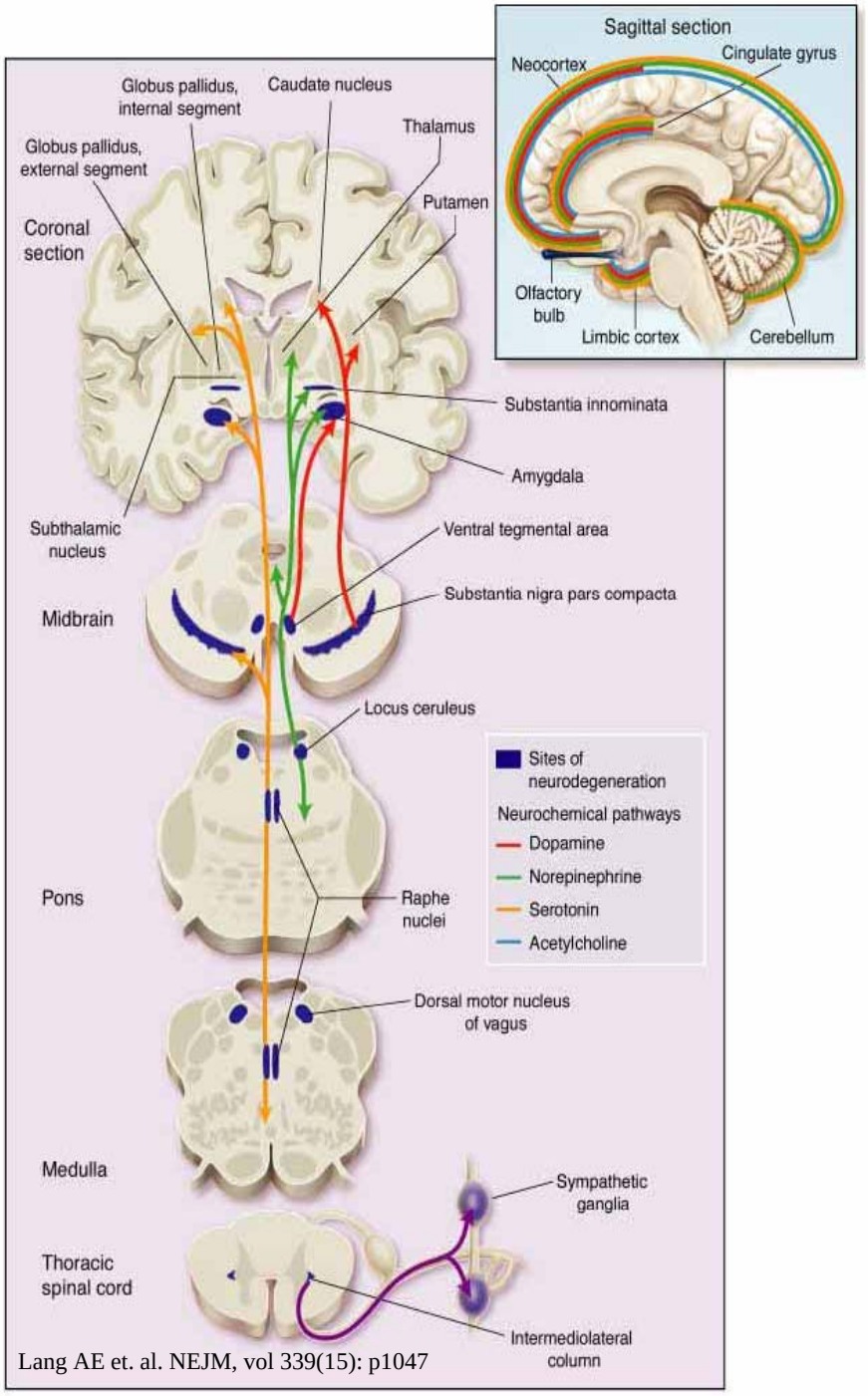


## *What Accounts For The Variability in Motor Benefit From STN DBS?*

- **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

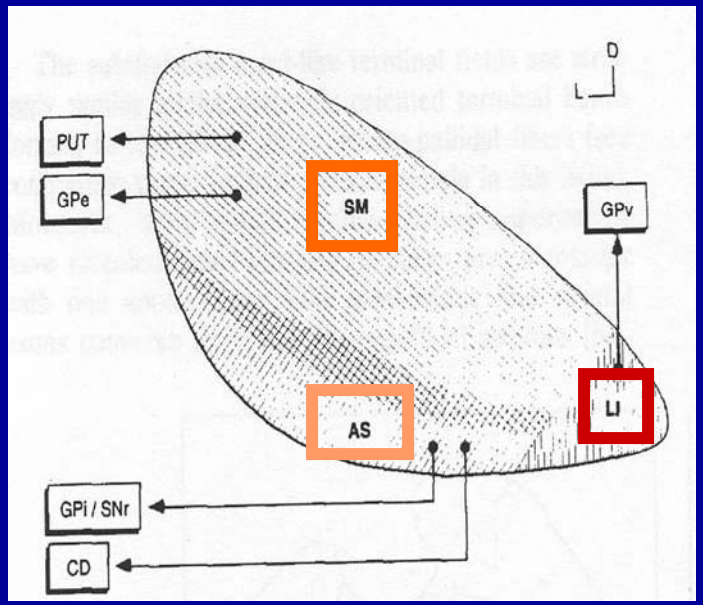
- Substantia nigra pars compacta
- Substantia innominata
- Amygdala
- Ventral tegmental area
- Locus ceruleus
- Raphe nuclei
- Dorsal motor nucleus of vagus nerve
- Intermediolateral column/Sympathetic ganglia




Lang AE et. al. NEJM, vol 339(15): p1047

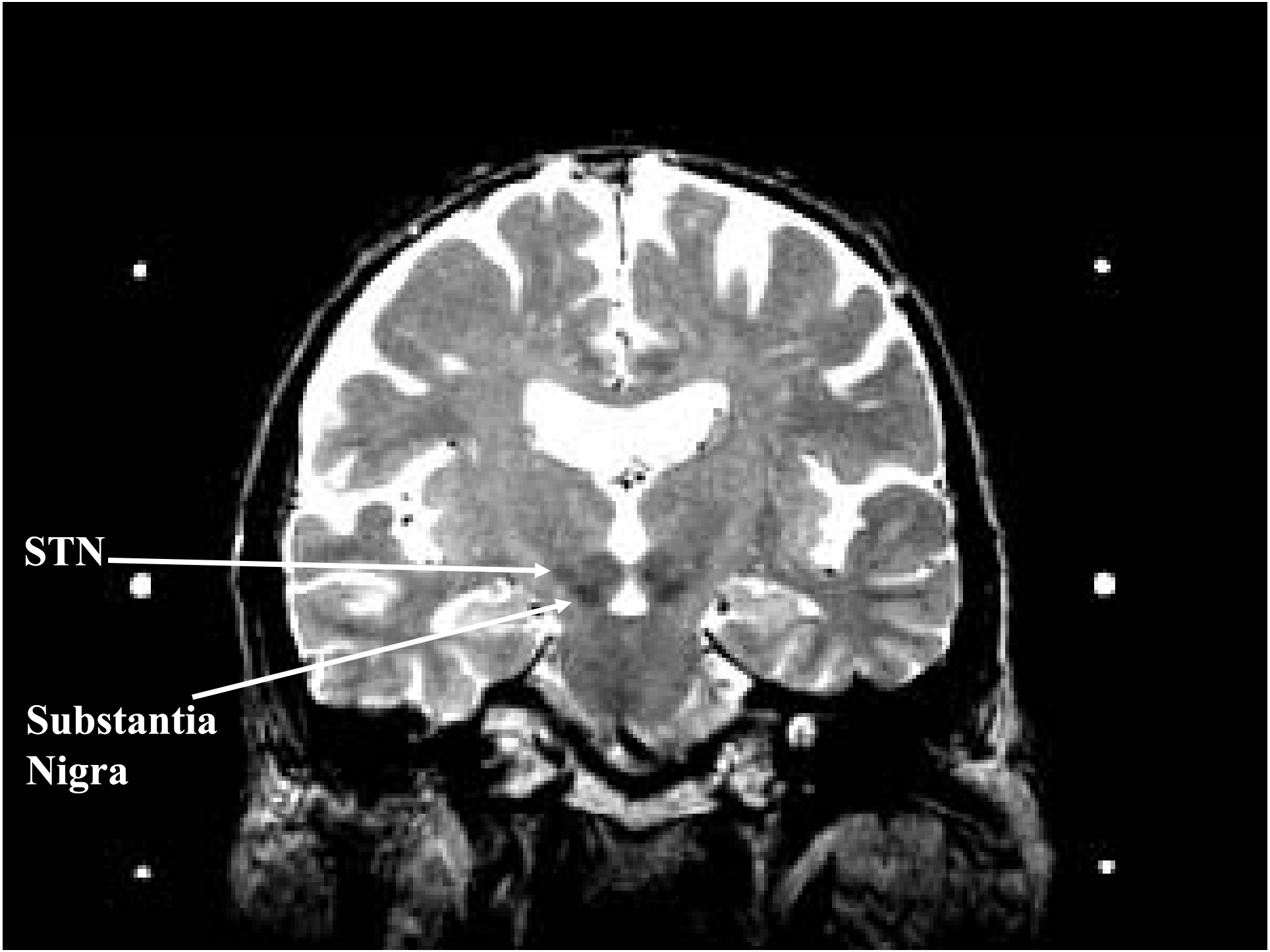
# *Functional Sections of the STN*

- **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

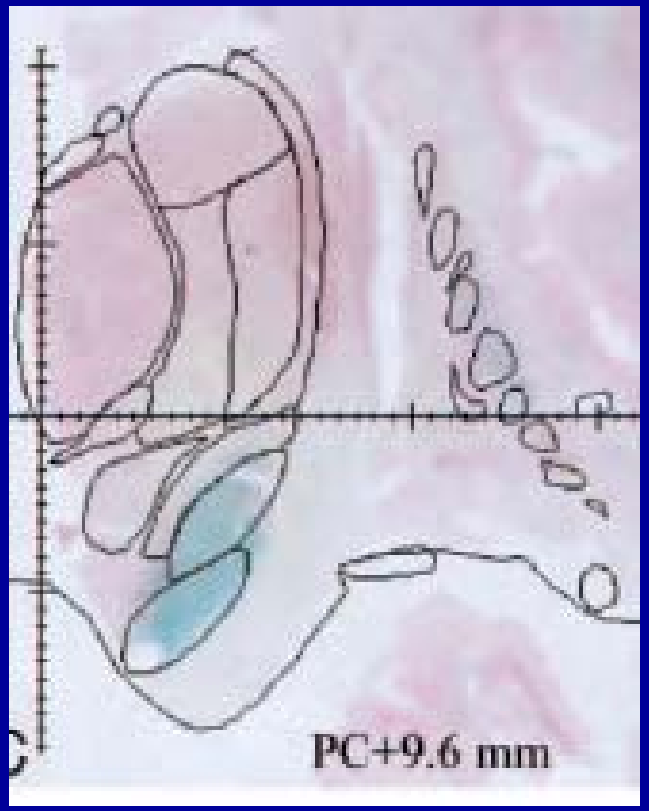
(Parent & Hazrati 1995)


