

Surgery for Parkinson's Disease:

Where We Are and Where We're Going

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PD surgery: Where we were

Ablative surgery

- Pallidotomy described 1947
- Anterior choroidal artery ligation 1952
- Thalamotomy 1958

Deep Brain Stimulation

- Thalamus for tremor 1987
- STN for PD 1994
- GPi for PD/dystonia 1994

Down the Road

- Neurotrophic factors?
- Stem cells?
- New stimulation targets and techniques?

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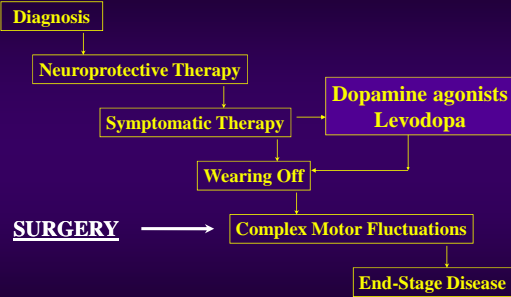
Surgery for PD

Current Status

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Role of Surgery for PD



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DBS OFF

DBS ON

56 yo man
 PD for 9 years
 1200mg L-Dopa

- Problems:
- On-Off fluctuations
 - Severe tremor
 - Freezing
 - Dyskinesias
 - OFF dystonia



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STN DBS for PD

➤ VA Study (2009)

- 255 patients randomized to meds vs GPi or STN DBS (60 STN/61 GPi)

	DBS		Meds	
	Pre	Post	Pre	Post
Good ON time	6.4	10.9	7.0	7.1
Dyskinesias	4.4	1.8	4.2	3.9
OFF time	5.2	3.4	5.6	5.7
L-dopa eq	1281	985	1289	1303

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STN DBS for PD

Motor benefits mostly maintained at 5 yrs

Improvement off meds:

	1yr	5yr
Total Motor	66%	54%
ADLs	66%	49%
Rigidity	73%	71%
Tremor	75%	75%

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STN DBS for PD

But PD continues to progress:

On-meds evaluation shows:

	1yr	5yr
Total Motor	20%	-48%
ADLs	0%	-92%
Rigidity	16%	-91%
Tremor	0%	-300%

PLUS – Dementia and frontal lobe function also worsen

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PD DBS – WHERE

➤ STN

- Best studied target for PD
- Provides excellent benefits for all cardinal sx of PD
- Possibly better for tremor than GPi
- Stimulation reduces dyskinesias through medication reduction
- Smaller target – 200mm³ -
 - ?easier to find
 - ?more motor side effects
 - ?Lower charge density needed
- Is nucleus the real target or are passing fibers?
- ?Increased incidence of mood and speech adverse effects

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PD DBS – WHERE

➤ GPi

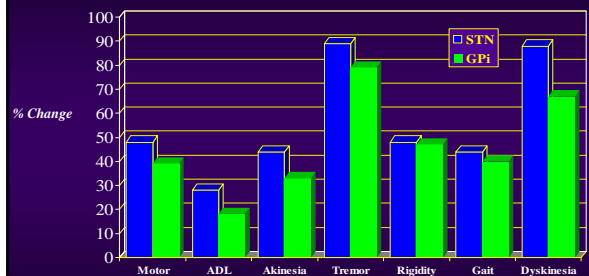
- More studies showing benefits of GPi
- Larger target (500 mm³)
- “Target within the target”
- Direct anti-dyskinesia effect – may actually be better for dyskinesias
- ?Allows reduction of medications
- More current needed but possibly fewer adverse events

➤ Await results from VA randomized trial

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STN versus GPi DBS

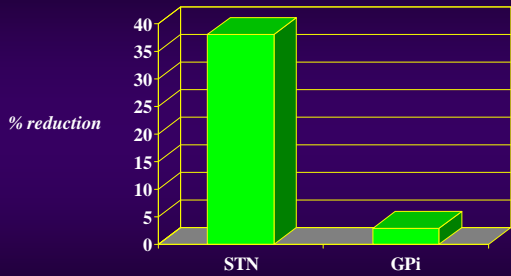


Anderson, Arch Neurol. 2005;62:554-560

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Dopaminergic Medication Reduction STN vs. GPi DBS



Anderson, Arch Neurol. 2005;62:554-560

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News about other aspects of Surgery for PD

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Timing of Surgery

➤ We know when it is too late, but is there a “too early?”

