



An Ethical Evaluation of Deep Brain Stimulation for Parkinson's Disease

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These studies are performed in collaboration with Sabine Müller (Charité Berlin), Hans-Werner Bothe (University Hospital Münster) and Peter Brugger (USZ).



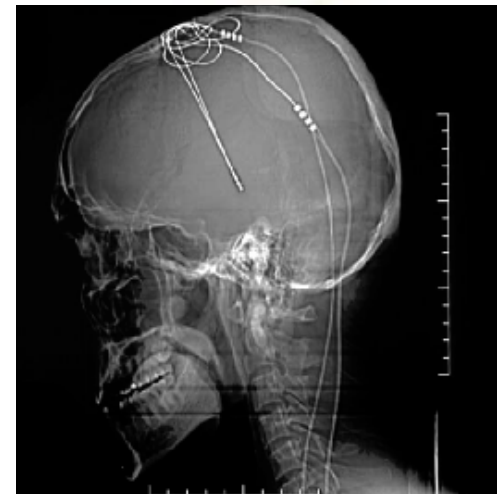
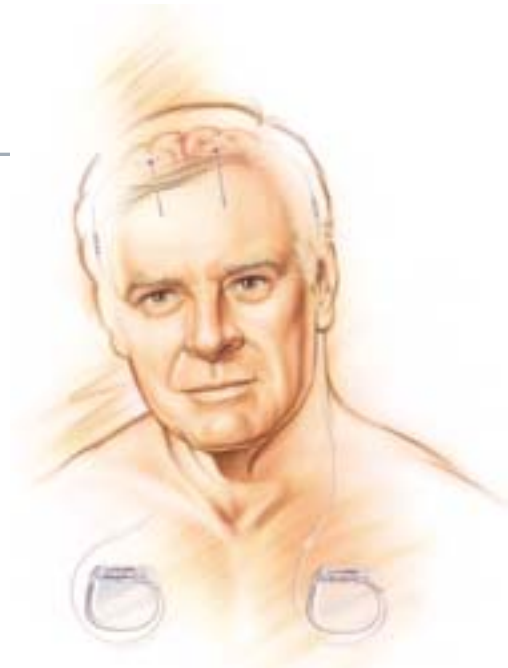
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What is Deep Brain Stimulation?

Key Elements (1)

- Based on pacemaker-technology (Medtronic has basically a monopoly)
- Targets: Several subcortical nuclei, dependent on disease (e.g. subthalamic nucleus), which are relatively precisely addressed.
- Stimulus parameters: monopolar cathodic square pulses (1-5 V amplitude, 60-200 ms duration, 120-180 Hz frequency).
- Mechanism on cellular level is unclear (generally: a inhibition effect)
- Surgical intervention is relatively safe. Local surgical intervention for battery change (after several m/y, dependent on stimulation)
- Patient may control stimulator to some extent



