

Deep Brain Stimulation

Disclosures

Objectives

- Describe DBS
- Review the role of DBS in Parkinson's Disease
- Discuss patient criteria and process
- Briefly mention surgical procedure
- Post DBS management including pitfalls and misconceptions
- Long term DBS benefits

DBS Introduction

- High frequency, pulsatile, electrical stimulation
- Stimulation via a stereotactically placed electrode into target nucleus
- Essential Tremor: FDA approved 1997
- Dystonia: FDA approved 2003
- Parkinson's Disease FDA approved in 2002

Role of DBS in Parkinson's Disease

- PD is a progressive neurodegenerative disorder with loss of dopaminergic neurons leading to progressive motor impairment
- PD also involves degeneration of non dopaminergic neurons leading to a variety of non motor symptoms.
- Cardinal motor signs:
 - Tremor, Bradykinesia and Rigidity
- Signs of advancing disease:
 - Increased off time
 - dyskinesia
 - balance impairment
 - falls

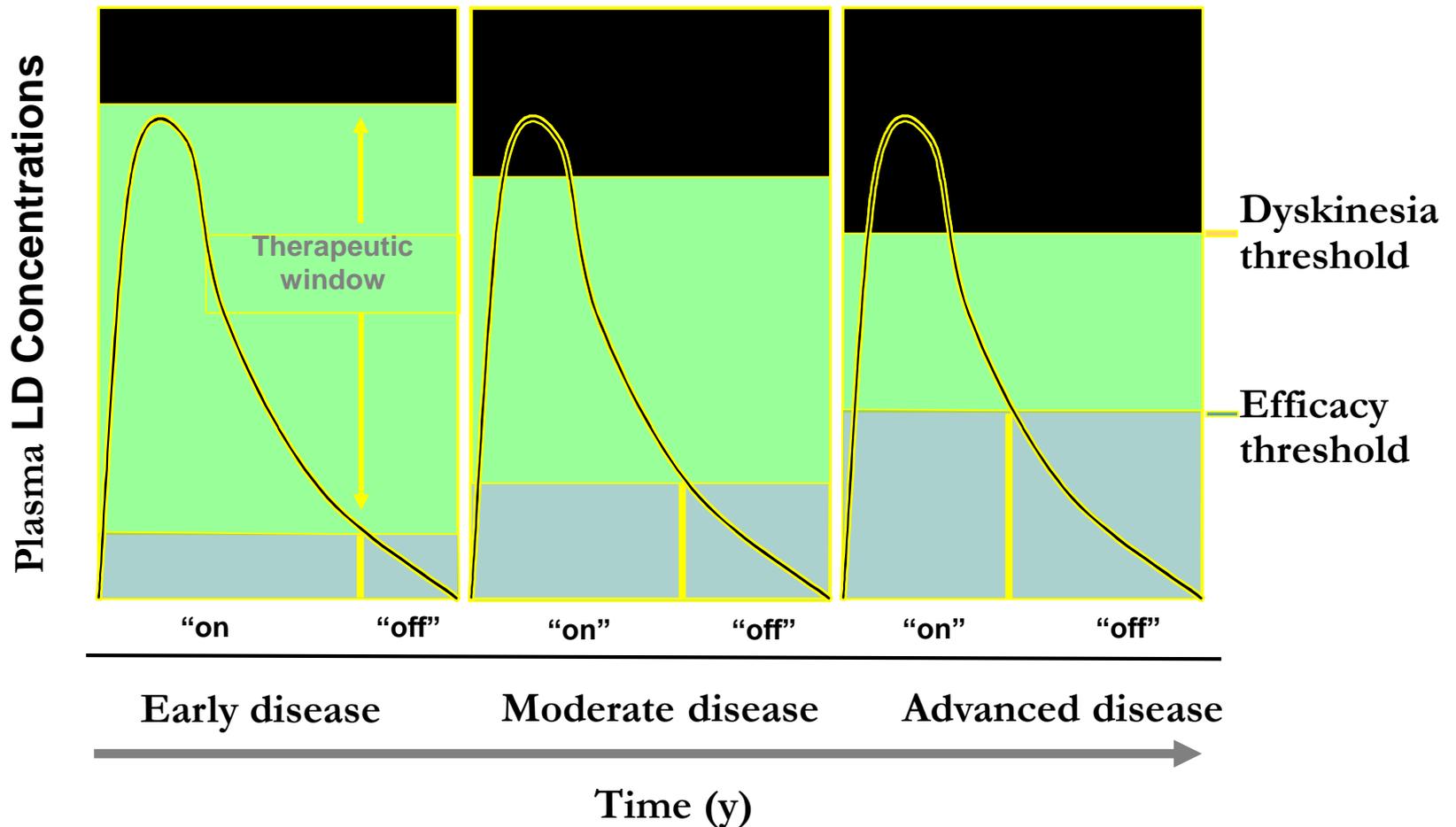
Patient Selection

- Patient Selection:
 - Advanced PD
 - motor fluctuations
 - Disabling dyskinesia or off time
 - Responsive to L-dopa
 - QOL impairment due to dyskinesia or off time
 - medically intractable tremors
 - Tremor is out of proportion to the rest of the PD symptoms
- Tremor impairs ADLs, iADLs

Patient Selection II

- No absolute age contraindication, but generally prefer $< 65-70$
- No significant cognitive dysfunction
- No significant mood disorder (or well controlled)
- Good support system at home
- Able to return for DBS programming
- Realistic expectations

Therapeutic Window in Parkinson's Disease



Management of Motor fluctuations

- Medical Management
 - Smoothen delivery of medications
 - Lower Levadopa dose and increase frequency
 - Less pulatile Levadopa
 - Rytary
 - Add / Increase dose of longer acting medications
 - MAO-B inhibitors
 - Rasagiline, Selegiline
 - Extended release DA
 - Pramipexole ER,
 - Ropinerole XL,
 - Rotigotine patch
- Medical Management
 - Dose adjustment may result in worsening compliance
 - Dose adjustment may reduce dyskinesia but increase off time
- Surgical Treatment
 - Deep Brain Stimulation (DBS)
 - CLES (Duopa)

