Surgery for movement disorders: 2007 update

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Surgical options for PD 2007

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<th>Current status</th>
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<td>DBS of Gpi or STN</td>
<td>Currently predominant surgery for PD</td>
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<td>RF lesioning of Gpi or STN</td>
<td>A good option for patients not appropriate for DBS</td>
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<td>DBS of STN</td>
<td>Early investigations for freezing of gait unresponsive to STN or Gpi DBS</td>
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<td>Fetal mesencephalic allograft</td>
<td>Two placebo controlled randomized trials performed in 1990 - ended clinical interest in this method</td>
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<td>Intrastriatal GDNF infusion</td>
<td>Phase II trial started 2004</td>
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<td>Intrastriatal injection AAV-AADC</td>
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Surgical treatments that modify abnormal basal ganglia output:

Gpi or STN lesioning
Gpi or STN DBS

theory, indications, technique, results

Basal ganglia function

• Scaling of movement (amplitude and velocity)
• Focusing of movement (selecting specific muscles to activate, while suppressing antagonist muscles)
• Two intrinsic pathways (direct and indirect) one of which facilitates, and the other arrests, movement

In PD, basal ganglia output (GPi and its upstream partner STN) have:

• Excessive firing rates
• Abnormal oscillatory activity in the 2-30 Hz range, which is an “antikinetic” frequency range normally associated with lack of movement
• Abnormal synchrony between parallel pathways that normally should be independent

Colleagues:
Paul Larson, Jill Ostrem, Alec Glass, William Marks, Alastair Martin, Monica Volz, Susan Heath
Parkinson’s Disease: How does STN or Gpi DBS suppress symptoms?

- DBS does NOT alter striatal dopamine release
- Lesioning or DBS of the Gpi or STN work by the correction of excessive and/or abnormally patterned activity in the basal ganglia output structures, with resulting normalization of activity in supplementary motor cortex

Indications for Gpi/STN DBS in PD

- Clear diagnosis of idiopathic PD
- Continued good motor response to levodopa/carbidopa, with independent ambulation in best on-medication state
- Complications of medical therapy (motor fluctuations and dyskinesias) producing significant disability

Contraindications to Gpi/STN DBS in PD

- Dementia
- Poor function in best “on” state
- Age > 80
- Contraindication for DBS: any patient with whom a productive long-term physician-patient relationship is unlikely (these patients may get pallidotomy/subthalamotomy)

Indications for pallidotomy and subthalamotomy

- Similar to DBS but reserved for patients who will not deal well with the complexity of DBS or should not have an implanted device, and patients who would benefit from unilateral surgery

Unilateral vs Bilateral DBS?

- Most patients except those with strongly asymmetric sx get bilateral surgery, but this is not universally agreed upon
- Surgery is staged in pts >70 or those with mild cognitive deficit

Gpi vs STN?

- Literature bias and referring neurology bias is for STN
- Await results of CSP-468, Multicenter randomized trial of Gpi vs STN
The technical goal of movement disorders surgery:

- Place an electrode or lesion within the motor territory of the desired nuclear target
- Do not encroach on neighboring white matter or grey matter structures as this may lead to major adverse effects

Surgical neuroanatomy to know:
Location of motor territory and surrounding tracts

<table>
<thead>
<tr>
<th>Target</th>
<th>Where is the motor territory?</th>
<th>Somatotopy of the motor territory</th>
<th>Surrounding structures to detect and avoid during surgery</th>
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<tr>
<td>STN</td>
<td>Dorsolateral</td>
<td>Leg, medial, arm, lateral, anterior, and posterior</td>
<td>CBT/CST, Medial lemniscus, N. II, nucleus and tract</td>
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<tr>
<td>Gpi</td>
<td>Posterior</td>
<td>Leg, dorsal and medial, arm, ventral and lateral</td>
<td>CBT/CST, Optic tract</td>
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Intended location of leads

SURGICAL METHODS

1.) Standard physiologically guided methods

2.) Trends for the future

MRI-based stereotaxy, software to reformat images and plan trajectories
Confirmation of nuclear location by recording spontaneous single unit activity

Confirmation of motor subcircuit by detection of movement related activity

During DBS, most stimulation-induced adverse effects reflect activation of neighboring white matter tracts

Parameters:
Bipolar 1-2+, 90 microseconds, 185 Hz

Postoperative MRI: lead location confirmation
Note manufacturer’s guidelines for safe MRI

Alternative surgical technique: placement of DBS in high field diagnostic MRI

• Patient may be under general anesthesia
• Eliminates headframe, physiology, and operating room
• Potentially shorter, safer, more accurate, but currently investigational

Patient within MR isocenter, showing draping of MR bore and bilateral trajectory guides
Patient moved into bore of magnet, high resolution images through target area and pivot point of alignment device are performed after brain shift has occurred.