STN
Substantia
Nigra

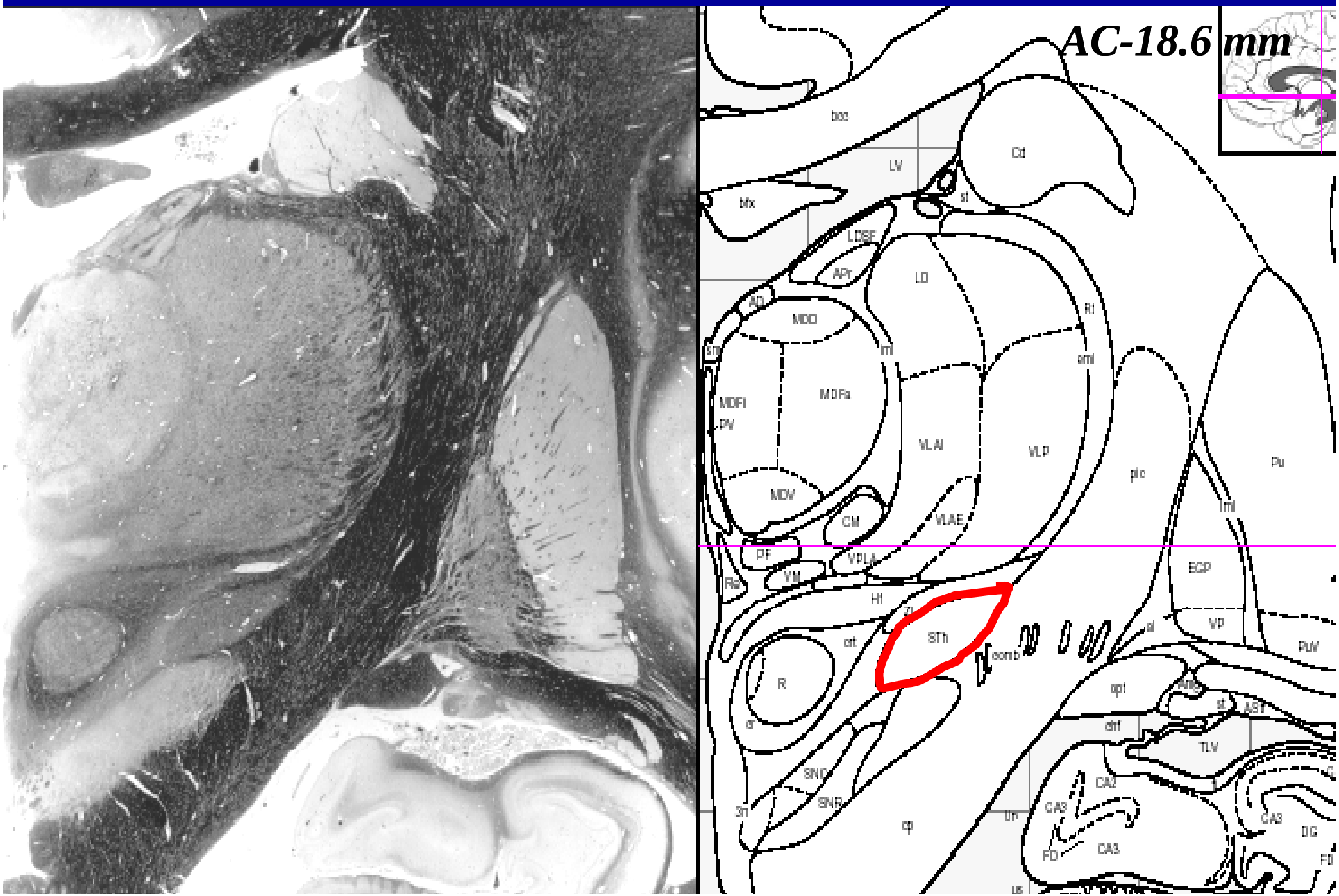
# Is the Subthalamic Nucleus Hypointense on T2-Weighted Images? A Correlation Study Using MR Imaging and Stereotactic Atlas Data

*AJNR Am J Neuroradiol* 25:1516–1523, October 2004

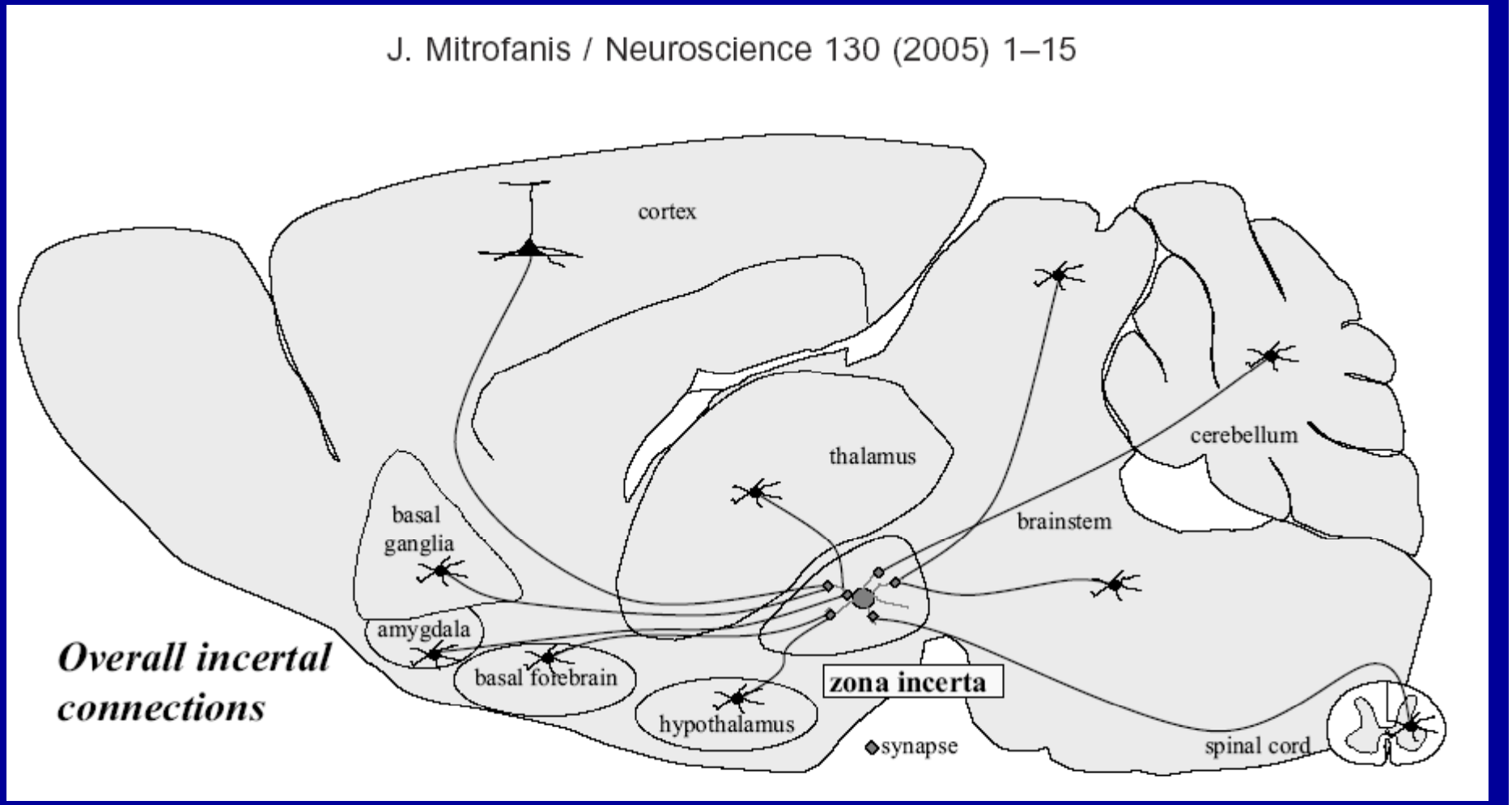
Didier Dormont, Kenneth G. Ricciardi, Dominique Tandé, Karine Parain, Carole Menuel, Damien Galanaud, Soledad Navarro, Philippe Cornu, Yves Agid, and Jérôme Yelnik