A “Good” DBS Candidate

- Indications:
 - Motor complications refractory to medical management
 - Refractory tremor
- Good response to levadopa
 - Levadopa responsiveness parallels DBS responsiveness
 - Patient has tried or is on a combination of medications.
- Cognitively intact
- Absence of severe depression
- Absence of severe balance problems
- No specific age cut off, though younger age patients do better

Red flags

- Poor or no response to levodopa
- Diagnosis of Parkinsonism
- Cognitive impairment / Dementia
- Presence of severe untreated depression

DBS Process: Pre-Initiation

- Review Patient Criteria
 - Check indications & red flags
 - Are symptoms medically refractory?
 - Review medications
 - Combination of Carb/Levo at reasonable doses + Adjuncts
 - Adjuncts: MAO-B Inhibitors, Dopamine agonists, COMT inhibitors
 - Either patient symptoms were not managed with medications or patient did not tolerate medication

DBS Process: Initiation

- Recommend DBS focused visit
- Discuss role of medications in PD
 - Mention that medications while helpful are not providing adequate relief
 - Focus on QOL
- Discuss with patient role of DBS
 - Deep Brain Stimulation is designed to manage symptoms that are responsive to medications
 - Best “on time” without dyskinesia
 - Analogy “electrical levadopa”
 - Tremor, bradykinesia, rigidity improve with DBS

DBS Process: Initiation

- DBS Benefits
 - Improve “on” time without dyskinesias
 - Reduction of dyskinesias
 - Reduction of “off” times
 - Better tremor control
 - Medication adjustments
 - Approximately 50% reduction in medications
- Bottom line: The reason to recommend DBS is to improve QOL with reduction of tremor, motor fluctuations and motor symptoms of PD

DBS Process: Initiation

- DBS side effects
 - During surgery
 - Stroke
 - Hemorrhage
 - Infection
 - After Surgery
 - Depression
 - Balance problems
 - Hardware Related
 - Infection at battery site
 - Lead migration / fracture
- Realistic Expectations
 - May not help balance
 - Will not help complex motor problems
 - Voice will not improve and may worsen
 - Does **not** change underlying disease progression.

DBS Process: The Road forward

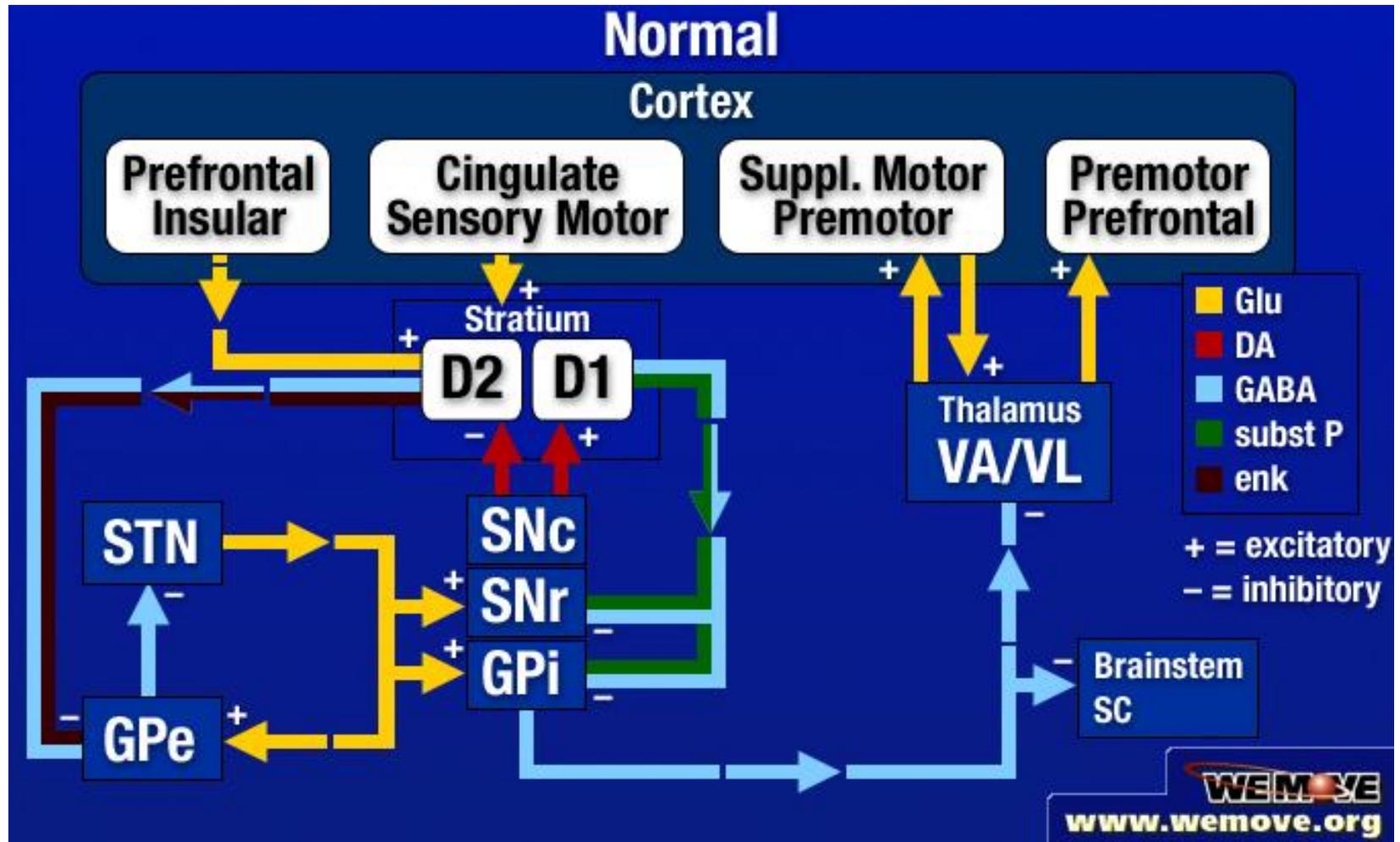
- Provide literature for review:
 - National Parkinson's Foundation Booklet
 - Medtronic guidebook
- Process:
 - Referral for Neuropsychological Testing
 - On / Off testing
 - Neurosurgical evaluation
- Expectation: DBS will need programming and may take 6 months to optimize benefits and adjust medications