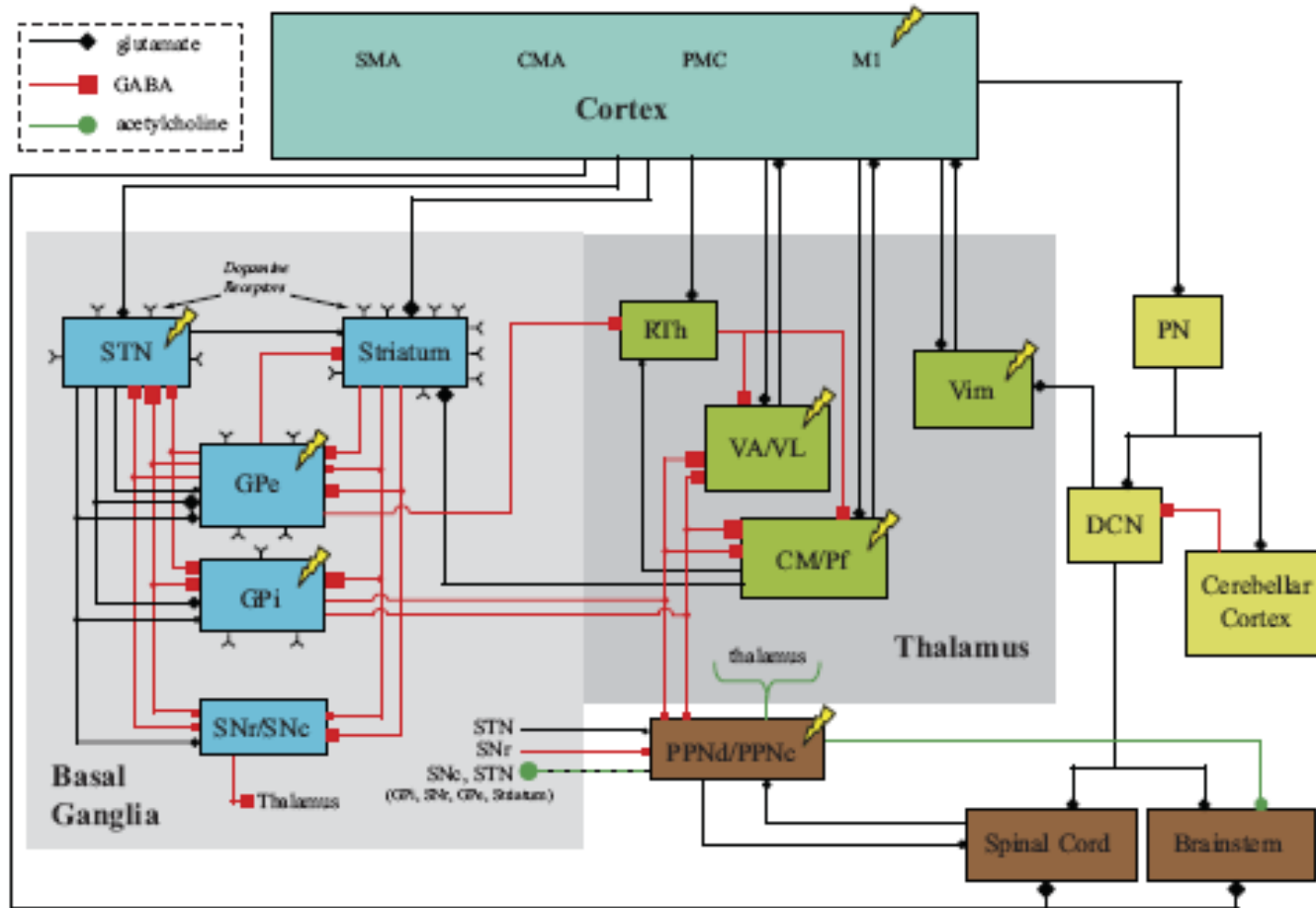
Source: Medtronic /
DANA-foundation



Key Elements (2)

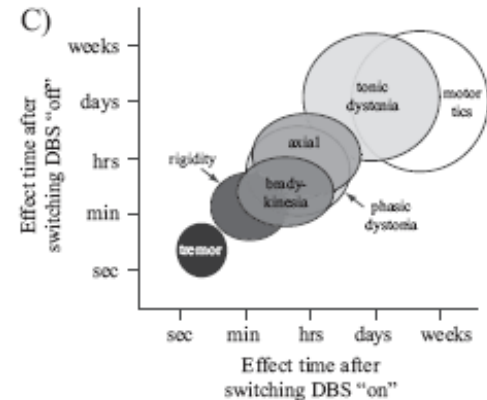
- Historical roots: mid 20th century (Penfield, Delgado).
- Today's technology has been developed in the 1980s, first for the therapy of pain and movement disorders (Parkinson, Dystonia, etc.).
- Currently: more than 80'000 patients are equipped with DBS devices.
- In the last few years, further applications have been tested in experimental studies:
 - Alzheimer (memory enhancement)
 - Anxiety disorders
 - Autism
 - Depression
 - Epilepsy
 - Multiple sclerosis
 - Obesity
 - Obsessive-compulsive disorders
 - Tourette syndrom

Mechanisms: Movement Disorders



Problems discussed in the scientific literature:

- Generally: good results for pharmaceutically resistant movement disorders.
- DBS failures (for movement disorders) are mainly caused by misplacement (48% of cases).
- Sudden “on-off-effects” appear, as well as changes on a longer timescale (several weeks to months, indicating lack of knowledge on physiological mechanisms).
- Dispute on increased suicide-risk (Burkhard et al. 2004; Albanese et al. 2005; Foncke et al. 2006).
- Dispute on validation of „quality-of-life“ after intervention (Diamond & Jankovic 2005), “satisfaction gap”.
- ***Anecdotic reports on complex behavioral changes in patients.***