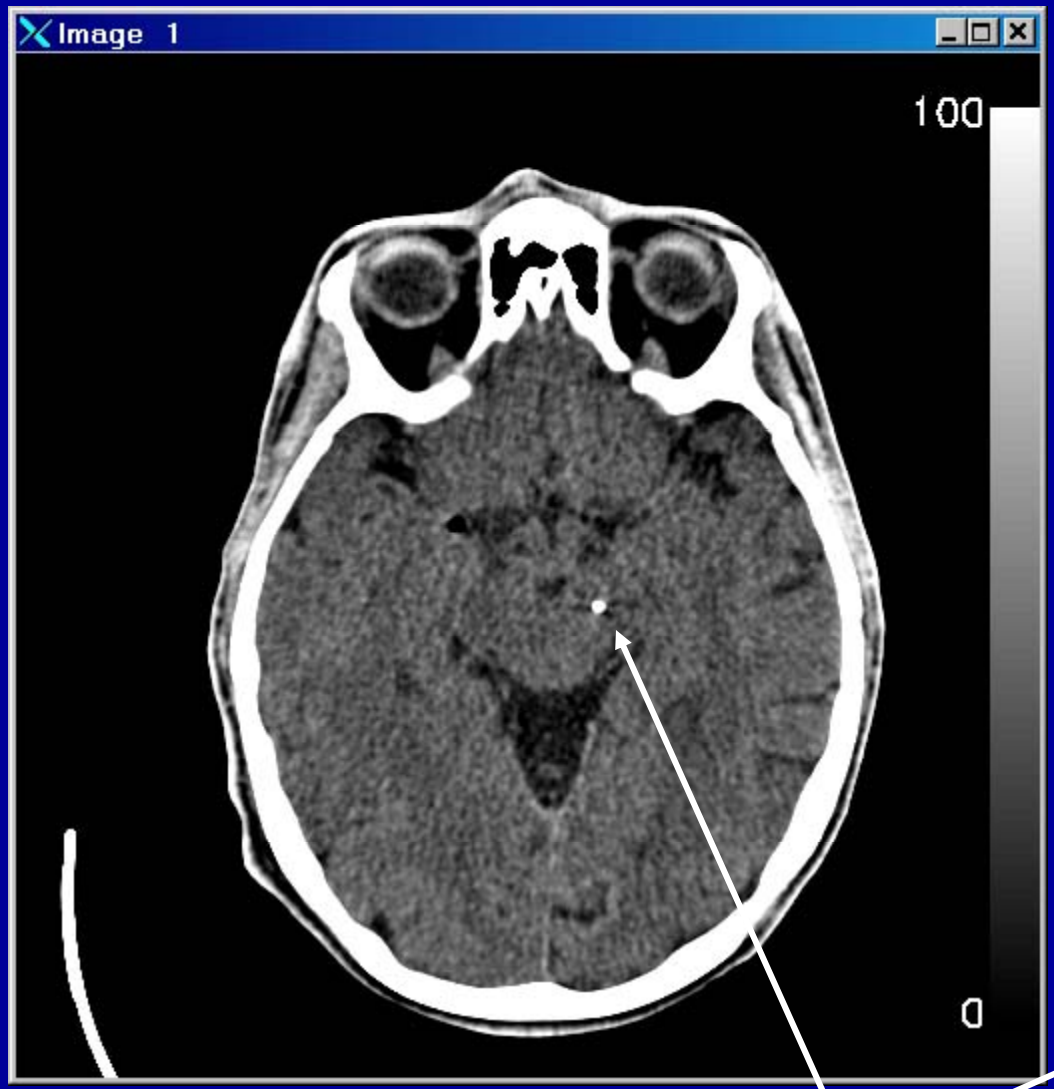

# Active Contact Localization

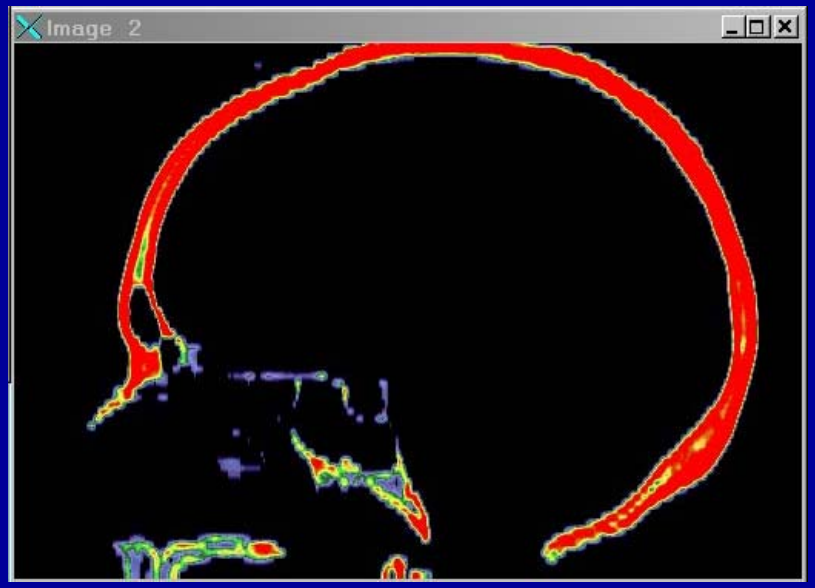


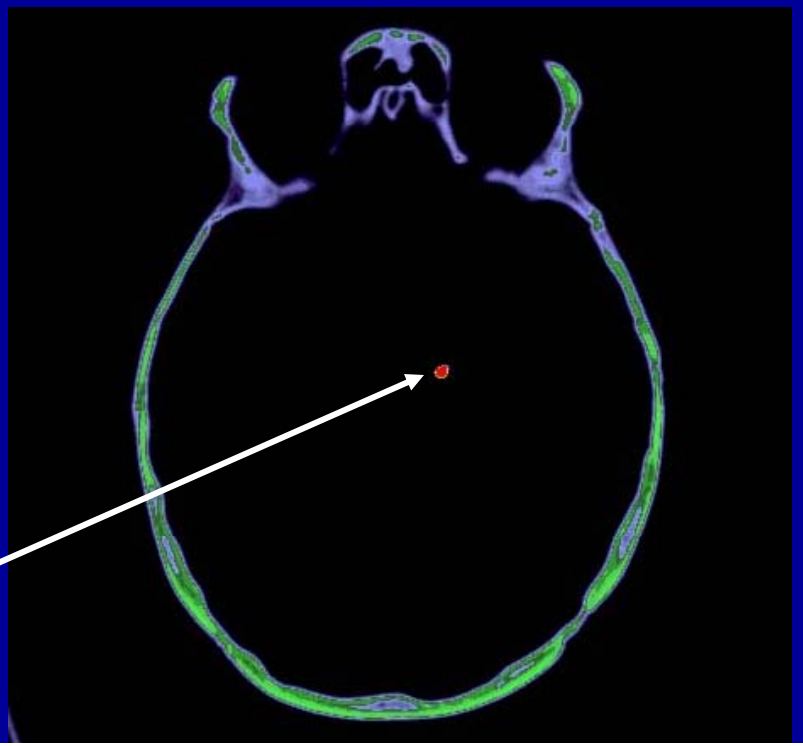
# *The Uncertainty of The Zona Incerta*



# *Post-Operative CT*



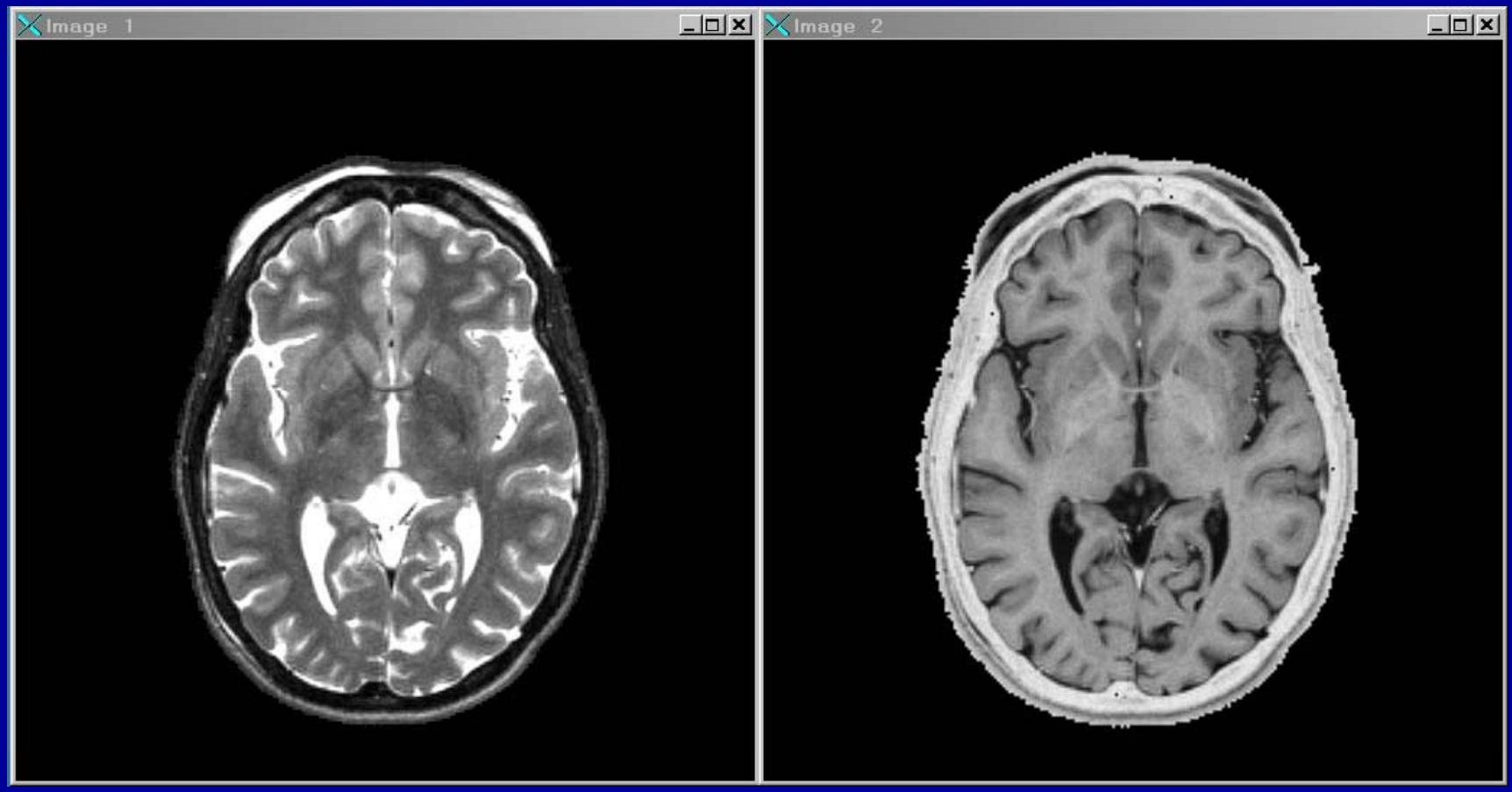



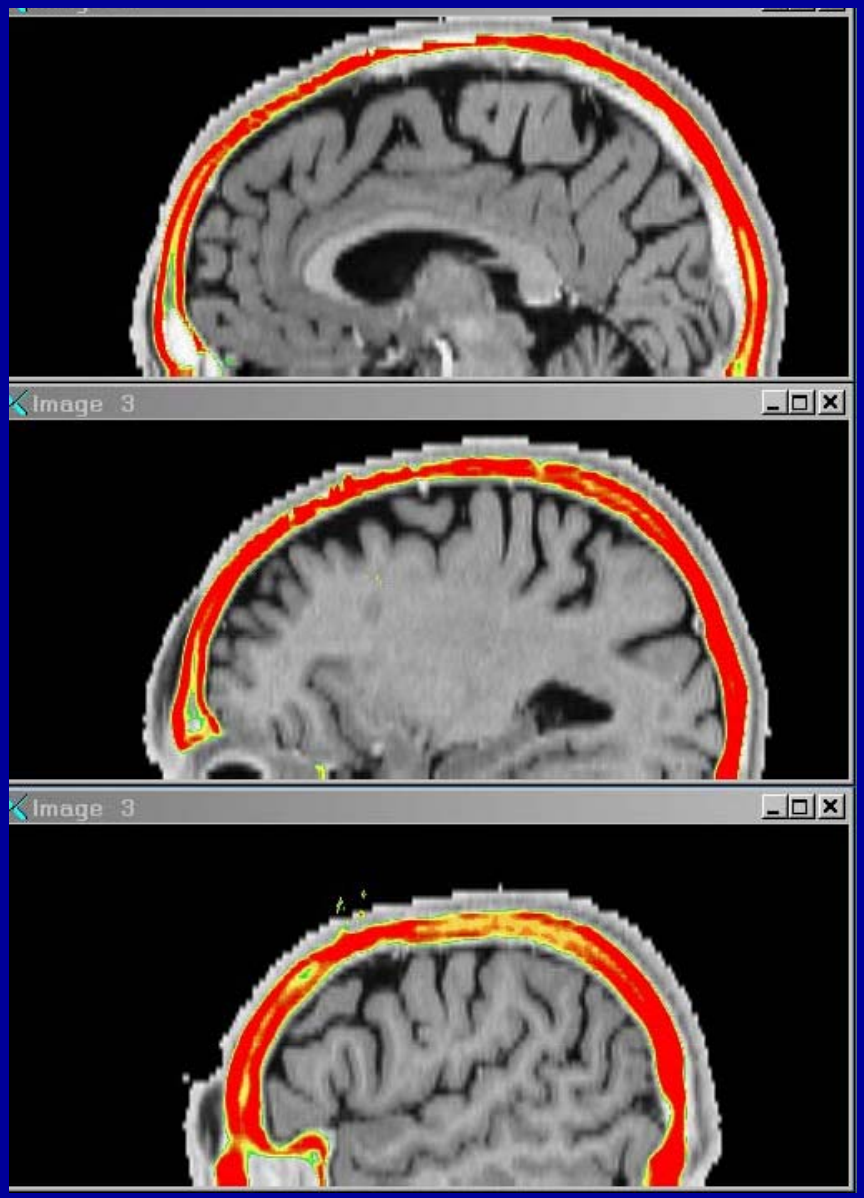
Tip of electrode

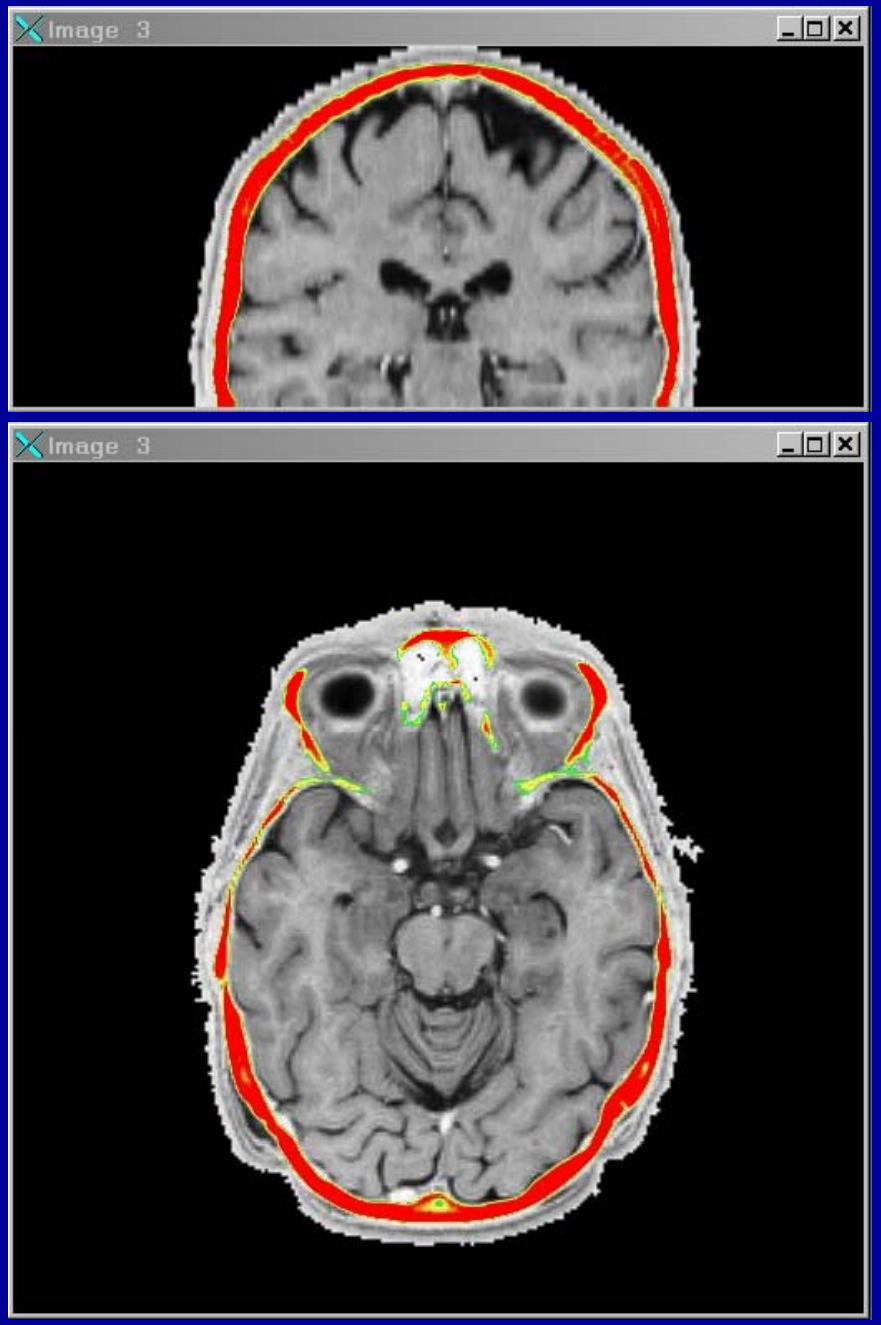
(Tom Videen, PhD)