DBS: Anatomical Basis, Targeting & Placement

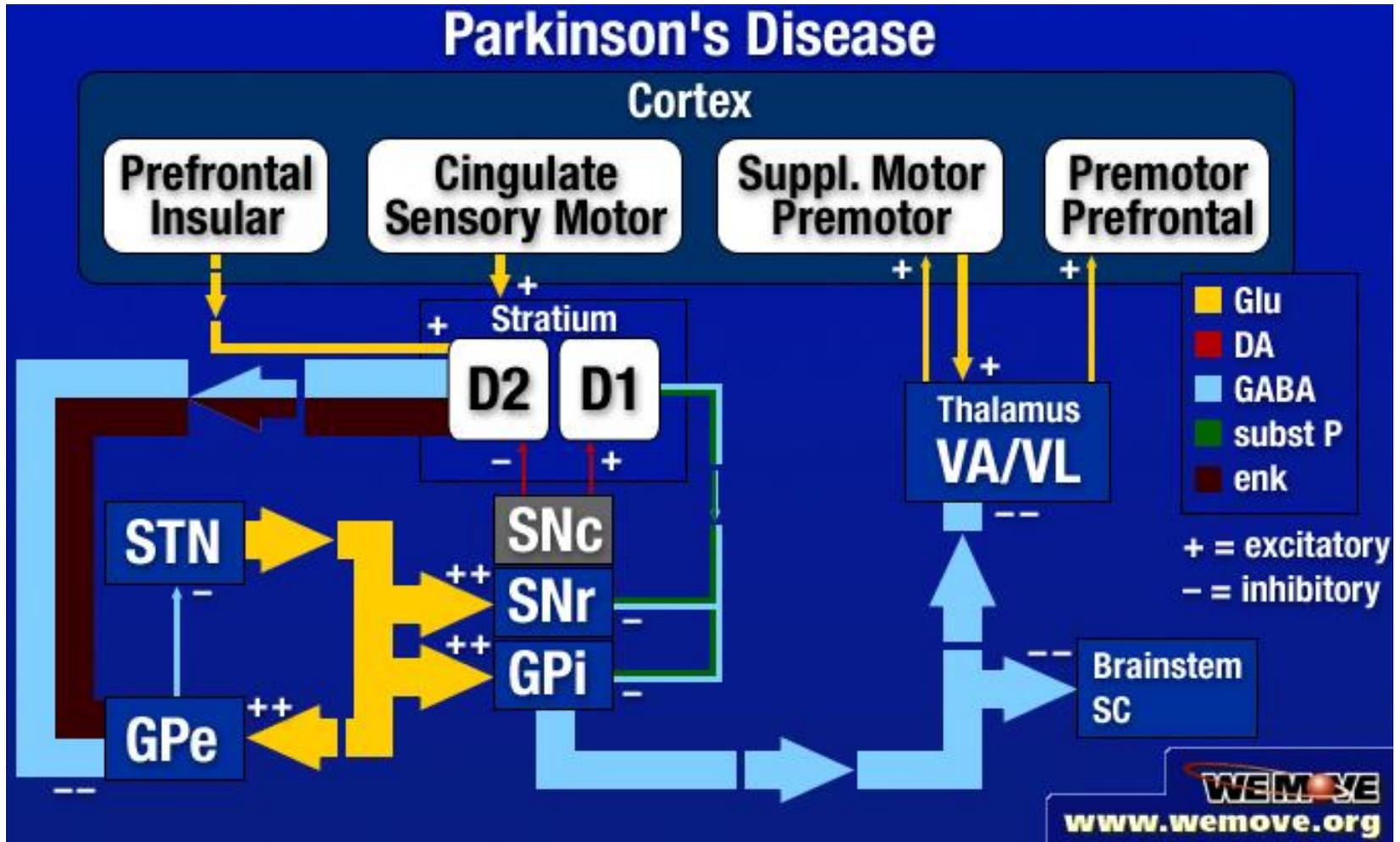
DBS vs other surgical options

- Ablative
 - thalamotomy
 - pallidotomy
- Electrical stimulation / DBS
 - VIM thalamus, globus pallidus internus, sub-thalamic nucleus
- Transplant
 - autologous adrenal
 - human fetal
 - xenotransplants
 - genetically engineered transplants
- Advantage of DBS
 - Reversible
 - Does not destroy normal brain tissue
 - Adjustable
 - Bilateral