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DBS: (Preliminary) Results of a Literature Review



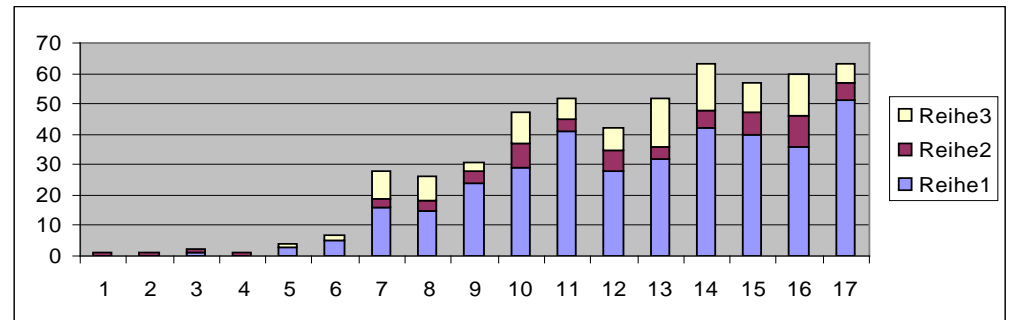
Outline of our DBS Literature Analysis

Search design:

- Focus: DBS in the nucleus subthalamicus (which has become the “standard target” in PD)
- Full-text search in 7 databases (Medline, SCI expanded, PsychInfo etc.)
- Search strategy: DBS & PD & STN & wording of adverse events
- Manual inclusion of additional papers (to obtain a “semi-closed” literature body)

This led to a database of of:

1. 351 outcome reports
2. 66 case reports
3. 113 reviews and comments
(1993-2009)

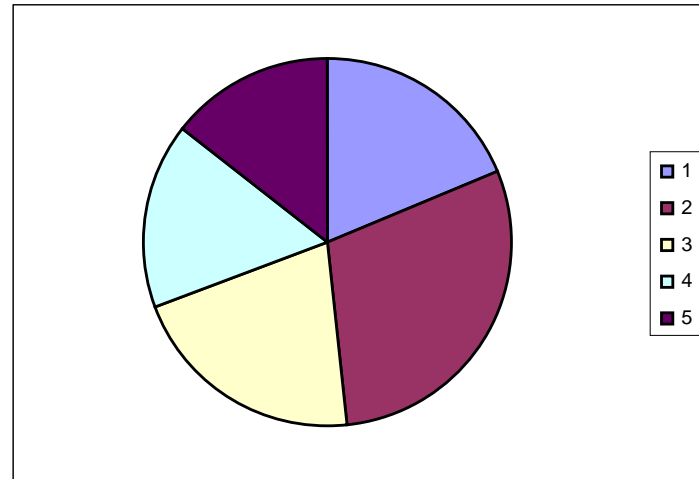




DBS Literature Analysis: Results (case reports)

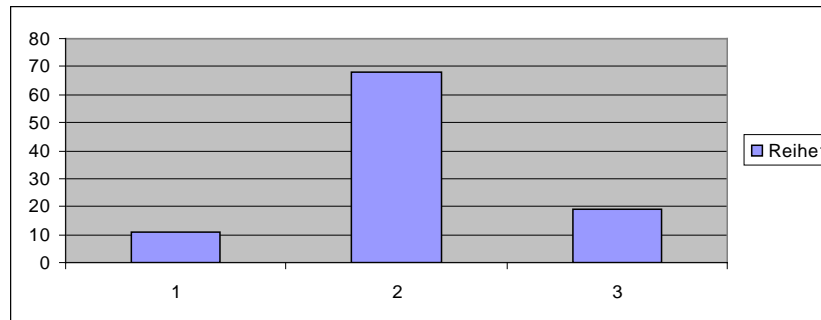
In total 97 patients originating from:

1. Northern America
2. France
3. Southern Europe
4. Europe (other)
5. Asia / Middle East



Type of report:

1. "neutral"
2. "negative"
3. "positive"