# *Intra-Operative MRI: Intensity Inverted*



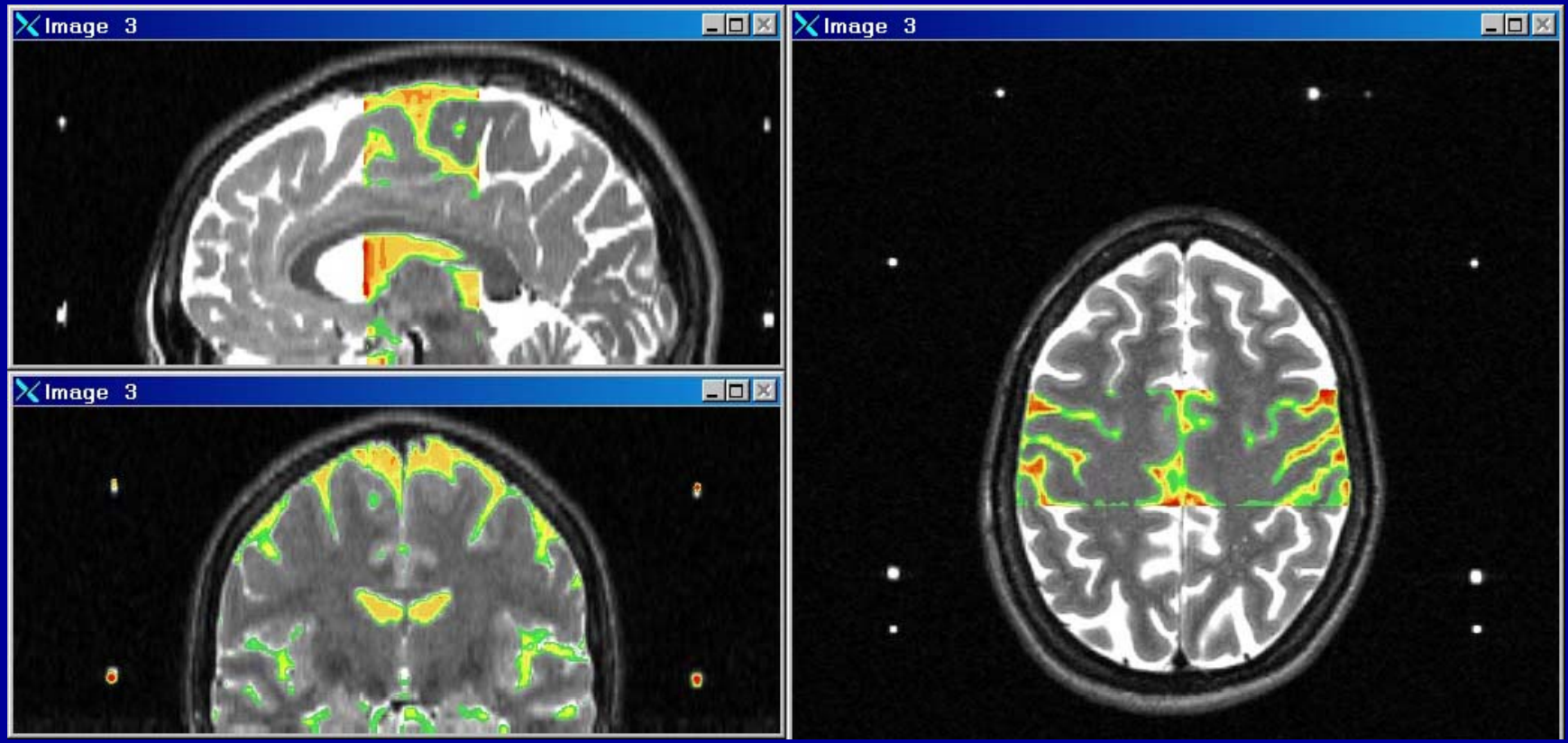
# *Overlap MRI/CT Images Using AIR* (Roger Woods, UCLA)*