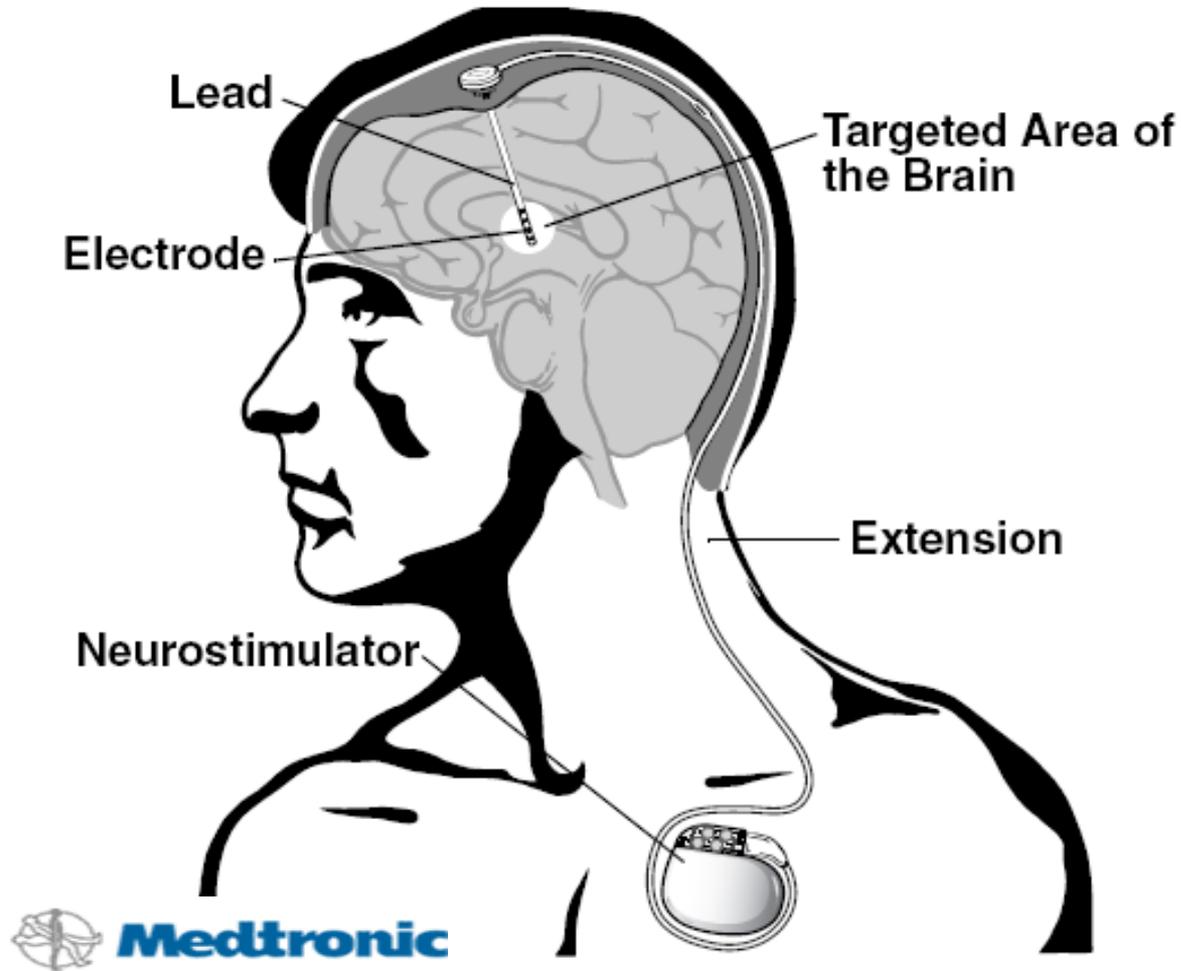
Normal Basal Ganglia Functional Anatomy

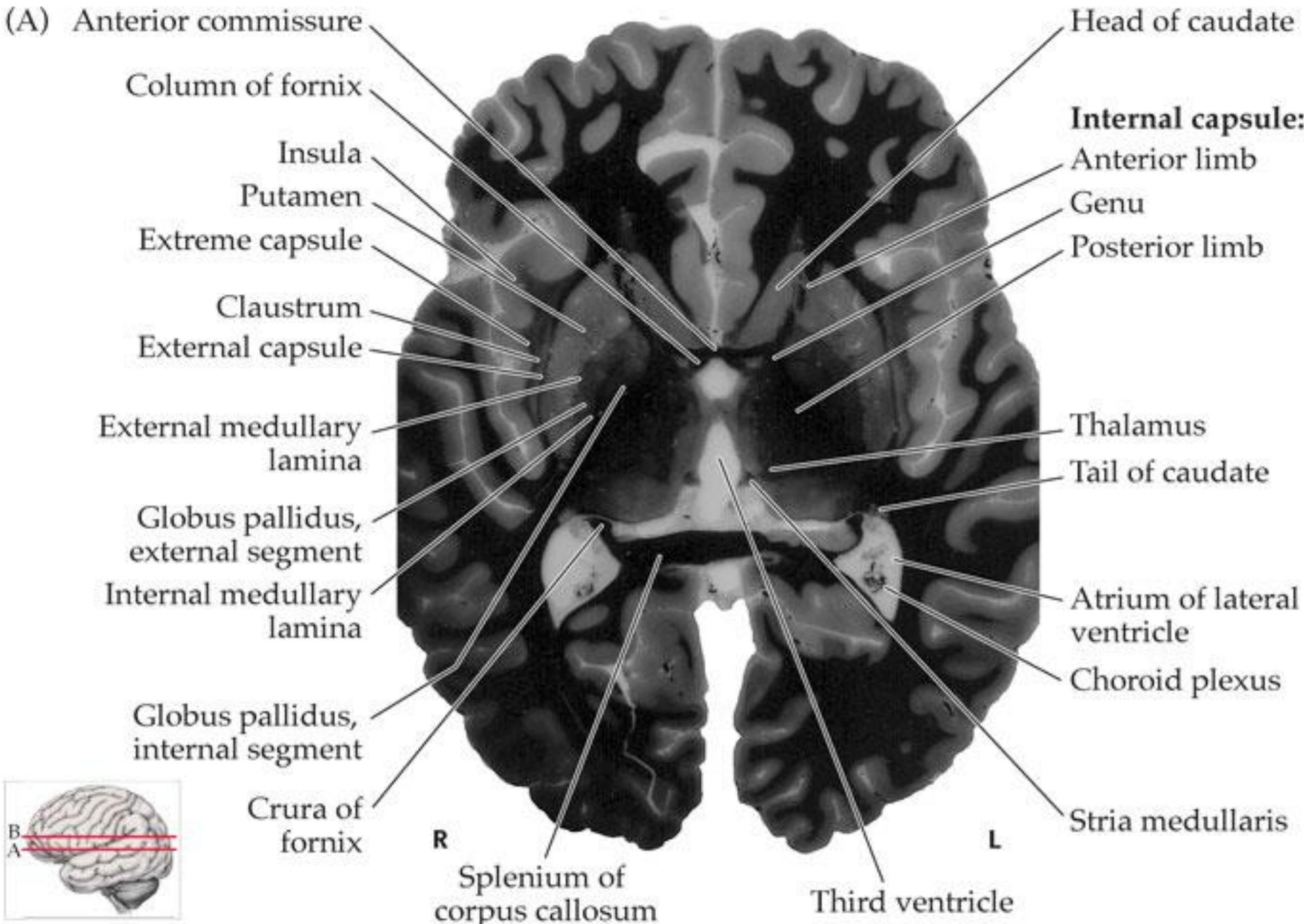


Function Anatomy of Parkinson's Disease



Deep Brain Stimulation

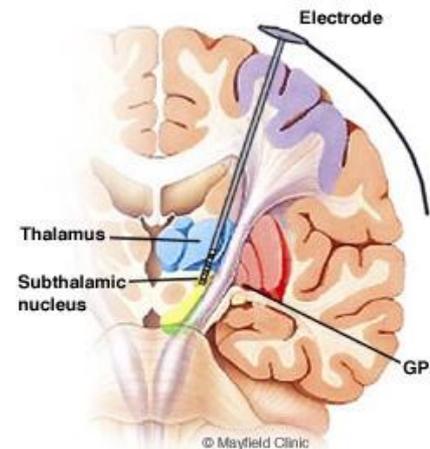




(From the Walter Reed Yakovlev collection.)