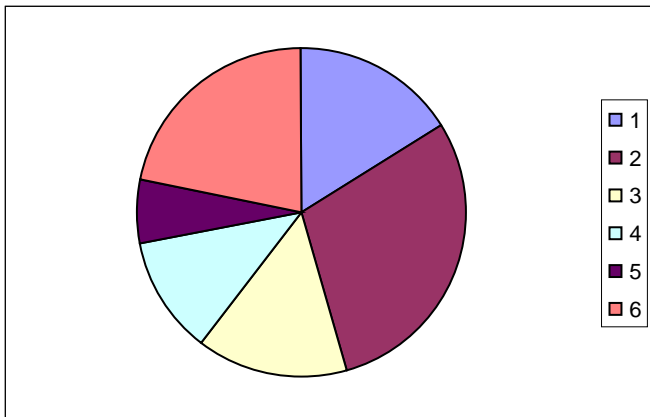




DBS Literature Analysis: Results (case reports)

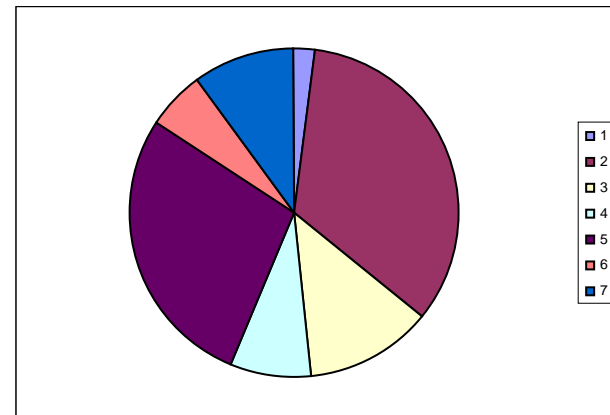
Timing of adverse events after surgery:

1. Immediate effect
2. Up to 7 days
3. Up to 10 weeks
4. Up to 12 month
5. After 12 month
6. Not specified



Type of adverse events:

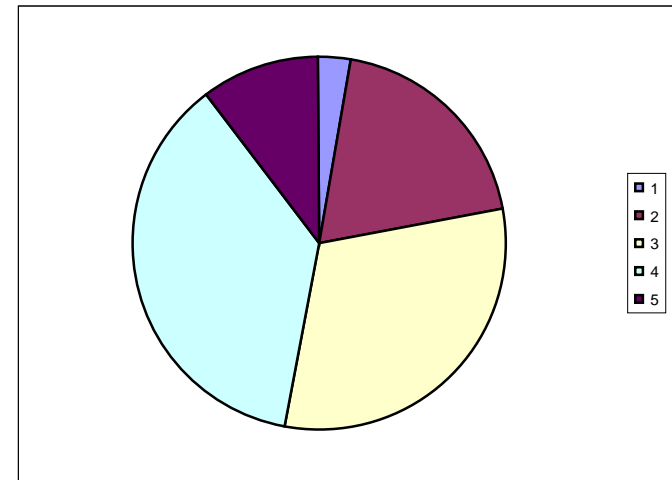
1. Motor
2. Behavioral
3. Cognition
4. Language
5. Mood
6. Surgery
7. Technical



DBS Literature Analysis: Results (review papers)

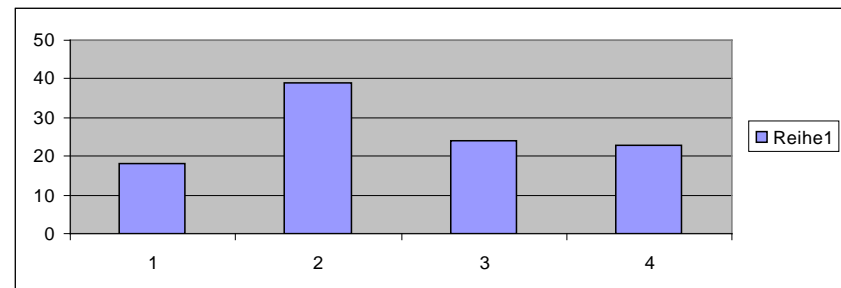
108 papers since 1997:

1. Standard meta analysis
2. “quasi” meta analysis
3. Narrative report
4. Comment
5. “programmatic” paper



Assessment of STN-DBS:

1. “critical”
2. “neutral”
3. “positive”
4. No clear statement





DBS Literature Analysis: Results (outcome studies)

Study type:

