Neurosurgery for Parkinson disease

- 1890s - Lesions in basal ganglia
  - Pallidotomy
  - Thalamotomy
- 1960s - “Levodopa era”
- Late 1990s – Deep Brain Stimulation
  - FDA approved in USA since 2002
  - Standard of care in advanced PD
  - More than 100 thousand patients implanted
Deep Brain Stimulation

Implanted electrode delivers continuous high frequency electrical stimulation to structures involved in the control of movements.

- Reversible
- Adjustable
The lead delivers mild, electrical stimulation to the thalamus.

The extension connects the pulse generator to the lead.

The implantable pulse generator is generally implanted near the collarbone.

DBS system components

DBS electrode

Programmer
Targets for DBS in PD

- STN (Subthalamic Nucleus)
- Gpi (Globus Pallidus)
Deep Brain Stimulation: surgery overview
Stereotactic frame
Surgical targeting

Anatomical targeting
- MRI
- CT
Microelectrode Recording

DBS lead = 5x thicker than a microelectrode!
- Model 3387: Four contacts over 10.5 mm
- Model 3389: Four contacts over 7.5 mm

Recording signal from individual single neurons in basal ganglia
Mapping of the basal ganglia structures by single neuron microelectrode recording

Border cells

STN

SNr
Precision of placement of a DBS electrode in the subthalamic nucleus (STN)

MER is performed to identify the sensorimotor region of the STN
Test stimulation
Deep Brain Stimulation
Programming parameters

- Electrode configuration
  - Choice of active electrode
  - Monopolar vs bipolar

- Pulse Width
- Frequency
- Amplitude

Amplitude (V) [intensity of stimulation]

Frequency (Hz) [number of pulses per second]

Pulse width (µs) [duration of each stimulus]
Therapeutic effects of DBS in PD
Therapeutic effects of DBS in PD

- Decrease dyskinesia
- Longer periods and better quality of mobility
- Improvement of quality of life
- Decrease medication intake
The expert consensus

In carefully selected patients, neurostimulation is a powerful treatment that alleviates the burden of advanced PD.

The prospect of the improved quality of life should be weighted against the surgical risks.
Potential complications and risks

- **Surgery-related** - uncommon
  - Stroke
  - Bleeding
  - Seizure
  - Transient confusion
  - Infection (more common and typically occurs at the site of generator)

- **Stimulation-related**: Usually can be minimized or eliminated by adjusting stimulation settings
  - Typically reversible: tingling, muscle pulling, speech problems, balance impairement
Long-term effects of DBS on motor symptoms of PD
5 year follow up after B-STN DBS

OFF-Medication Motor Score Improvements

<table>
<thead>
<tr>
<th></th>
<th>6 m</th>
<th>1 y</th>
<th>3 y</th>
<th>5 y</th>
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<tr>
<td>Tremor</td>
<td>79%</td>
<td>75%</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>Rigidity</td>
<td>58%</td>
<td>73%</td>
<td>74%</td>
<td>71%</td>
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<tr>
<td>Slowness</td>
<td>42%</td>
<td>63%</td>
<td>52%</td>
<td>49%</td>
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Review and meta-analysis of published literature, reporting long-term outcomes of STN DBS on motor function in PD patients
Review of published outcomes of STN DBS in PD

- Analyze the long-term effects of STN DBS on the progression of motor disability, measured by UPDRS.
- Compare the rate of progression with estimated expected natural progression.

Results:
- 38 articles were included in the analysis. The total number of subjects was 1,341.
- The maximum follow-up time was 11.7 years.
Long term effect of DBS on motor scores

Expected score, based on natural progression

Reported mean score

Study
Limousin
Pinter
Fraix
Lanotte
Ostergaard
Thobois
Liang
Pahwa
Tir
Zangaglia
Schupbach
Gan
Wider
Gervaid-Berna
Kishore
Castrioto
Jahanshahi
Romito
Blahak
Vingerhoets
Zibetti
Rodriguez-Oroz
Simonin
Zabek
Krause
Simuni
Funkiewicz
Kiener-Fisman
Derost1
Derost2

Time(years)
Mean UPDRS score
DBS in earlier stages of PD

- Controlled Clinical trial of DBStimulation for Early Patients with Parkinson disease. German Parkinson Study Group

- Prospective study to compare results of STN DBS between early-treated and late-treated PD patients. Italian Parkinson Association

- DBS for Early Stage Parkinson disease: prospective clinical trial. Vanderbilt University, USA

- Prospective, randomized, double-blind, placebo-controlled clinical trial evaluating safety and efficacy of DBS in early PD. Multicenter clinical trial, USA, approved, study initiation pending (UCD is participating)
Future of the DBS technology

- "On-demand" stimulation
  System automatically adjusts stimulation based on ongoing changes in brain activity

- More advanced electrodes
  - "steering of electrical current"

- Surgical targeting technique
  - Implantation under direct MRI guidance
    - "Clear Point" technique available at UCH

- Computerized programming process
Experimental surgical treatments

- Fetal dopamine transplant
- Spheramine
  - Human retinal pigment epithelial cells implantation
- Trophic factor infusion
- Gene therapy
  - Neurturin
  - GAD
- Stem cells
Gene Therapy

- Uses harmless virus as vehicle for gene delivery (viral vector)
- Genetically engineered gene of a neurotransmitter or enzyme critical in pathological pathway causing PD symptoms
- Surgically delivered to the part of the brain responsible for motor control
- Virus replicates, increasing amount of neurotransmitter, leading to improvement of the PD symptoms

[Image of brain with virus delivery point]
AAV2-GAD gene therapy for advanced Parkinson’s disease:
a double-blind, sham-surgery controlled, randomised trial


Lancet Neurol 2011; 10: 309–19

Conclusion

The efficacy and safety of bilateral infusion of AAV2-GAD in the STN supports its further development for PD and shows the promise for gene therapy for neurological disorders.
Questions?