Target selection in DBS

- VIM: Tremor predominant
- STN: PD motor fluctuations
- GPi-: PD motor fluctuations
- STN Vs GPi: selection
- Exact physiology unknown
 - high frequency stimulation mimics cellular ablation, not stimulation



Subthalamic DBS

- All cardinal features of PD noted to improve in open label trials
- “Off” UPDRS improved 60%
- “On” UPDRS improved 10%
- Increased “on” time
- Reduced dyskinesia
- Reduced medication requirements

Optimal Surgical Site

- Comparisons between STN and GPi placement have generally shown similar motor efficacy, however, STN placement allows for more reduction of medications
- STN placement is more widely performed and felt by some to be more efficacious

STN side effects

- STN location
 - Some suggestion of reduced executive function
- Cognitively impaired patients:
 - Surgery should be done cautiously in cognitively compromised subjects
 - Consider GPi location
 - Consider staged procedure rather than bilateral

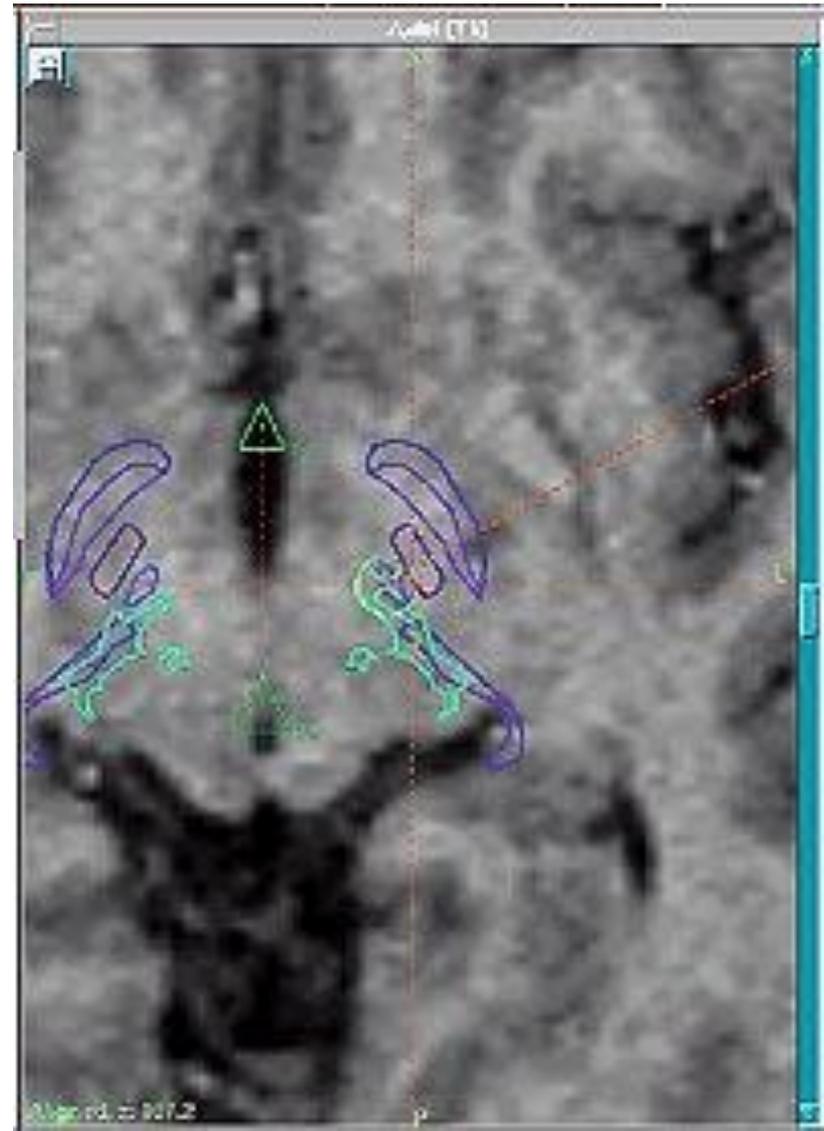
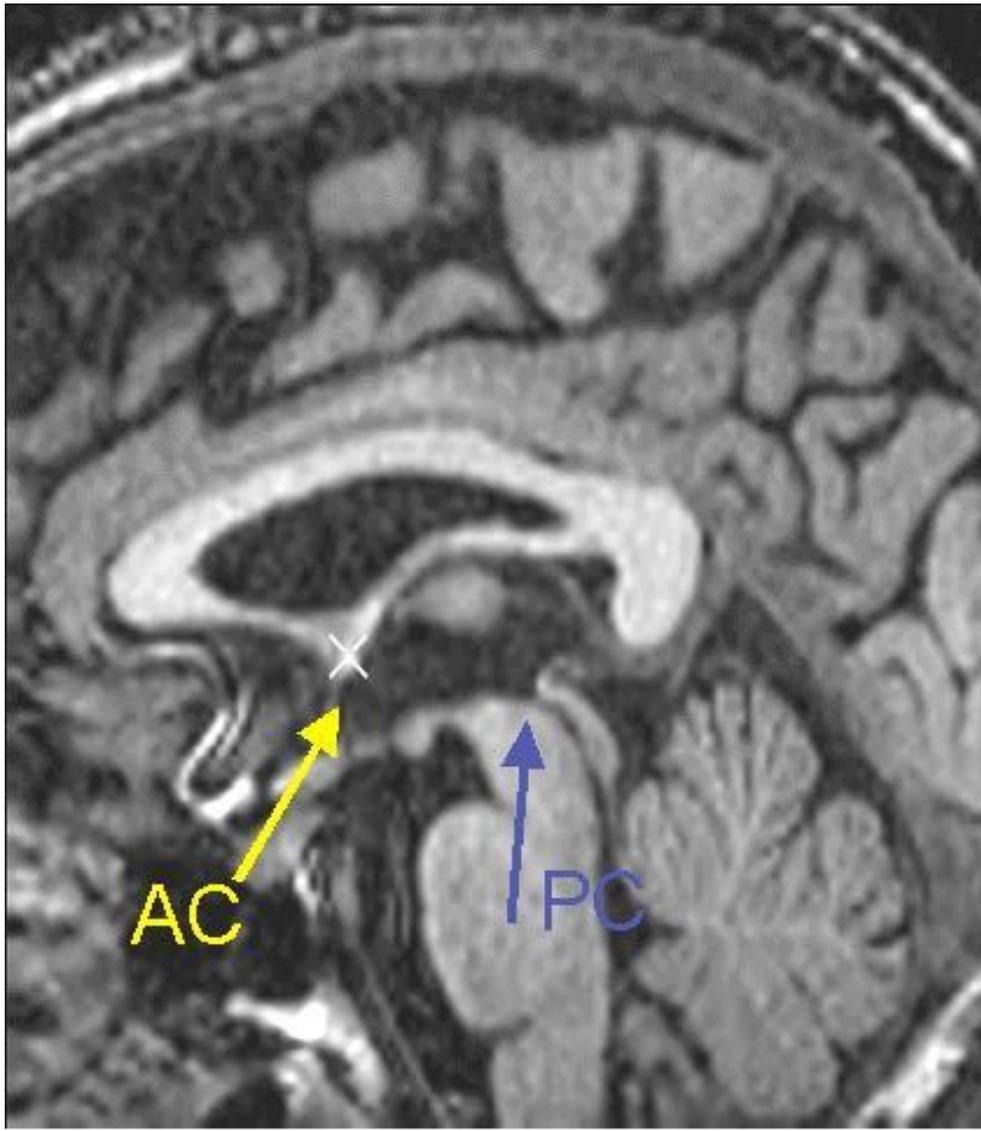
Deep Brain Stimulation