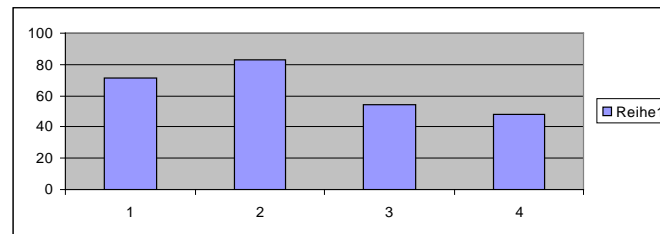
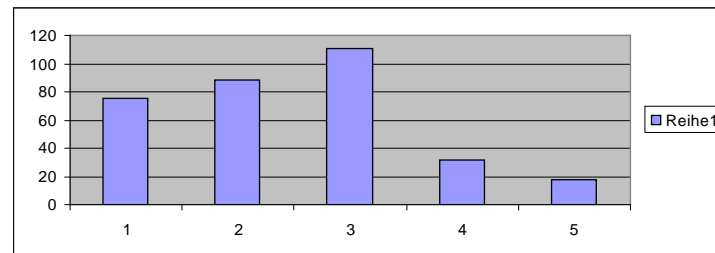
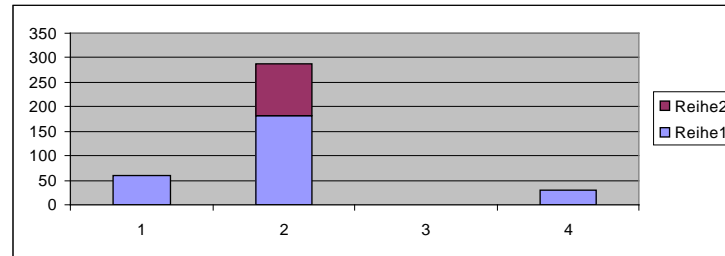
1. Retrospective
2. Prospective (case control)
3. Multicenter (both RS and PS)

Study size:

1. Up to 10
2. Up to 20
3. Up to 50
4. Up to 100
5. > 100

Follot-up time:

1. Up to 6 month
2. Up to 12 month
3. Up to 24 month
4. > 24 month



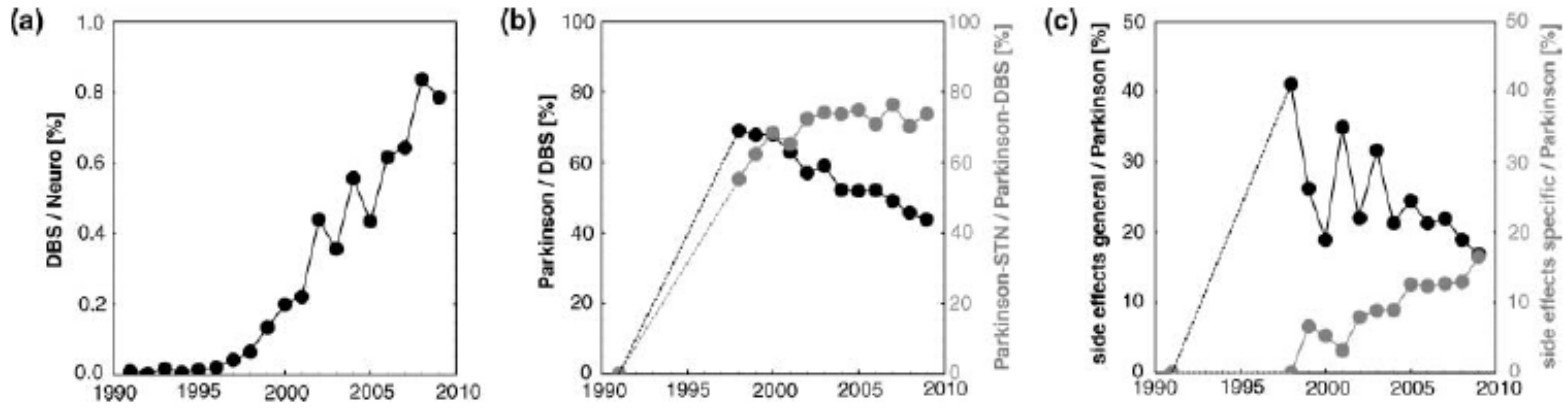


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Discussing DBS in the Scientific Community

Temporal development (1)