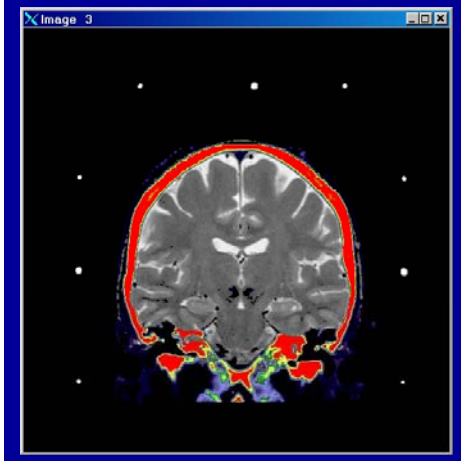



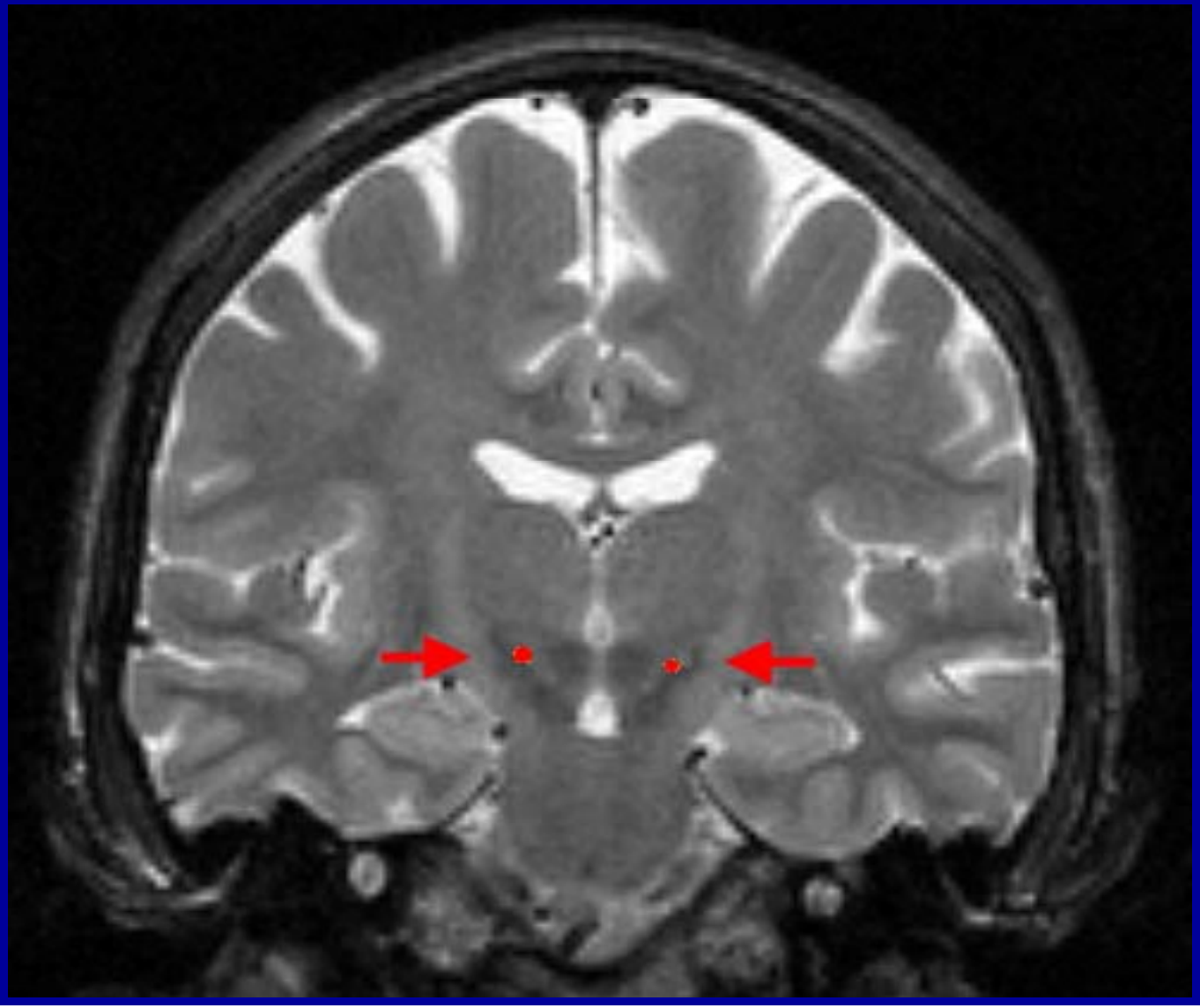

***Automated Image Registration**

# *Overlap Coronal MRI on Whole Brain Co-registered MRI/CT*

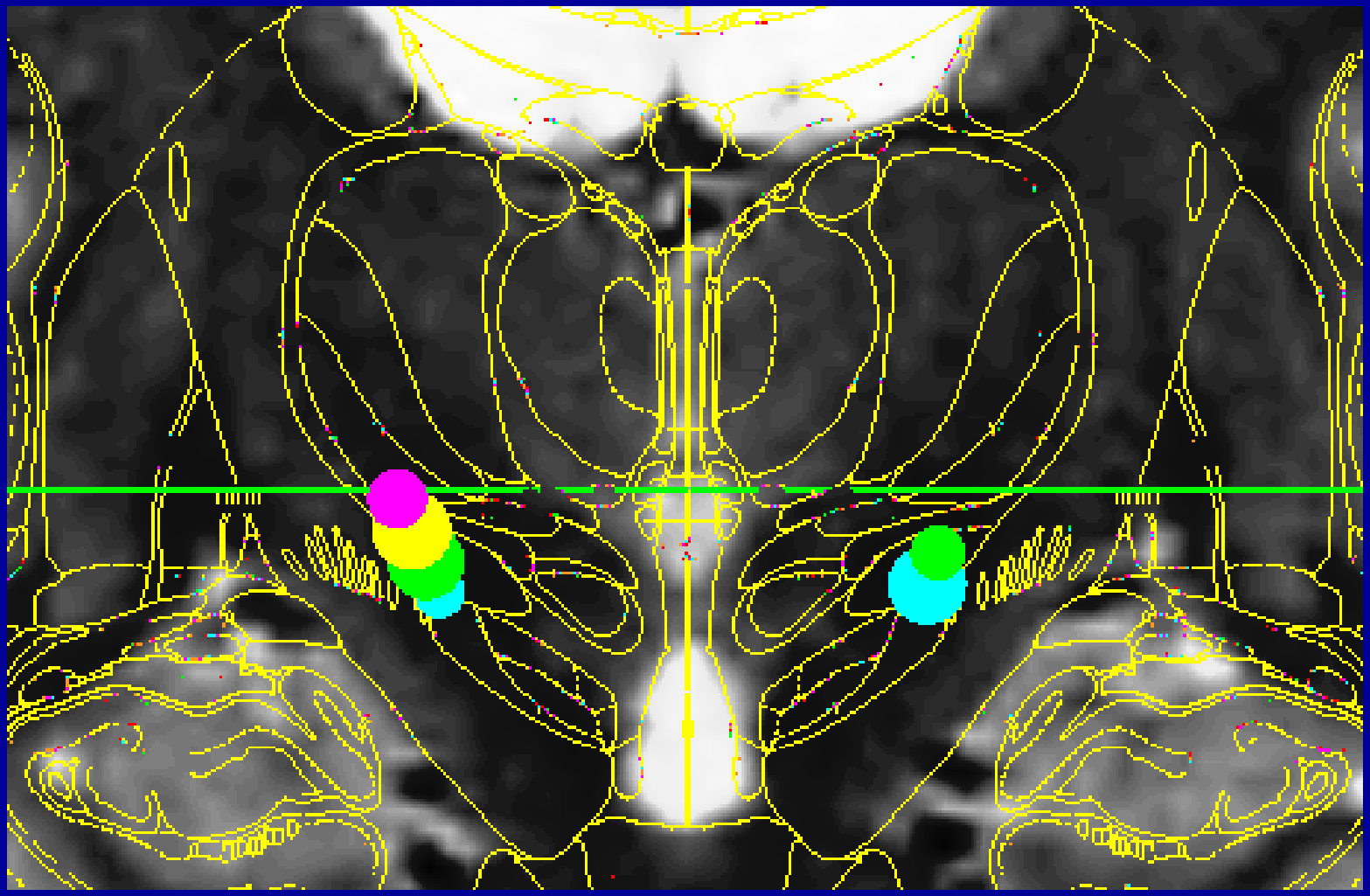


# *Overlap Active Contacts on Coronal MRI*



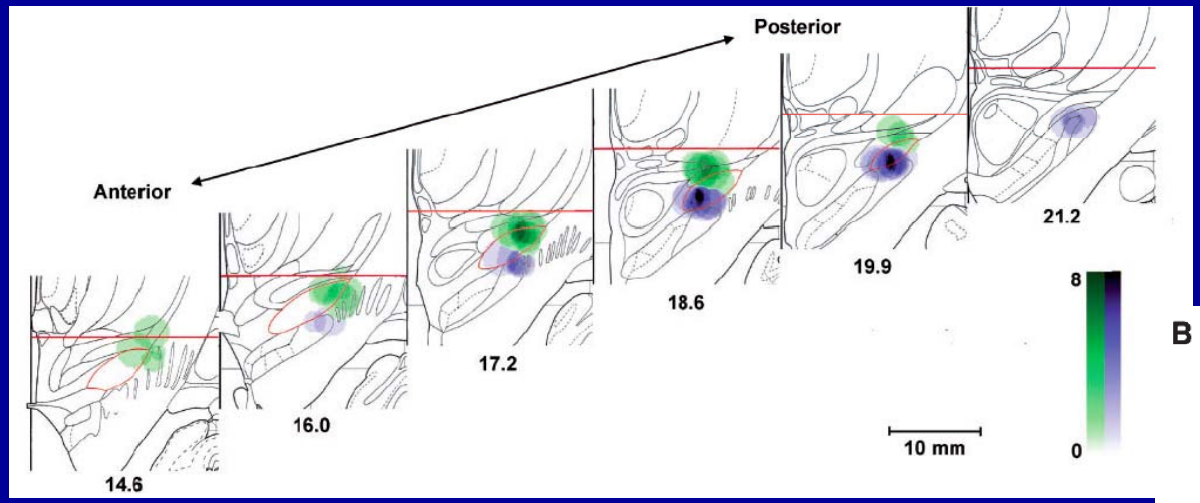



# *Active Contact Localization*

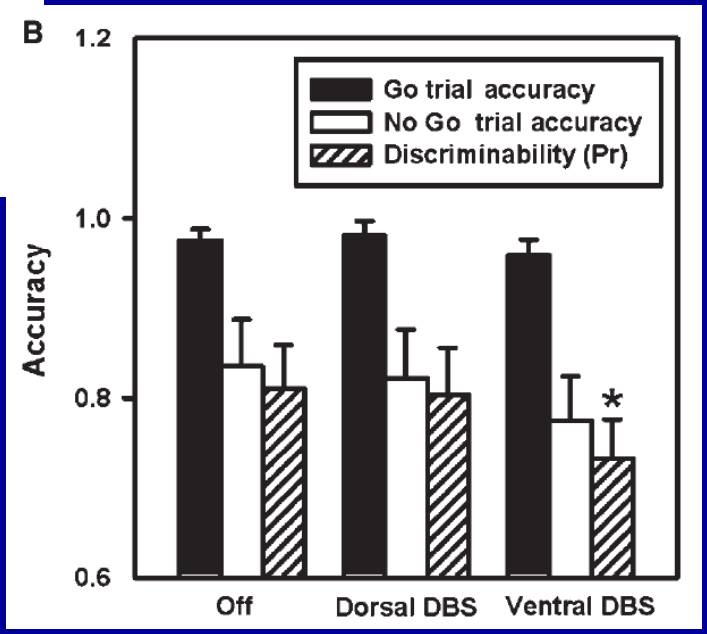


# *Unilateral Dorsal vs Ventral STN DBS*

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



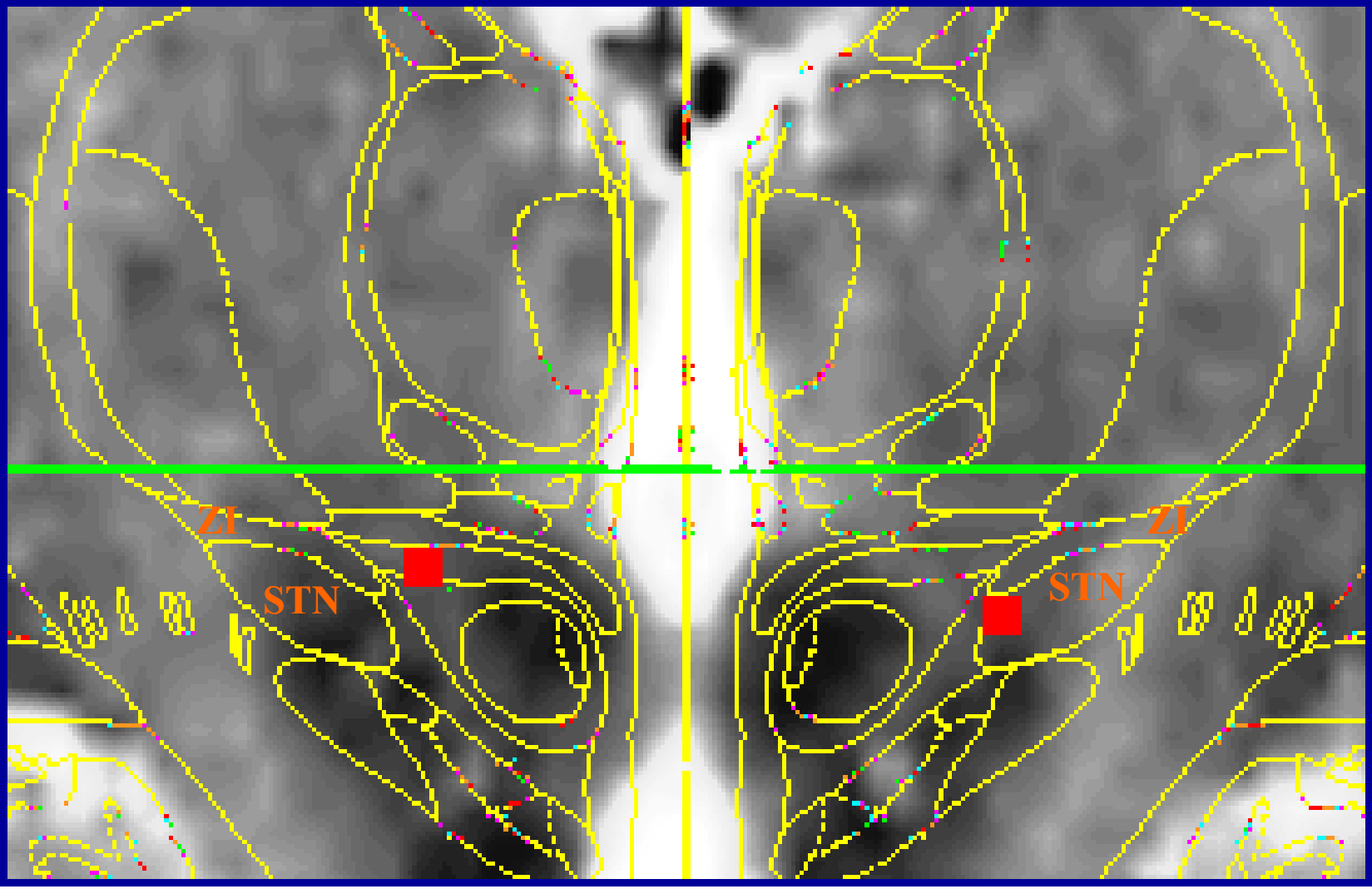

- **Ventral STN DBS caused definite impairment of response inhibition (Go-No-Go)**



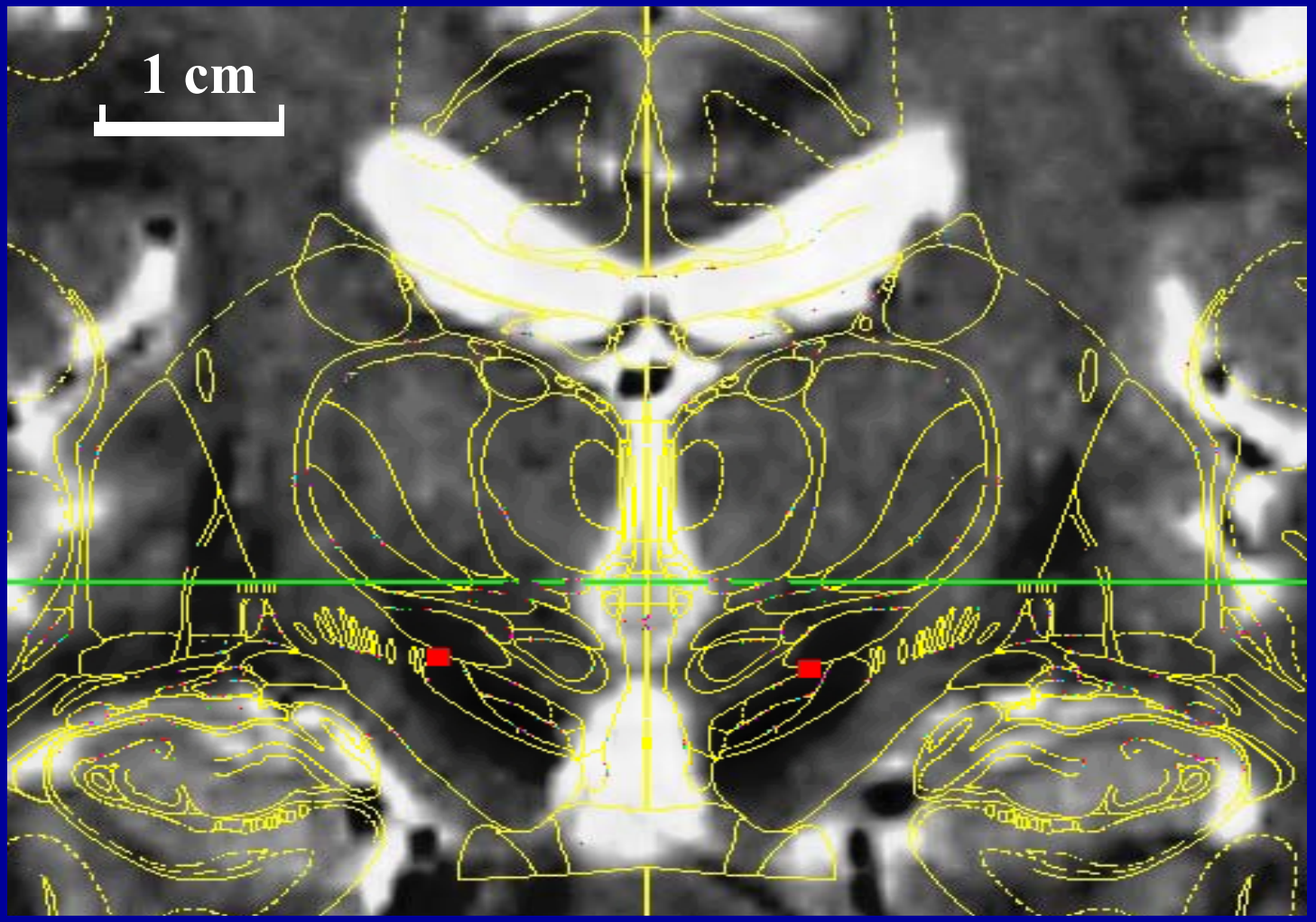
# Sami Harik

- Mentor
- Best Friend
- Best Squash partner!