- 2 Stage surgery:
 - Phase 1: Electrode implantation- 24 hour hospital stay
 - Phase 2: Pacemaker implantation- same day surgery
- Post Surgical Care:
 - Site care
 - Continue anti PD medications
 - Review DBS expectations

Electrode Implantation

- Target selection:
 - VIM, STN, zona incerta
- Application of stereotactic head frame
- Stereotactic MRI
- Surgical Planning
- Microelectrode Recording
- Permanent Electrode implantation- unilateral or bilateral
- Intraoperative testing

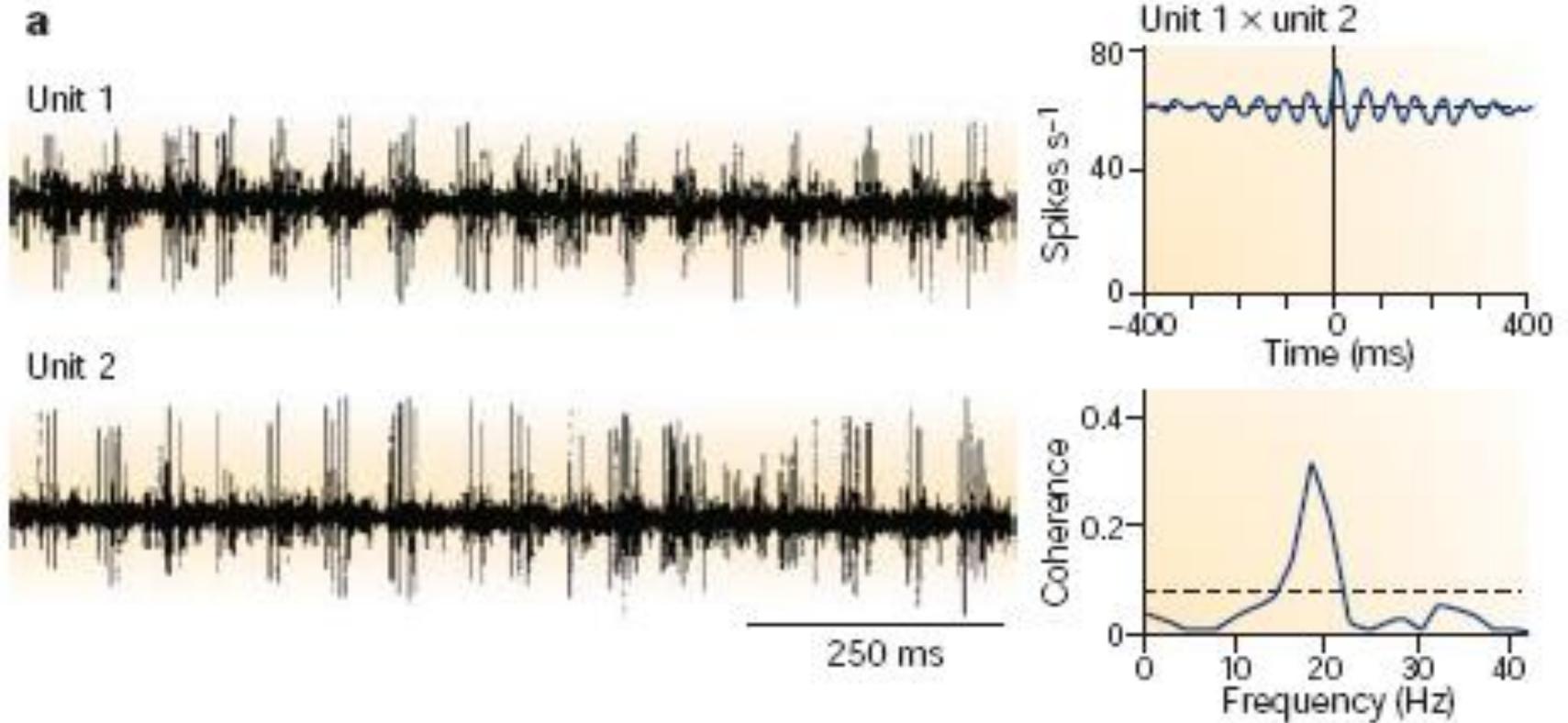
Stereotactic Plan



Frame Application



Microelectrode Recording



Permanent Lead Implantation



Post DBS Process

- Honeymoon period
 - Associated with surgical implantation of electrode
 - Patients note a reduction in medication need
 - Reduction of tremor / bradykinesia / rigidity
 - Highly variable: may last from a few days to a few weeks. In extreme circumstances: it may last several months
- First Programming
 - 2-3 weeks after surgery
 - Start medication adjustment
 - Long Session
 - Try a large combination of settings
 - Done in the “off” state
 - Medication given after programming to evaluate response