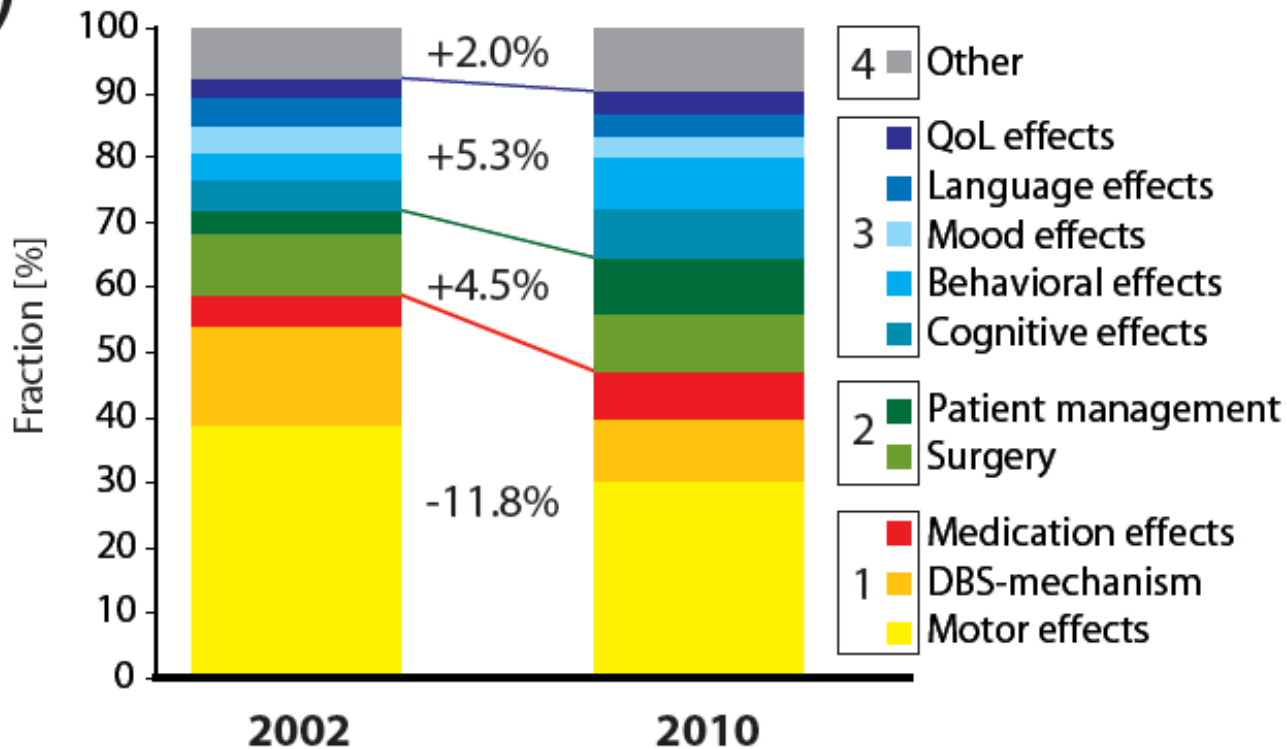
Bibliometric study based on SCI expanded and Medline.

- a) Rise of DBS as a topic in neuroscience
- b) Relative importance of PD-DBS / STN-DBS
- c) More focused discussion on specified side effects.



Temporal development (2)

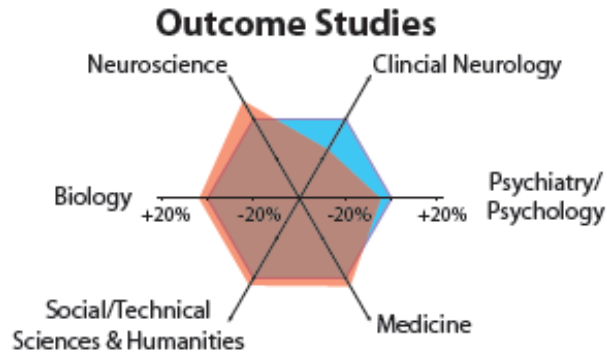
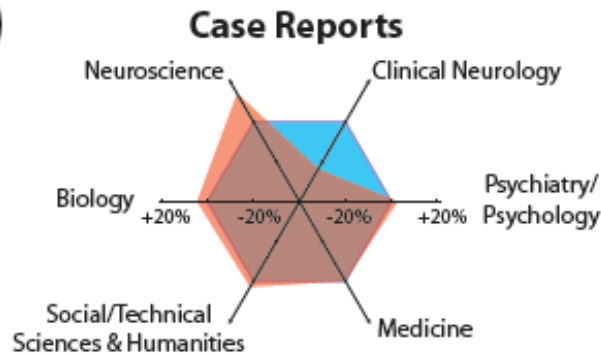
(A)





Transdisciplinary Transfer

(B)





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An Ethical Framework for Evaluating DBS Effects



Main topics in the ethical discussion

1. Issues for the individual patient: Side effects / adverse events; risk-benefit-assessment; getting informed consent.
2. General /societal issues: cost-benefit-issues (cost-effectiveness of DBS), justice issues (DBS vs. lesion procedures / selection criteria).
3. “Philosophical questions”: Changing “personality” / “identity” due to DBS. Enhancement (?).