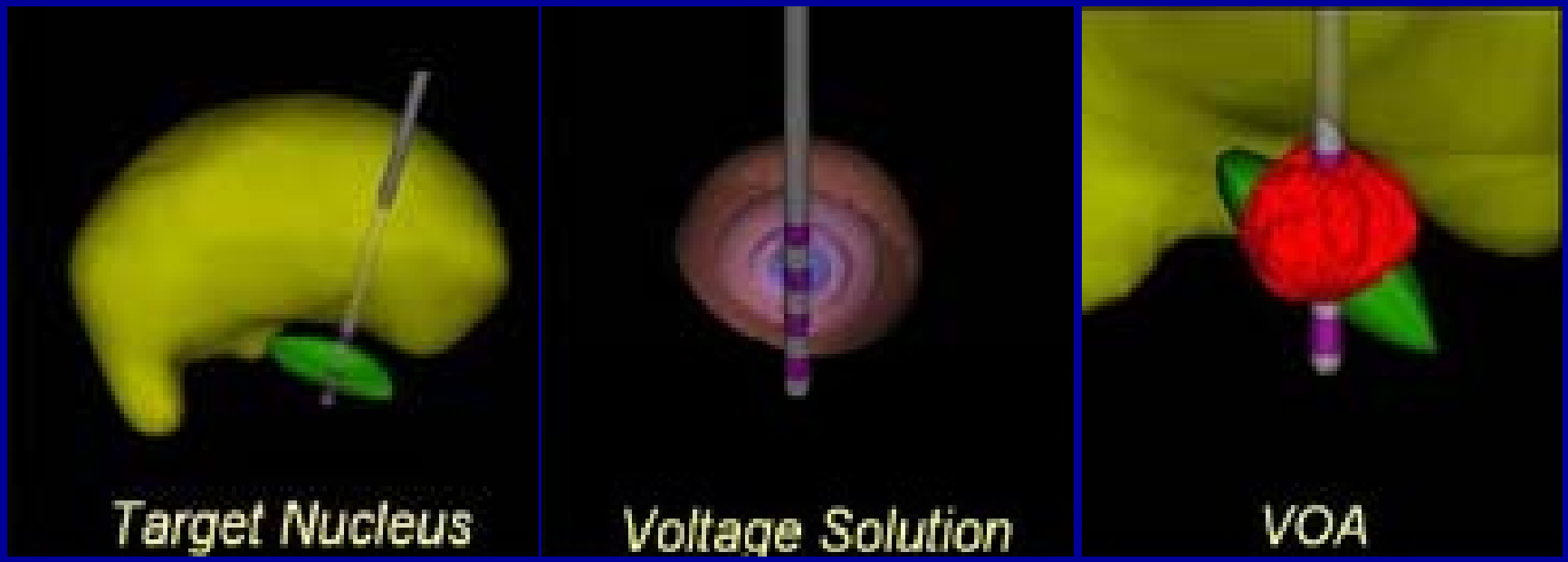
# *Active Contact Localization*



# *Active Contact Localization*

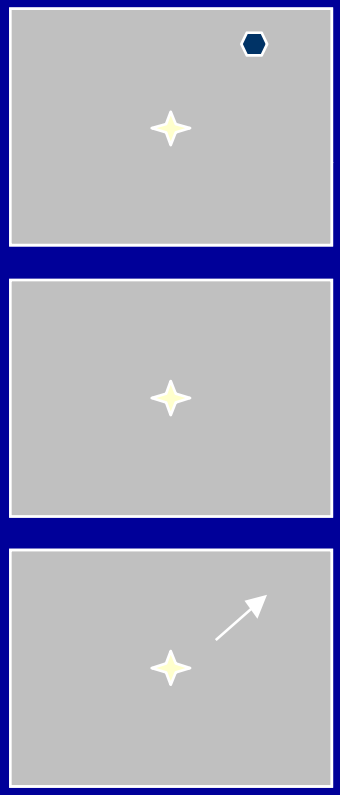


# *Volume of Activation*




**Cameron McIntyre**
**Cleveland Clinic, Dept of Biochemical Engineering**

# *Spatial Delayed Response Task*



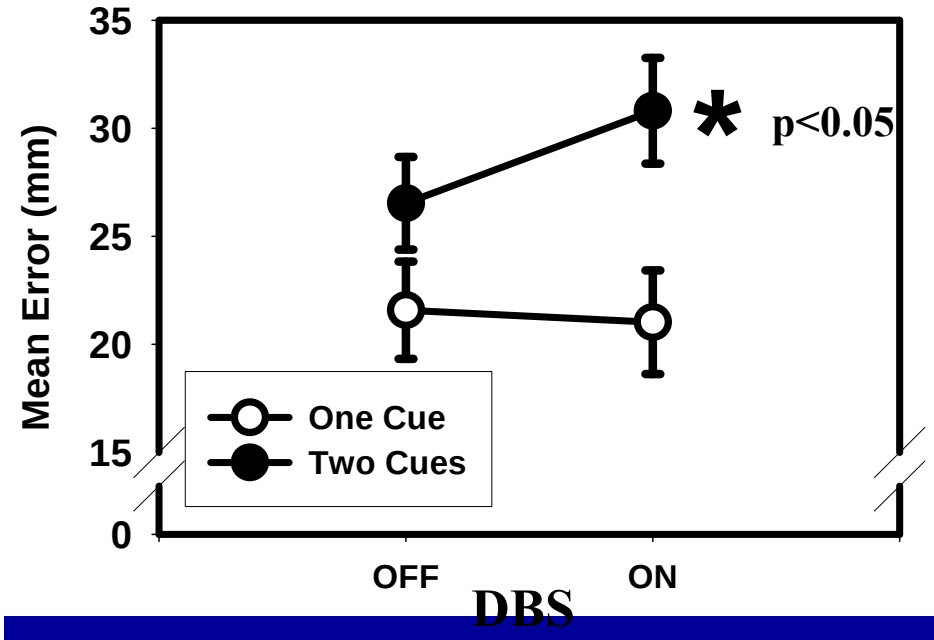
**Cue**

**Delay**

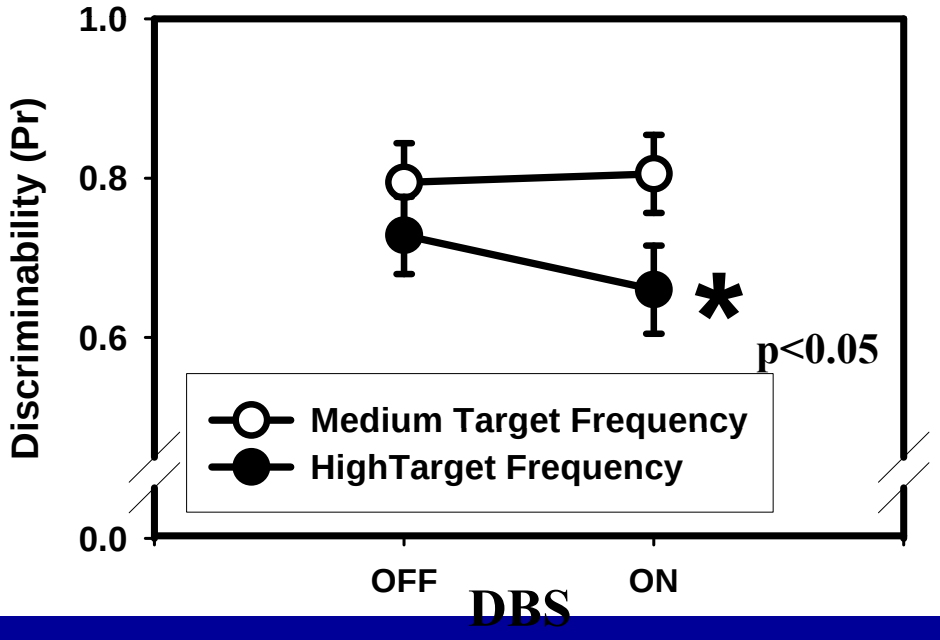
**Response**

# *STN DBS May Affect Higher Cognitive Function*

## Spatial Delayed Response



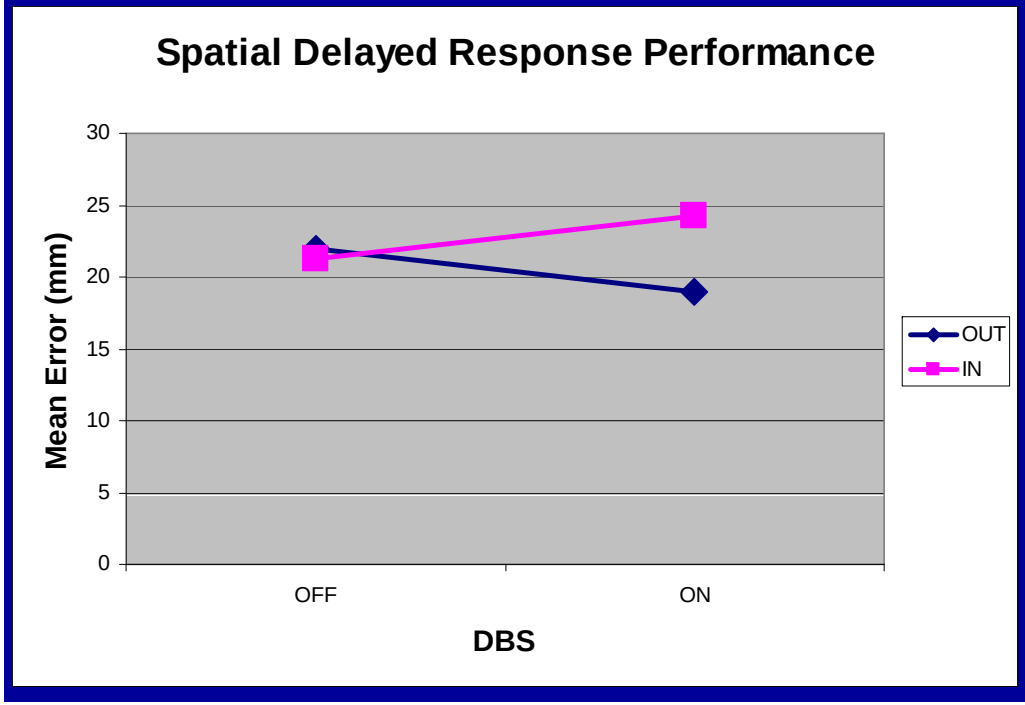

## Response Inhibition

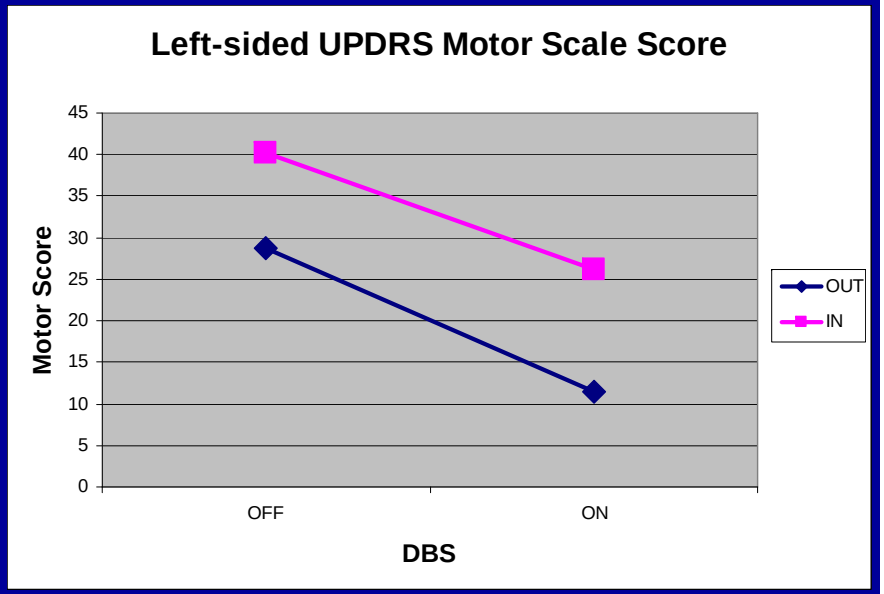



Hershey at al, 2004