Adjustable Features

- Electrode Selection Monopolar / Bipolar
- Voltage (1-7 volts)
- Pulse width (65-450 msec)
- Frequency (130-180 Hz)
- Constant Voltage: typical option
- Constant Current: alternate option

DBS Programming

- First Programming:
 - Monitor response to medication
 - Gradual reduction of medication
 - Avoid rapid taper to avoid withdrawal or depression
- Second Programming
 - Approximately 4 weeks after 1st programming
 - DBS fine tuning
 - Medication Adjustment
 - Further reduction
 - Set rehabilitation goals
 - Review expectations

DBS Programming

- Subsequent Adjustments
 - Time range from 1 – 3 months
 - DBS fine tuning and adjustment of programming
 - Medication adjustment
 - Make medication regimen smoother, eliminate peaks and troughs
- Optimal control may take several programming & medication adjustments

DBS programming

- Side effects of DBS Programming
 - Due to spread of electrical field outside of target area
 - Voice changes
 - Diplopia
 - Parasthesias
 - Limb dystonia / rigidity
 - Dyskinesias
- These side effects are generally reversible with adjustment of DBS
- Turn DBS off to see if symptoms improve

Pitfalls

- Depression
 - Post surgical stress
 - Medication taper
 - Failure to meet expectation
 - Adjustment to post DBS changes
- Rehabilitation
 - Further improve motor function
 - Improve complex motor impairment (handwriting, speech, balance)
- Personality Changes
 - Due to location of electrode
 - Due to electrode passes
 - Post surgical stress
 - Early Dementia
- Dyskinesia at low DBS setting
 - Adjust medications (over-medication)
 - Adjust electrodes
 - Extended honeymoon period

Pitfalls II

- Limited benefit
 - Subjective:
 - False patient expectations
 - Depression
 - Objective:
 - Rapid medication lowering
 - Due to improper electrode placement
 - Consider MRI to evaluate
 - Due to improper DBS programming
 - Review DBS settings
 - Check impedance and resistance
- MRI
 - No body MRI
 - Head MRI with parameters
 - Radiology should be aware of DBS
- Diathermy
 - Avoid heating battery or wire at all costs

DBS Pitfalls III

- Sudden loss of benefit
 - Battery EOL
 - Exposure to electrical field
 - Damage to battery or wires
 - Movement of electrodes
- EKG / EEG
 - Turn DBS off to avoid electrical interference
- Other Procedures:
 - Recommend antibiotic prophylaxis
 - Bipolar cautery
 - Turn DBS off

DBS Long term

DBS Programming

- Advanced programming
 - Constant Current option
 - Interleaving option
 - Groups
- Need to follow up with 3-4x per year
- Battery replacement: 3 – 5+ years depends on the amount of stimulation needed
- Patient control options

ORIGINAL ARTICLE

Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease

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Adnan Koudsie, M.D., Patricia Dowsey Limousin, M.D., Ph.D.,
Abdelhamid Benazzouz, Ph.D., Jean François LeBas, M.D., Ph.D.,
Alim-Louis Benabid, M.D., Ph.D., and Pierre Pollak, M.D.

Patients with advanced Parkinson's disease who were treated with bilateral stimulation of the subthalamic nucleus had marked improvements over five years in motor function while off medication and in dyskinesia while on medication. There was no control group, but worsening of akinesia, speech, postural stability, freezing of gait, and cognitive function between the first and the fifth year is consistent with the natural history of Parkinson's disease.

Table 2. Effect of Bilateral Stimulation of the Subthalamic Nucleus on Off-Medication UPDRS Subscores.*

Subscale	Range of Possible Scores	Base Line (N=49)	1 Year after Surgery (N=43)	3 Years after Surgery (N=42)	5 Years after Surgery (N=42)	P Value	
						5 Years after Surgery vs. Base Line	5 Years after Surgery vs. 1 Year after Surgery
Motor examination							
Total	0–108	55.7±11.9	19±11.1	22.8±11.6	25.8±12.3	<0.001	<0.001
Tremor	0–28	5.2±4.8	1.3±1.8	0.9±1.5	1.3±1.7	<0.001	0.91
Rigidity	0–20	13.4±3.4	3.6±3.5	3.5±2.0	3.9±3.0	<0.001	0.52
Akinesia	0–32	18.5±5.7	6.9±5.8	8.8±5.7	9.5±6.2	<0.001	0.004
Speech	0–4	1.9±1.0	1.3±1.0	1.8±1.0	1.9±1.0	0.56	<0.001
Postural stability	0–4	2.5±0.9	0.9±0.9	1.3±0.9	1.4±1.0	<0.001	0.09
Gait	0–4	3.1±0.8	1.0±1.0	1.2±1.1	1.5±1.1	<0.001	0.04
Activities of daily living							
Total	0–52	30.4±6.6	10.3±6.9	14.8±6.0	15.6±8.5	<0.001	<0.001
Writing	0–4	3.5±0.7	2.2±1.2	2.6±1.2	2.2±1.4	<0.001	0.72
Freezing of gait	0–4	2.6±0.2	0.7±1.0	1.3±1.2	1.4±1.2	<0.001	<0.001

* Plus-minus values are means ±SD. UPDRS denotes the Unified Parkinson's Disease Rating Scale. A reduction in scores indicates an improvement in function. Off-medication evaluations were performed when the patient had taken no anti-parkinsonian medications for 8 to 12 hours. Writing and freezing of gait are complex motor functions that are not represented in the motor scores.