➤ Schupbach 2007

- 20 patients, mild/moderate PD
- Randomized to either DBS or medical management

➤ At 18 months:

	<u>Surgical</u>	<u>Medical</u>
▪ Quality of life	Improved 24%	No change
▪ OFF Motor score	Improved 69%	Declined 29%
▪ Motor complications	Improved 83%	Worsened 15%
▪ Medications	Decreased 57%	Increased 12%
▪ Cognition	Stable	Stable
▪ Psychiatric problems	Improved	Stable

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DBS Reprogramming

➤ Moro 2006

- 44 patients, all with stable DBS settings
- Brought in for attempt at intensive reprogramming by movement disorders neurologist with expertise in DBS management

➤ 24 patients improved

- 26% improvement in UPDRS scores
- 26% reduction in medications
- Improvements seen across tremor, rigidity, bradykinesia, dyskinesias, walking

➤ 16 patients not improved

➤ 4 worsened

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Cost Effectiveness of DBS Surgery

➤ Fraix, 2006

- Compared costs of care for 6mo before DBS and 6mo afterwards
- Before DBS - €10,087
- After DBS - €1673
- Surgical cost - €6,000
- Estimated that DBS saves health care costs after 2.2 years
- Included consultations, medications, doctor and hospital visits and ancillary care

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Technical Advances:

Frameless DBS

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Frame Placement



Functional Neurosurgery OR



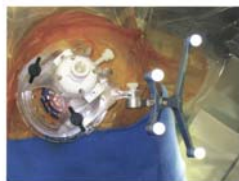
IGN NexFrame



Frameless DBS Surgery



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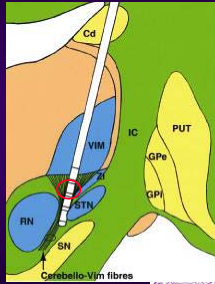
New Targets for Stimulation for Parkinson's Disease

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Posterior Subthalamic Area

- Behind and medial to STN
- Located in white matter – nerve fibers, not cell bodies
- No mapping needed
- Possibly affects fibers as they travel to the thalamus in a tight group
- Small series published for PD, tremor of various types



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Posterior Subthalamic Area

	STN	PST
Total Motor	55%	76%
Tremor	62%	93%
Rigidity	50%	76%
Bradykinesia	59%	65%

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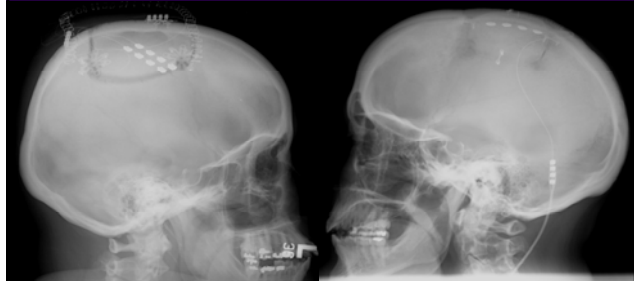
Motor Cortex Stimulation

- Theoretically sensible
 - Cortex is origin of motor nerve fibers
 - PD is associated with abnormal cortical firing patterns
- Procedure would be less invasive than DBS
 - No brain penetration for mapping or electrode placement
 - Procedure outside dura
- Already being performed successfully for pain
- Small series presented with motor improvements in stroke patients

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MCX Stim: Electrodes



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Cortical Stimulation for PD

- Arle 2007
 - 4 patients, 12 month follow up
 - Some very good initial benefits in first few months
 - Much of benefits lost by end of 1 year follow up period
- Pagni 2005
 - 6 patients, 4months – 2.5 yrs postop
 - 32-83% improvement in UPDRS motor score
 - In patients who improved, all cardinal signs improved
 - Medications cut by half in improved patients (range 11-70%)