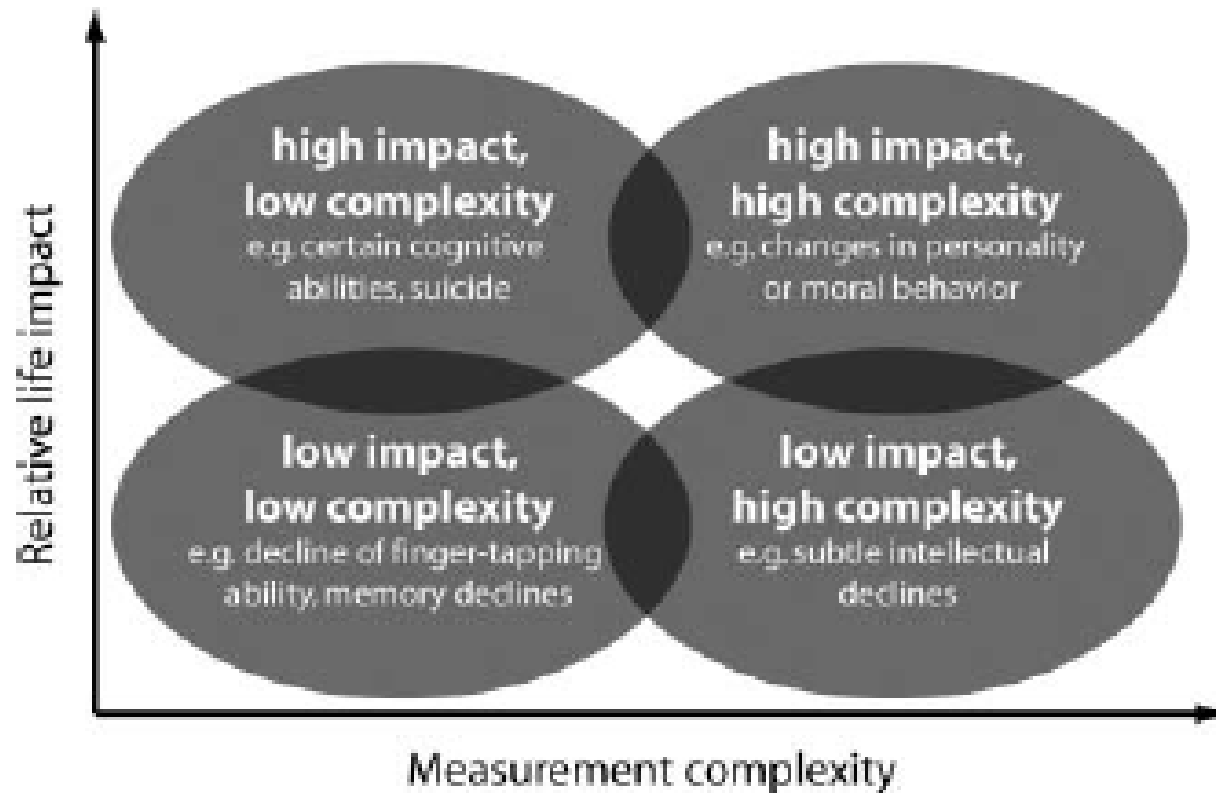
Mayor difficulty of an ethical evaluation of DBS

- First, some side effects are difficult to measure and to quantify, which exacerbates the determination of the incidence of certain side effects.
- Second, the impact of some side effects on the patient's life is hard to determine, especially in comparison with the impact of the disease's natural progression or alternative (medication-based) therapies, which complicates the evaluation of their severity.

(these problems are not exclusively related to STN-DBS)



A scheme of analysis





Cluster 1

Cluster 1 side effects are relatively easy to measure but do not have a high relative life impact,

They have been the subject of many studies and several meta-studies.