Table 3. Effect of Bilateral Stimulation of the Subthalamic Nucleus on On-Medication UPDRS Subscores.*

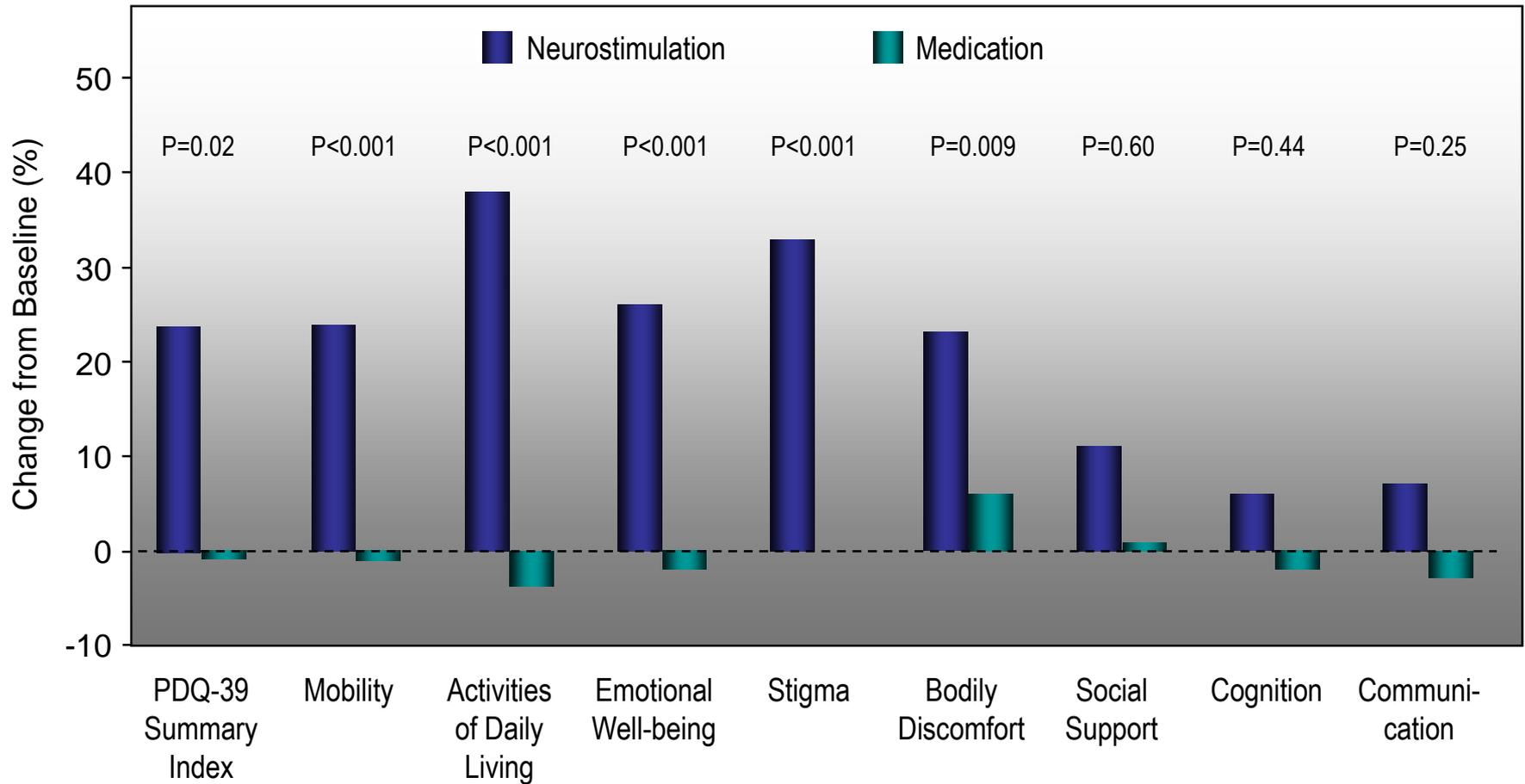
Subscale	Range of Possible Scores	Base Line (N=49)	1 Year after Surgery (N=43)	3 Years after Surgery (N=40)	5 Years after Surgery (N=39)	P Value	
						5 Years after Surgery vs. Base Line	5 Years after Surgery vs. 1 Year after Surgery
Motor examination							
Total	0–108	14.3±7.0	11.4±8.9	15.3±9.5	21.1±12.2	0.003	<0.001
Tremor	0–28	0.4±0.8	0.4±0.8	0.1±0.5	0.2±0.5	0.07	0.17
Rigidity	0–20	3.6±2.7	2.1±2.9	2.2±2.9	2.8±2.7	0.27	0.09
Akinesia	0–32	4.4±3.6	3.7±4.4	6.3±5.4	8.4±6.7	0.001	<0.001
Speech	0–4	0.8±0.6	0.9±0.7	1.4±0.9	1.8±0.7	<0.001	<0.001
Postural stability	0–4	1.0±0.7	0.7±0.7	1.0±0.8	1.3±0.9	0.08	<0.001
Gait	0–4	0.5±0.6	0.6±0.8	0.8±1.0	1.0±0.9	0.02	0.04
Activities of daily living							
Total	0–52	7.3±4.2	7.4±4.8	10.7±6.4	14.0±7.0	<0.001	<0.001
Writing	0–4	1.7±1.1	2.0±1.2	2.2±1.2	2.4±1.4	0.008	0.04
Freezing of gait	0–4	0.3±0.7	0.3±0.6	0.7±1.0	1.2±1.2	<0.001	<0.001
Motor complications							
Duration of dyskinesia	0–4	2.1±1.1	0.6±0.9	0.6±0.9	0.6±0.9	<0.001	0.94
Dyskinesia disability	0–4	1.9±0.8	0.7±0.8	0.6±0.6	0.8±0.8	<0.001	0.65

* Plus–minus values are means ±SD. UPDRS denotes the Unified Parkinson’s Disease Rating Scale. A reduction in scores indicates an improvement in function. On-medication evaluations were performed during periods of maximal clinical benefit after administration of a suprathreshold dose of levodopa. The numbers of patients who were evaluated in the on-medication and off-medication condition vary because some patients who could stop all dopaminergic treatment postoperatively did not tolerate a levodopa challenge. Duration of dyskinesia represents the portion of the waking day spent with dyskinesia, and dyskinesia disability represents the severity of the dyskinesia as assessed subjectively by the patient.

5-year Follow-up Bilateral Stimulation Results

- Marked improvements
 - Motor function while off medication (\uparrow 54%, $p=0.001$)
 - Activity of daily living (\uparrow 49%, $p<0.001$)
 - Dyskinesia while on medication
 - Severity (\downarrow 58 %, $p<0.001$)
 - Duration (\downarrow 71%, $p<0.001$)
- No control group, but worsening of akinesia, speech, postural stability, freezing of gait, and cognitive function between the first and the fifth year consistent with the natural history of PD

Impact of DBS on QOL



Future

- Better DBS targeting
- Improved DBS technology
- Longer Battery life
- Improved Stimulation and newer devices
 - Boston Scientific Vercise
 - St Jude Brio
- Improved options for motor fluctuations

Thank you