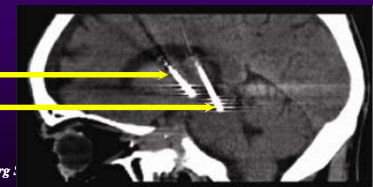
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PPN Stimulation for PD

- Pedunculopontine Nucleus
 - Located in upper brain stem, deeper than STN
 - Involved in locomotor region
 - Theorized as a better target for axial symptoms (gait, falling, posture)
 - Several small reports previously published

STN DBS
PPN DBS



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PPN Stimulation for PD

➤ Stefani, 2007

- 6 patients implanted both STN and PPN
- PPN stimulation best at 25Hz (STN stimulation best at 130 Hz or 185 Hz)
- Some tingling produced, usually for <3mins
- OFF meds evaluation
 - STN stimulation – 54% improvement PPN stimulation – 36% improvement
 - No increase in effect when both activated
- ON meds evaluation
 - PPN stimulation – 44% STN/PPN – 66%
 - Axial scores significantly improved

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Restorative Surgery for PD

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Restorative Options

- Closest to true “cure”
- Recreate normal physiology
- Stop or even reverse reverse degeneration of DA cells
- Possibly remove need for medication

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Restorative Techniques

- Cell transplantation
 - Fetal cells of defined type– nigral, adrenal, etc.
 - Stem cells (allograft) – mesenchymal, neuronal, embryonic (ES)
 - Stem cells (autograft) - externally cultured or internally activated
 - Other DA cells – pigmented retinal epithelial (RPE) – Spheramine
- Trophic factors (GDNF, BDNF, NGF, HGF)
 - Infusion pumps
 - Via engineered cells

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Embryonic Dopaminergic Cell Transplant

- PET shows survival of transplants in most patients
- 28% total UPDRS improvement in transplant group
 - 14% in pts >60yrs, 38% in pts <60yrs
- 15% developed “runaway” dyskinesias or dystonia

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GDNF

- Neurotrophic factor
- Both neuroprotective and neurorestorative effects
- Theory that infusion into the putamen could both halt progress of disease and/or restore function
- Open label trial showed :
 - 57% Improvement in UPDRS motor score
 - Akinesia almost eliminated
 - Dyskinesias improved by 73%

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Amgen GDNF Clinical Trial

- Double-blind – gold standard trial
- No significant benefit to GDNF infusion
- Trial terminated, medication withdrawn
- Patients angry
- Controversy persists

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Other Studies

- Spheramine
 - Retinal pigmented epithelial (RPE) cells produce dopamine
 - Injected into the putamen
 - Intended to engraft and regenerate pathways
- AV201
 - Direct infusion of the gene carrier viral vector for the production of AADC
 - AADC converts levodopa to dopamine
 - Enhances production of dopamine

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Other Studies

- AAV2 – Neurturin
 - Neurturin (NTN) is related to GDNF
 - Infusion into the putamen on both sides
- Phase 1 completed
 - 6 subjects for each of 2 doses (4-fold difference)
- Failed in double blinded studies

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Neurologix Study

- AAV – GAD infusion
- Glutamic acid decarboxylase – helps produce GABA
- Animal models showed neuroprotection and symptom improvement
- Theory – increased GABA calms down abnormally active STN and possibly convert STN outflow to inhibitory from excitatory
- Infused into both STN
- Blinded trial
- Initial safety data good

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Neurologix Study

- First study to use viral vector for neurodegenerative disease
 - Kaplitt, et al *Lancet* 2007
- 12 patients, single side injection into the STN, 1 year follow-up
 - 3 different dose levels – 3.5, 10 or 35 billion virus particles
 - Infusion done in operating room over 100 minutes
- 27% improvement at 1 year in UPDRS ON motor scores for treated side
 - No change on untreated side or in OFF state
 - Dyskinesias unchanged
- ADL improvements not significant
- PET scans show decrease in abnormal metabolism on treated side

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Thank you for coming!



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