# *Effect Of Active Contact Location On Spatial Working Memory*

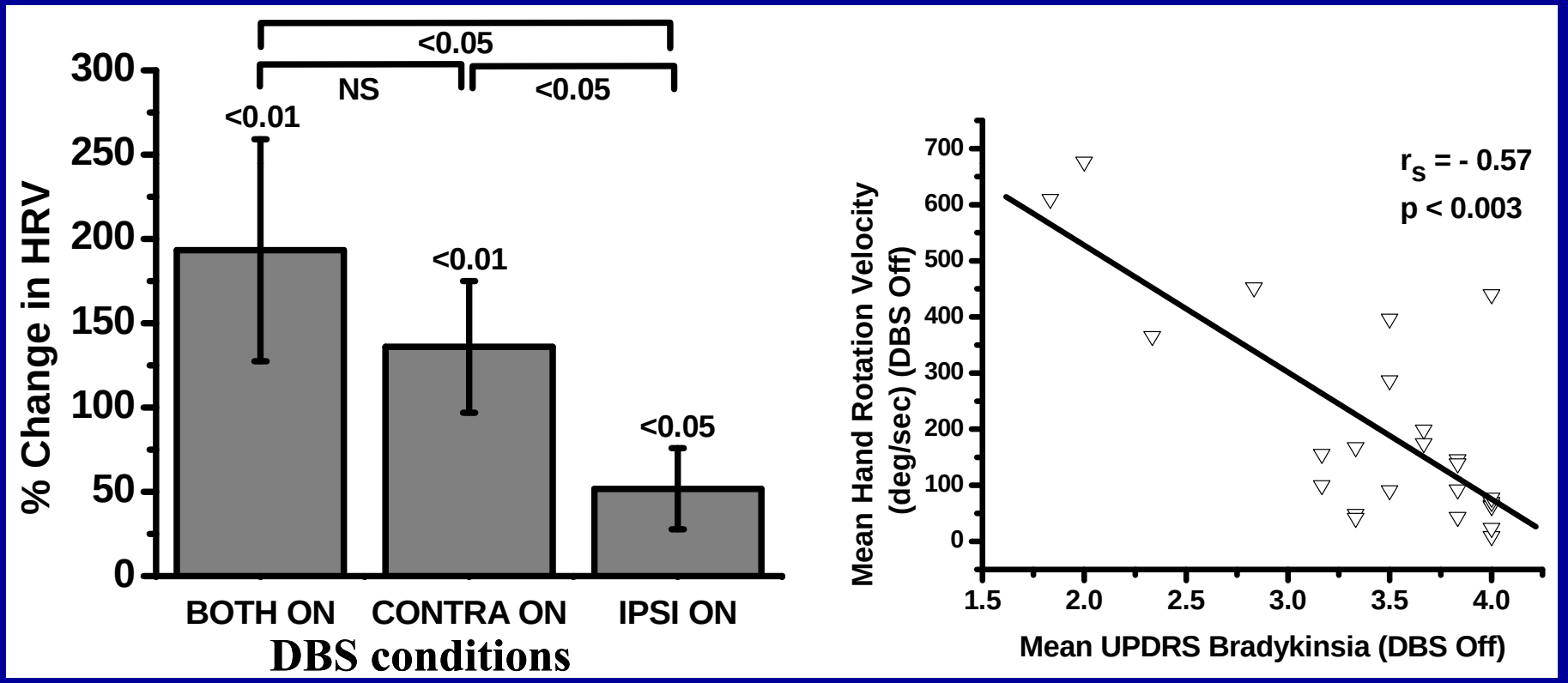
- **Spatial working memory (rated by SDR performance):**
  - ***improved*** **on DBS when the active contact was located *out* of the STN.**
  - ***worsened*** **when the active contact was located *in* the STN.**




**Hershey at al, 2006**

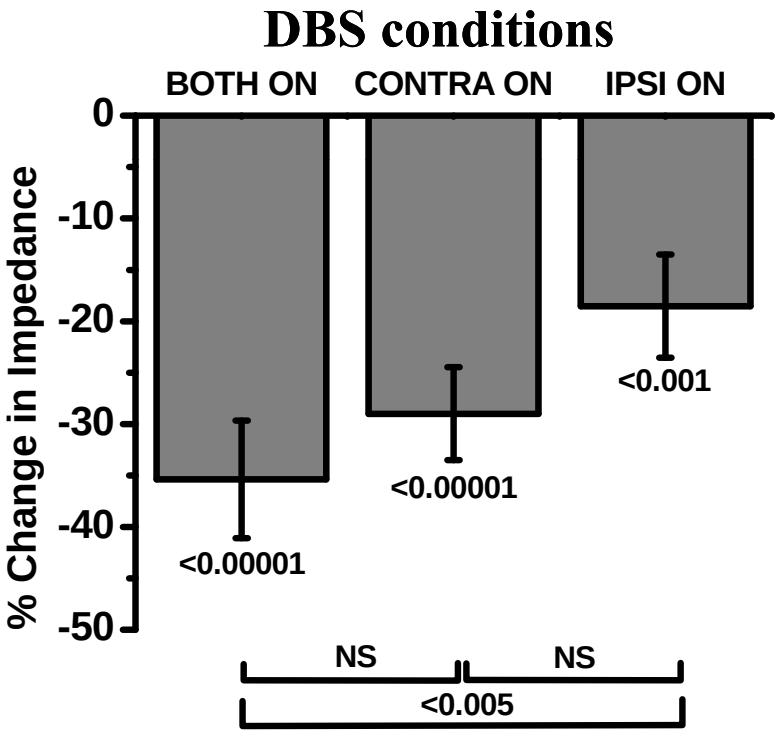
# *Unilateral STN DBS Improves Bradykinesia Bilaterally*



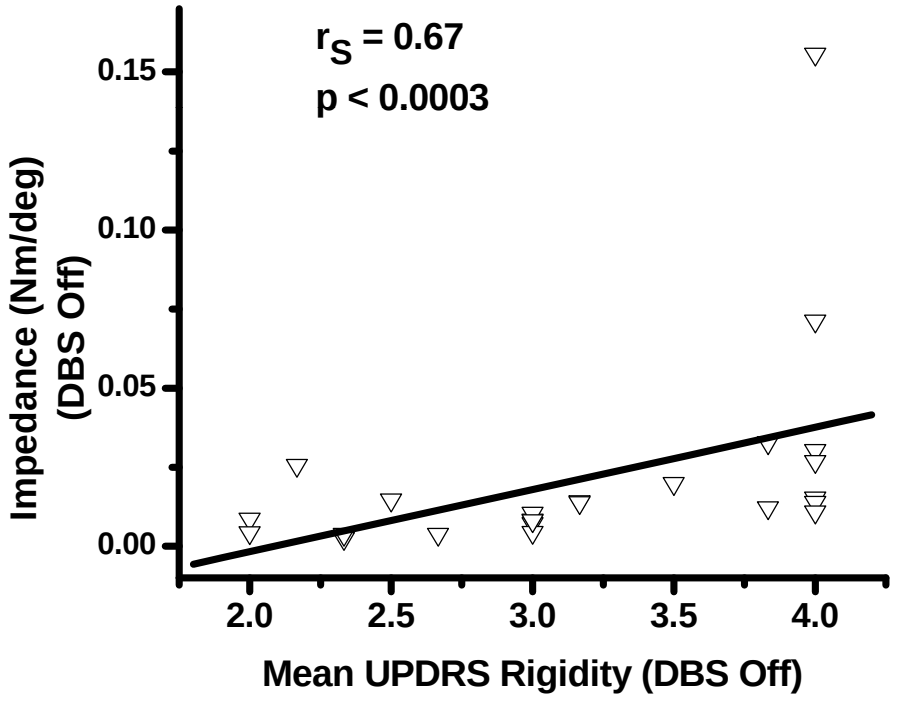

(N=38)

(N=25)

# *Unilateral STN DBS Improves Rigidity Bilaterally*

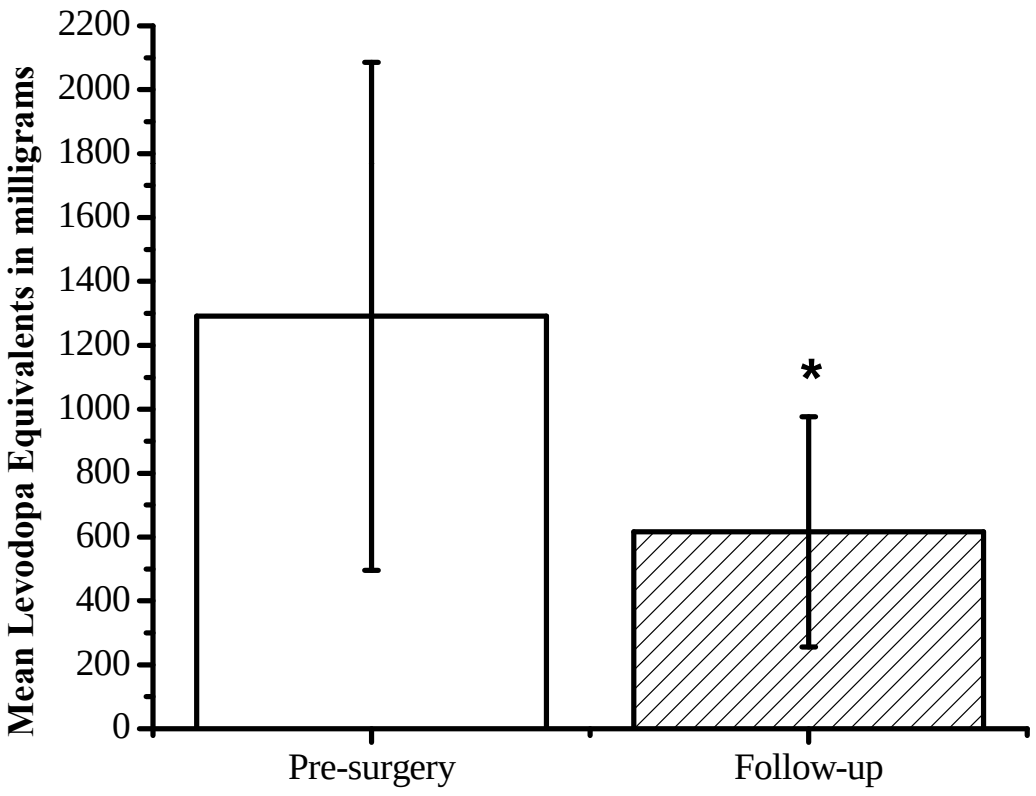



(N=42)