Small cognitive declines belong to this cluster (that were observed in up to 41% of the patients): Standard neuropsychiatric tests verified significant, although small, declines in executive functions, verbal learning and memory.

Moderate changes were proven only in semantic and phonemic verbal fluency.

As PD progression also affects cognitive functions, it is not surprising that patients generally do not evaluate them as decisive for their quality of life (Witt et al. 2008).



Cluster 2

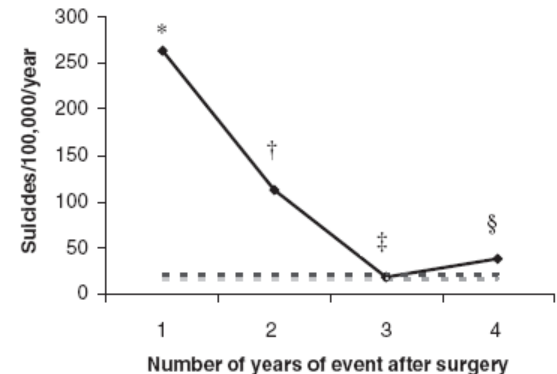
Cluster 2 side effects are relatively easy to measure and have a high relative life impact.

The paradigmatic example of a cluster 2 side effect is suicide.

Suicides after successful DBS have been reported in various studies with highly variable outcomes (1% to 12.5%)

A meta-analysis by Voon and colleagues (2008) (5,311 patients) reported a suicide rate of 0.45% plus a suicide attempt rate of 0.90%, which is significantly higher than the age-, gender-, and country-adjusted World Health Organization (WHO) expected suicide rates in the general population.

Thus, the suicide (attempt) rate after STN DBS has high ethical relevance.





Cluster 3

Cluster 3 side effects are comparatively hard to measure, while their relative life impact compared to disease progression is small.

This cluster comprises subtle intellectual declines, which can be compensated by the patients, as well as more serious declines, whose incidence after DBS does not differ significantly from their incidence in the natural disease history.

An example is apathy, which often occurs after stimulation, but also in the natural disease history.

Depression is a phenomenon with high measurement complexity, as clinical tests for its diagnosis and measurement require psychiatric experience. Additionally, there is an ongoing debate on whether these tests measure the phenomenon adequately (Rickards 2006).

Its weighted life impact is unclear. Furthermore, depression caused by STN DBS usually resolves under pharmacological treatment.



Cluster 4

Cluster 4 side effects are comparatively hard to measure, whereas their relative life impact is high.

Examples are subtle intellectual problems that are overlooked in neuropsychological tests but have a great impact on the ability to work, namely, difficulties in ordering complex actions and thoughts, anticipating and planning, problems with attention, and distractibility

Also neurobehavioral and psychiatric side effects with a significantly higher incidence after DBS than in the normal disease history belong to cluster 4 (hypomania, hypersexuality etc.)

Cluster 4 side effects of STN DBS are not predictable, and sometimes seem to be paradoxical. E.g. affective and social problems, especially in partnership and work, often occur in spite of a good clinical outcome



Remarks

Our classification scheme is intended to be a tool for better understanding the problem, not a tool for ethical judging (e.g. in the sense that cluster 1 effects are ethically irrelevant).

An ethical evaluation (e.g. along the lines of the principles of biomedical ethics) still is oriented toward the individual patient.

But the scheme points out that this ethical analysis can be confronted with a measurement problem.

We do also not claim that “personality changes” that may be induced by DBS are *per se* an ethical problem.



Recommendations (selection)

- The informed consent procedure has to take these “measurement problems” into account
- Assessments of the decision-making capacity and its implication for informed consent should involve an interdisciplinary team including psychiatrists, psychologists, and ethicists
- At least some centers should also offer DBS in targets other than the STN and ablative surgery.
- The adaptation of the stimulation parameters should not only optimize motor functions, but additionally aim at saving or restoring the patient’s autonomy and compatibility with his or her surroundings.
- Research on the causes of cognitive, affective, behavioral, and social side effects of STN DBS should be intensified.



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Your Input: DBS Questionnaire



Goal of the Questionnaire

Target group: ~560 DBS researchers that appear at least twice as authors in our publication body. We try:

1. Capturing the personal experience of the respondent regarding DBS
2. Capturing the general procedure of the clinic regarding DBS
3. Capturing opinions regarding actual clinical and ethical controversies of DBS
4. Capturing appraisals of future applications of DBS