Target coordinates determined after brain shift.

Brain Shift

Pivot Point

STN

Monitoring sheath/stylet during advance into brain using one-minute acquisition T2-weighted oblique sagittal images.

Final lead location confirmed intraoperatively with high resolution images.

Results of DBS for PD

- Results measured with a standardized rating scale of motor function, Unified Parkinson’s disease rating scale (UPDRS)
- Results at 5 years for STN DBS well characterized (Krack et al. NEJM 345 p. 1925, 2003): 50% improvement in UPDRS off medication, without dyskinesias, and 50% reduction in sinemet dose
- Results for Gpi DBS not well characterized; await CSP-468 trial results
- Results of unilateral Gpi lesioning (pallidotomy): (Vitek et al. Annals of Neurology 53 p. 558), 30% improvement in UPDRS

Effect of DBS in advanced PD in the off medication state:

Video of fluoroscopic MR for alignment

• Probe Alignment

Alignment achieved with fluoroscopic MR imaging.
DBS of the PPN for freezing of gait: 8 cases published, off-label use, too early to tell if this has a role in PD therapeutics

Fetal mesencephalic allograft for PD: status
- Two major randomized placebo control double blinded studies completed
- Fetal allograft survives without immunosuppression in adult brain, forms synaptic connections
- Benefit of bilateral grafting is modest (30% improvement in UPDRS) and 15% of patients have serious complication of "runaway dyskinesias"

Intrastriatal GDNF: possible first neuroprotective therapy for PD
- 1993- shown to restore DA phenotype to "sick" DA neurons and protect from toxic insult in MPTP nonhuman primate model
- 1990's – GDNF intraventricular delivery ineffective
- 2003- Gill et al show 40% UPDRS improvement and fluorodopa PET increase in 5 patients
- 2003-2004 Phase 2 trial of 30 patients failed to show efficacy
- Trials with different dose and different injection systems currently being designed

Gene therapy strategies for PD
- Cornell: AAV-GAD into STN to "turn it off" Phase I trial
- UCSF: AAV-AADC in Phase 1 trial. Theory: In primates with partial striatal dopamine denervation, Aromatic Amino Acid Decarboxylase (DOPAC to dopamine) is rate limiting enzyme, not Tyrosine Hydroxylase. Goal: treat motor fluctuations
- UCSF: AAV-Neurturin in Phase II trial. Theory: Neurturin, a neuroimmunophilin related to GDNF, has both symptomatic and neuroprotective effects in nonhuman primate models of PD

Surgery for PD: summary
- No therapy is currently proven to be neuroprotective, which is the ultimate goal
- For mid-stage PD patients who have developed complications of medical therapy, STN or Gpi DBS offer greatly improved function for at least 5 years. This has had a high impact on PD therapeutics and is the most major advance since introduction of levodopa/carbidopa in 1968
- Lesioning remains a good option for some patients who should not have an implanted device
- Fetal mesencephalic autografting has been abandoned clinically
- Intrastriatal GDNF is a promising therapy held back by poorly designed trials, but new studies are under consideration
- Intrastriatal AAV-Neurturin entered Phase II trial in 2006, may have a neuroprotective effect.

GPi-DBS in juvenile onset generalized dystonia
GPi DBS in adult onset craniocervical dystonia

DBS for Dystonia: summary
- 1000 cases published, including 2 recent Class I studies
- FDA approval under limited “humanitarian device exemption”
- Effective for primary dystonias prior to onset of fixed orthopedic deformity
- Mechanism of action unknown
- Predominant current target is GPi but this is based on empiric findings not theory
- Less effective for dystonias due to strokes, trauma, or cerebral palsy

DBS for tremor
- Target: thalamic ventrolateral nucleus
- In essential tremor, 90% long term major tremor relief
- Less effective for other tremors: MS, post-stroke, post-traumatic