(N=24)

# *Levodopa-Equivalents Reduction at 6 Months After STN DBS*




*p≤ 0.001

# *Effect of STN DBS on UPDRS Motor Scores*

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

# *Demographic Profile*

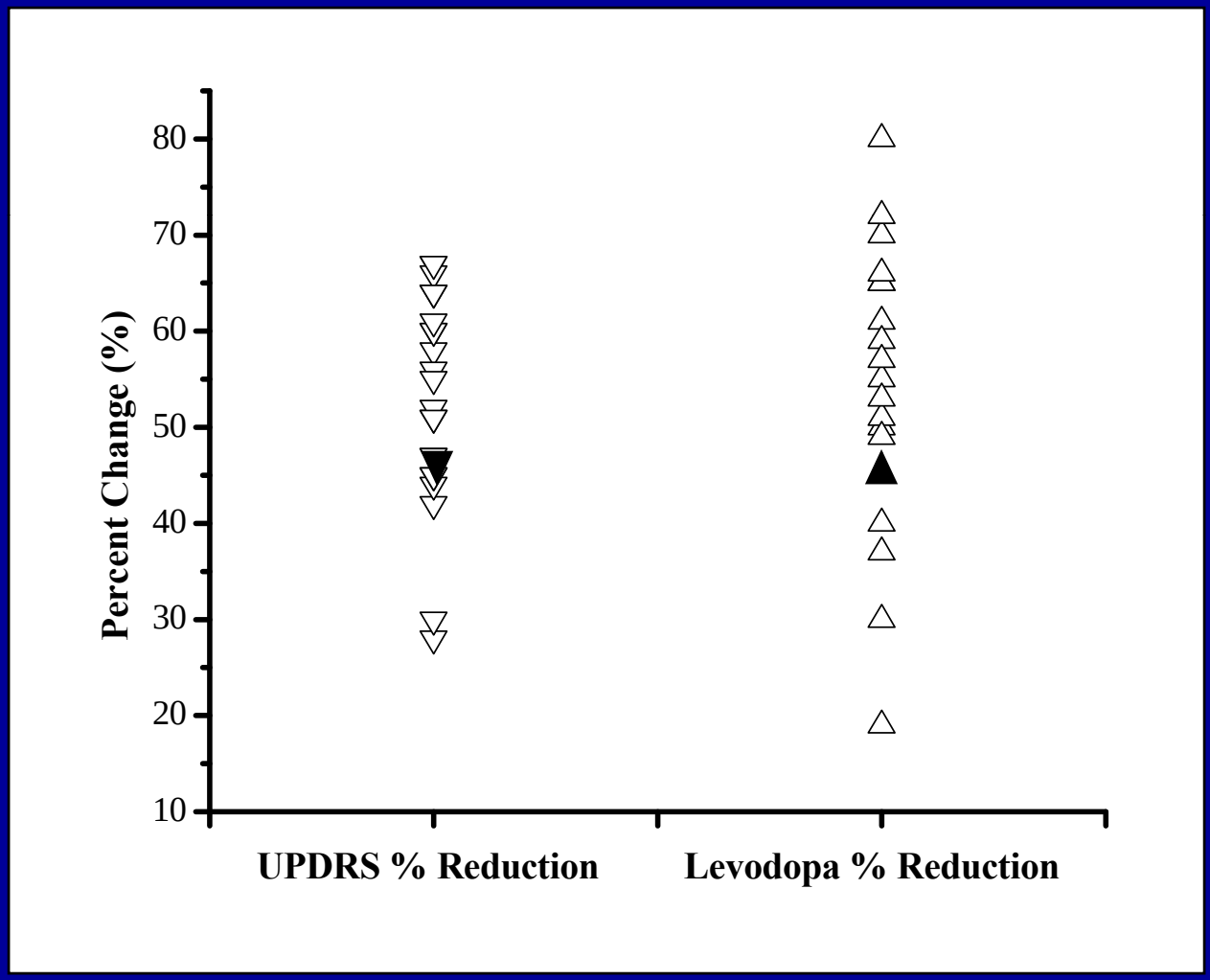
| | All operated patients (N=110) | Outcome Analysis Subgroup (N=72) |
|---|---|---|
| **Gender**<br>**Male**<br>**Female** | <br>**66**<br>**44** | <br>**41**<br>**31** |
| **Age at onset of symptoms (in years)** | **47.9 ± 10.2 (22-69)** | **48.4 ± 9.8 (28-69)** |
| **Age at time of surgery (in years)** | **62.6 ± 8.8 (31-84)** | **63. 0 ± 8.2 (45-78)** |
| **Duration of Parkinson disease at time of surgery (in years)** | **14.5 ± 6.3 (4-29)** | **14.5± 6.5 (4-29)** |

| Leading Author | Year of publication | Number of patients | Duration of follow-up (months) | Reduction in motor UPDRS score | Reduction in daily levodopa-equivalent dose |
|---|---|---|---|---|---|
| Limousin | 1998 | 24 | 12 | 60 % | 50 % |
| Kumar | 1998 | 7 | 6-12 | 58 % | 40 % |
| Moro | 1999 | 7 | 16 | 42 % | 65 % |
| Burchiel | 1999 | 5 | 12 | 44 % | 51 % |
| Pinter | 1999 | 9 | 3-12 | 45 % | - |
| Bejjani | 2000 | 12 | 6 | 64 % | 70 % |
| Houeto | 2000 | 23 | 6 | 67 % | 61 % |
| Rodriguez-Oroz | 2000 | 15 | 6 | 60 % | - |
| Molinuevo | 2000 | 15 | 6 | 66 % | 80 % |
| DBS for PD Study Group | 2001 | 91 | 6 | 51 % | 37 % * |
| Lopiano | 2001 | 16 | 3 | 56 % | 72 % |
| Volkmann | 2001 | 16 | 12 | 67 % | 65 % |
| Ostergaard | 2002 | 26 | 12 | 64 % | 19 % |
| Simuni | 2002 | 12 | 12 | 47 % | 55 % |
| Starr | 2002 | 10 | 12 | 45 % | - |
| Thobois | 2002 | 18 | 6 | 55 % | 66 % |
| Vesper | 2002 | 38 | 12 | 52 % | 53 % |
| Voges | 2002 | 15 | 6-12 | 61 % | 59 % ** |
| Pahwa | 2003 | 33 | 12 | 28 % | 57 % |
| Herzog | 2003 | 48 | 6 | 51 % | 49 % |
| Ford | 2004 | 30 | 12 | 30 % | 30 % |
| Tabbal | 2006 | 72 | 3-12 | 47 % | 45 % |

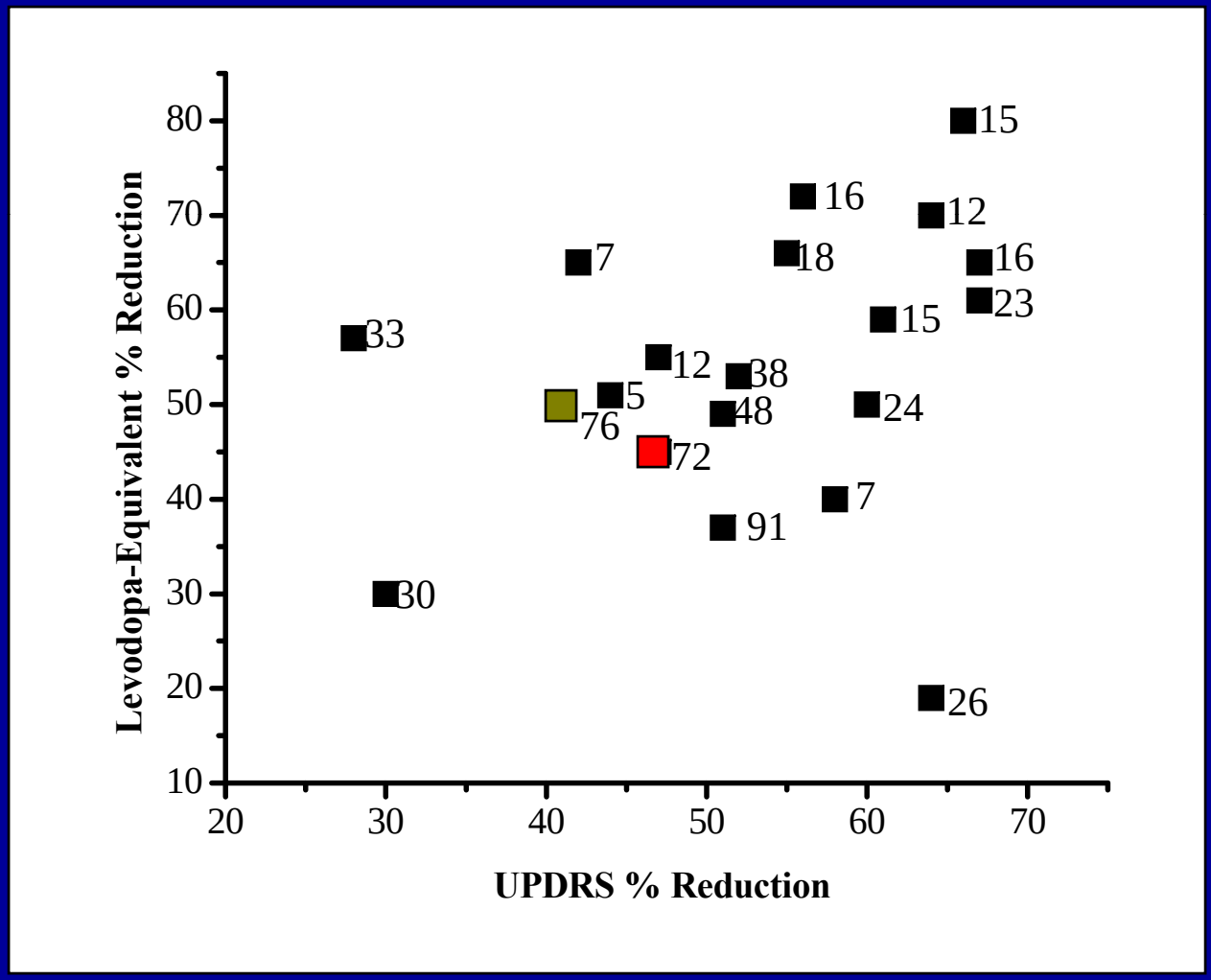
# *First 110 STN DBS Patients at Washington University in St Louis*

- **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*

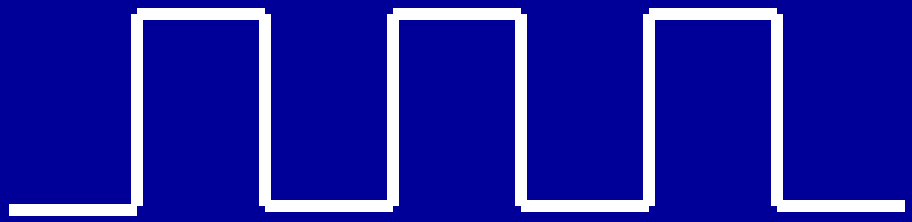


# *STN DBS Studies from 1998 to 2006:*
## *UPDRS vs Levodopa-Equivalent % Reduction*

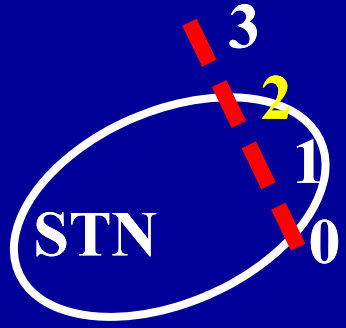


# *STN DBS Parameters*

- **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-commisural plane)
  - Anterior tip of the putamen (in commisural plane)
  - Red nucleus
  - Brain edge (in commisural 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