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

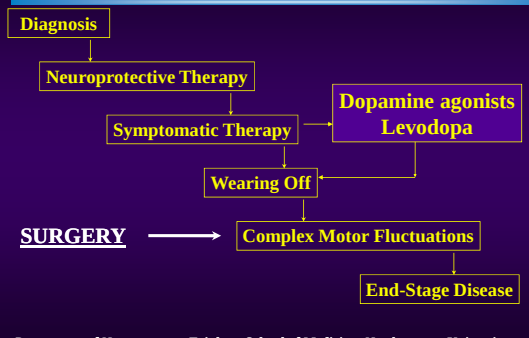
Deep Brain Stimulation
- Thalamus for tremor 1987
- STN for PD 1994
- GPi for PD/dystonia 1994

Down the Road
- Neurotrophic factors?
- Stem cells?
- New stimulation targets and techniques?

Surgery for PD

Current Status

Role of Surgery for PD



DBS OFF DBS ON

56 yo man
PD for 9 years
1200mg L-Dopa
Problems:
•On-Off fluctuations
•Severe tremor
•Freezing
•Dyskinesias
•OFF dystonia

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

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%

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

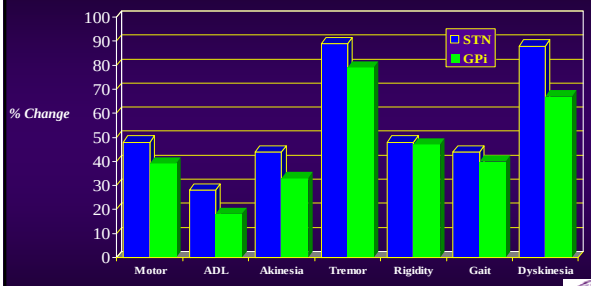
PD DBS – WHERE

- 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 – 200mm^3 -
    - ?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

PD DBS – WHERE

- GPi
  - More studies showing benefits of GPi
  - Larger target (500 mm^3)
  - "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

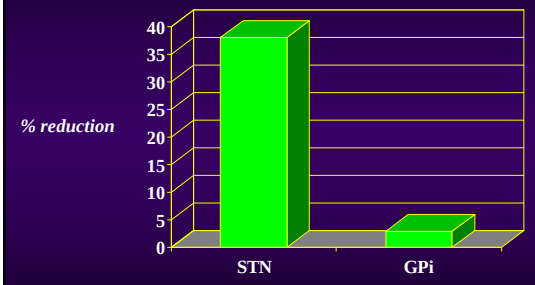
STN versus GPi DBS



UPDRS Off Medication Scores

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

Dopaminergic Medication Reduction STN vs. GPi DBS



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

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:

	Surgical	Medical
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, brasykinesia, 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 - €36,000
  - 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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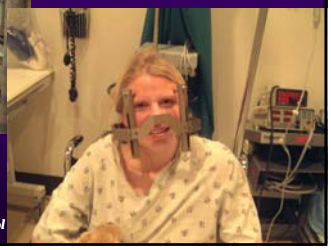
Frame Placement



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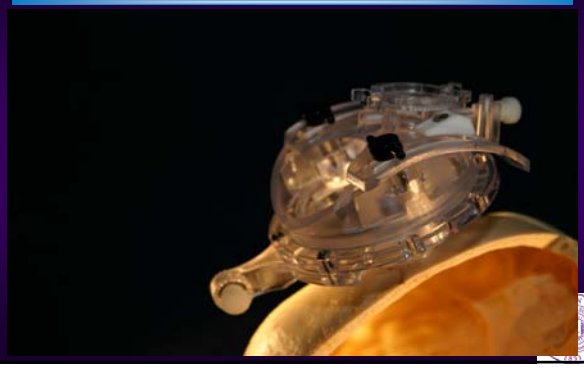
Functional Neurosurgery OR

IGN NexFrame



Frameless DBS Surgery

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New Targets for Stimulation for Parkinson's Disease

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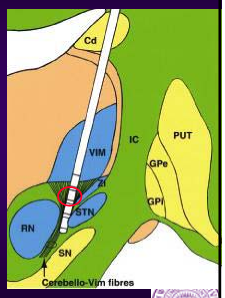
Posterior Subthalamic Area

- 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



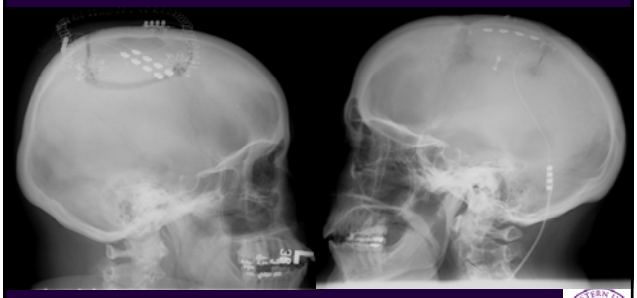
Posterior Subthalamic Area

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

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

MCX Stim: Electrodes

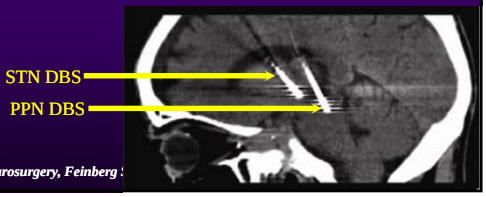


Cortical Stimulation for PD

- 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%)

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



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

Restorative Surgery for PD

Restorative Options

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

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

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

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%

Amgen GDNF Clinical Trial

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

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

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

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

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

Thank you for coming!

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