DBS in PD: where do we stand and how may technical innovations help improving?

Jens Volkmann
Deep brain stimulation matches the best levodopa effect
DBS in PD – hypothetical mode of action

- Neurodegeneration
- Circuit dysfunction

Modulation of abnormal circuit function

Acute symptomatic benefit
Fluctuations in Parkinson’s disease

<table>
<thead>
<tr>
<th>Hyperdopaminergic behaviour</th>
<th>Motor: dyskinetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-motor: relaxed, sensation and pleasure seeking, creative, socialising, talkative, joking, teasing, self-confident, euphoric, self-satisfied, hyperactive, messy, myopic of the future, disinhibited, manic</td>
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<th>Normodopaminergic behaviour</th>
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<th>Hypodopaminergic behaviour</th>
<th>Motor: akinetic, rigid</th>
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<td>Non-motor: feeling dull, weak, tired, slow, apathetic, indifferent, withdrawn, vulnerable, without self-confidence, anxious, having panic attacks, craving for levodopa, dysphoric, sad, suicidal</td>
<td></td>
</tr>
</tbody>
</table>

Castrioto et al., Lancet Neurology, 2014
The basal ganglia: a global behavioral go-nogo-system

Volkmann et al. Nature Rev Neurol, 2010

Krack et al. MovDis 2001
Deep brain stimulation

Class I evidence favoring DBS over BMT for treating motor fluctuations, dyskinesia, severe tremor and QoL impairment

(25% patient in BMT arm of PD-SURG trial had apomorphine pumps!)
Evidence for new devices

Multiple-source current steering in subthalamic nucleus deep brain stimulation for Parkinson’s disease (the VANTAGE study): a non-randomised, prospective, multicentre, open-label study

Methods: We did a prospectively, multicentre, non-randomised, open-label intervention study of an implantable (evidence for new devices) treatment plan. The treatment plan included the use of a new device, the VERCISE™ system, which was designed to deliver constant-current stimulation to the subthalamic nucleus. The device was implanted in patients with Parkinson’s disease who had not responded adequately to existing therapies. The primary outcome was the improvement in the UPDRS III score over a 52-week period.

Results: The study enrolled 40 patients, with a mean follow-up of 52 weeks. The mean improvement in the UPDRS III score was 20.5 points (95% CI 15.6 to 25.4) at week 52. The improvement was significant compared with baseline (p<0.001). There were no serious adverse events related to the device.

Conclusion: The VERCISE™ device was effective in improving the UPDRS III score in patients with Parkinson’s disease who had not responded adequately to existing treatments. Further studies are needed to evaluate the long-term safety and efficacy of this device.
DBS in PD – hypothetical mode of action

neurodegeneration

chronic effects
(motor function, non-motor functions, medication, etc.)

Acute symptomatic benefit

circuit dysfunction

Modulation of abnormal circuit function

Acute benefit

Chronic effects
(motor function, non-motor functions, medication, etc.)
Long-term evolution of motor symptoms with STN-DBS

- Slow worsening of On-period motor symptoms 5-10 years after surgery
- Parallel decline of motor score in Med Off/Stim ON
- But: 40-50% reduction of off-period motor score by DBS 5-10 years after surgery
Differences in long-term outcome related to age
Window of opportunity

Honeymoon phase
Motor fluctuations
L-Dopa resistant motor symptoms/dementia

late onset

young onset

DBS currently:
age ca. 65 Y
Disease duration ca. 14 Y

Kempster et al., Brain, 133, 2010
Earlier deep brain stimulation? – The EARLYSTIM trial

- 251 patients, mean age 52 Y, mean disease duration 7.5 Y, fluctuations ≤ 3Y
- Randomized to either immediate STN-DBS or best medical treatment for 2 years
- German-French multicenter trial (EARLYSTIM)
- Results:
  - Overall morbidity and mortality comparable in both treatment arms!
  - Improved hrQoL in DBS group
  - No difference in SAE between both groups!

How can we make DBS better?
Experience is simply the name we give our mistakes.

— Oscar Wilde —
long-term (36 mo)

**B**

![Graph showing statistical significance levels with asterisks.

**D**

![Bar graph showing improvement in lateralized UPDRS III.]

Wodarg, Herzog, Reese et al., Mov Dis, 2012
Fiber tract anatomy of the subthalamic area

- **Corticospinal fibers** (pyramidal tract)
- **Corticobulbar fibers** (pyramidal tract)
- **Corticosubthalamic fibers** (pyramidal tract collaterals)
- **Pallidosubthalamic fibers** (lenticular fasciculus)
- **Pallidosubthalamic fibers**
Fiber tract anatomy of the subthalamic area

- **Corticospinal fibers** (pyramidal tract)
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- **Pallidosubthalamic fibers**
Segmented electrodes - Current Steering
Directional deep brain stimulation of the subthalamic nucleus: A pilot study with a novel neurostimulation device
Steigerwald F, Müller L, Johannes S, Matthies C & Volkmann J
Visualized programming – VTA (volume of tissue activated)

Definition of the optimal target volume – probabilistic outcome maps (Würzburg)

Poor responders  Good responders
DBS goal II: Pathway selectivity

- **Corticospinal fibers** (pyramidal tract)
- **Corticobulbar fibers** (pyramidal tract)
- **Corticosubthalamic fibers** (pyramidal tract collaterals)
- **Pallidosubthalamic fibers** (lenticular fasciculus)
- **Pallidosubthalamic fibers**
The calculated total charge delivered per pulse was lower at 30 µs (mean 77.6 nC/pulse; -18.4%) compared to 60 µs (mean 95.1 nC/pulse)
Short PW - Dysarthria
DBS in PD – hypothetical mode of action

**neurodegeneration**
- Glutamatergic excitotoxicity
- Neurotrophin release
- Exercise induced neuroplasticity
- Drug related circuit dysfunction
- ...

**circuit dysfunction**
- Modulation of abnormal circuit function

**Chronic effects**
(motor function, non-motor functions, medication, etc.)

**Acute symptomatic benefit**
Making DBS „better“: reverse translation
Reduction of behavioral deficits and less neurodegeneration in STN-DBS treated AAV A53T aSyn rats

**Pre operation**
Pellet reaching task

**Day 0**
Stereotactic AAV injection

**Day 21**
DBS treatment

**Day 42**
Pellet reaching task

**A**
AAV1/2 A53T aSyn stim-ON, treated side
AAV1/2 A53T aSyn stim-OFF, treated side

**B**
AAV1/2 A53T aSyn stim-ON, untreated side
AAV1/2 EV stim-OFF

**C**
Relative success in single pellet reaching task

**D**
Number of dopaminergic neurons in the substantia nigra

**E**

**F**
TH+ SN neurons
German DBS Week
Nov. 28 - Dec. 2

Register at
abstract-registration@charite.de
www.kfo247.de
Collaborators

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C. Alzheimer, F. Zheng

Forschungszentrum Jülich, Institut für Medizin
P. Weiss-Blankenhorn, G. Fink

„German“ DBS for dystonia study group

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K. Bathia (London), J. Vitek (Minneapolis)

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  - G. Deuschi, M. Pinsker, D. Falk, M. Mehdorn
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