Neuropsychological effects of deep brain stimulation for Parkinson’s disease

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Abstract

Background: Putative changes of cognition after deep brain stimulation (DBS) in patients with Parkinson’s disease (PD) are a matter of debate. The aim of this study was to assess cognitive abilities before and following bilateral subthalamic nucleus (STN) DBS and to review the available literature.

Methods: Twenty patients underwent bilateral DBS of the STN. Cognitive skills were assessed in a standardized fashion before and at least at 12 months after the surgical intervention.

Results: There was a significant decline of both semantic and phonematic verbal fluency and a mild trend for a deterioration of verbal memory after DBS. Mood, general cognitive screening, and visuospatial abilities remained unchanged.

Conclusion: STN DBS in the treatment of PD has resulted in a significant reduction of motor symptoms and improved independence and quality of life in appropriately selected patients. However, it may have isolatable effects on verbal fluency and related function. Case series in the literature reported similar findings. Potential candidates for DBS should be counseled about the risk of mild cognitive declines.

Key Words: Cognitive decline, deep brain stimulation, memory, Parkinson’s disease, subthalamic nucleus, verbal fluency

INTRODUCTION

Parkinson’s disease (PD) is a common neurodegenerative motor disorder, clinically characterized by the progressive impairment of motor function and associated cognitive decline.[21] Deep brain stimulation (DBS) of the bilateral subthalamic nuclei (STN) treatment was proven to be surgically safe in well-selected candidates. DBS improves dopamine sensitive symptoms and dyskinesia and allows for reduced drug doses.[1,5,8,12,18,30] However, short- and long-term investigations of STN DBS in PD patients yielded variable findings regarding the nature and extent of cognitive changes after surgery. Therefore cognitive changes and the predictors for such changes are still a matter of debate.[3,6,8,10,12,14,17,19,26,32,37,38,42-44,49,51,52] We had already demonstrated an improved performance of executive functions, complex motion sequences, and complex reaction time shortly after DBS.[13] The aim of our present study was to assess cognitive outcome in PD patients by a standardized performance of a neuropsychological test battery following STN DBS after an interval of at least several months lasting interval.
PATIENTS AND METHODS

Patients
20 PD patients (13 men) participated in this trial. They received bilateral DBS of the STN. The selection criteria were clinically diagnosed PD, severe levodopa-related motor complications despite prior optimal adjustment of antiparkinsonian medication, no surgical contraindications, no dementia or major ongoing psychiatric illness and no other neurological disorders. The characteristics of the patients are summarized in Table 1.

Surgical techniques
The procedures were staged in all patients with implantation of bilateral STN electrodes in one session and implantation of the pulse generators in a second session 3-5 days later. A Leksell stereotactic head frame (Elekta Instruments, Stockholm, Sweden) was placed. The dorsolateral (sensorimotor) portion of the STN was localized using a proportional geometric scheme based on the distance between the anterior commissure and the posterior commissure, as well as the location of the midcommissural point. The electrodes were implanted under local anesthesia during a single operative session, using a combined approach of intraoperative recording and stimulation. The electrode position was controlled either by postoperative computed tomography (CT) or magnet resonance imaging (MRI). The definitive quadripolar electrodes (model 3389; Medtronic) were connected to a subcutaneous programmable pulse generator (Kinetra; Medtronic) in the subclavicular area in a second operative session. Electrical parameters (pulse width, frequency, and voltage) were adjusted progressively using an electromagnetic programmer (7532 neurological programmer; Medtronic).

Cognitive and behavioral assessment
Cognitive assessment was carried out with an extensive neuropsychological test battery. It included:

1. Cognitive screening by the Mini Mental State Examination (MMSE)\(^\text{[16]}\) and the Parkinson Neuropsychometric Dementia Assessment (PANDA)\(^\text{[23]}\)
2. Verbal memory with a German version of the Rey Auditory Verbal Learning Test (verbal memory test [VLMT])\(^\text{[33]}\) and the verbal digit span forward and backward (German version of Wechsler memory scale-Revised [WMS-R])
3. Determination of amnestic disorders (Berlin amnesia test [BAT])\(^\text{[31]}\)
4. Investigation of visuospatial abilities by the Clock drawing test\(^\text{[41]}\) and the Leistungsprüfsystem (LPS) subtests 3 and 7\(^\text{[20]}\)
5. Performance of language phonological and semantic verbal fluency (“Regensburg verbal fluency test” [RWT])\(^\text{[2]}\)
6. Execution of the Becks Depression Inventory (BDI).\(^\text{[4]}\)

The raw scores were assessed for each patient. The raw scores for WMS-R, VLMT, RWT, BAT, and LPS were then adjusted for age-matched percentile-ranges.

Table 1: Patient characteristics

|                      | Mean±Standard deviation |
|----------------------|-------------------------|
| Age (years)          | 62.8±8.5                |
| Duration of illness  | 15±4.8                  |
| UPDRS I mental behavior | 2.6±1.7               |
| UPDRS II activities of daily living | 11±5.0             |
| UPDRS III on         | 15.3±9.3                |
| UPDRS III off        | 37.6±16.7               |
| Amplitude left (V)   | 2.77±0.7                |
| Amplitude right (V)  | 2.70±0.7                |
| Premorbid intelligence\(^a\) (IQ) | 112.6±17.9          |

\(^a\)Assessment of premorbid intelligence as revealed by the German version of the Multiple Choice Vocabulary Test (MWT-B)\(^\text{[27]}\), UPDRS: Unified Parkinson's disease rating scale

Table 2: Neuropsychological assessment results

|                      | Preoperative | Postoperative | P value |
|----------------------|--------------|---------------|---------|
| General cognitive screening |              |               |         |
| Mini mental state examination\(^a\) | 26.3 | 26.8 | n.s. |
| The parkinson neuropsychometric dementia assessment\(^a\) | 17.7 | 19.0 | n.s. |
| Memory |              |               |         |
| Verbal digit span forward\(^b\) | 53.5 | 37.9 | **    |
| Verbal digit span backward\(^b\) | 31.1 | 24.1 | *     |
| Episodic verbal memory (VLMT) |              |               |         |
| Trial 1-attention\(^b\) | 48.5 | 35.3 | n.s. |
| Trial 5-attention\(^b\) | 46.3 | 35.3 | **    |
| Interference\(^b\) | 51.0 | 35.0 | **    |
| Trial 6\(^b\) | 41.5 | 33.8 | n.s. |
| Immediate recall\(^b\) | 31.8 | 28.8 | n.s. |
| Delayed recall\(^b\) | 29.0 | 24.6 | n.s. |
| Berliner amnesia test\(^b\) | 25.0 | 25.7 | n.s. |
| Language |              |               |         |
| Phonematic Verbal fluency\(^b\) (RWT) | 53.9 | 32.1 | ***   |
| Semantic Verbal fluency\(^b\) (RWT) | 43.1 | 31.2 | *     |
| Visuospatial abilities |              |               |         |
| Clock drawing\(^b\) | 2.1 | 2.2 | n.s. |
| Logical thinking\(^b\) (LPS subtest 3) | 33.3 | 37.5 | n.s. |
| Geometric figures\(^b\) (LPS subtest 7) | 37.4 | 33.5 | n.s. |
| Mood |              |               |         |
| Becks depression inventory\(^b\) | 10.0 | 9.8 | n.s. |

\(^a\)Raw-scores, \(^b\)Percentile, n.s.: Not significant, **P<0.05, ***P<0.01, ****P<0.001
Design
Cognitive assessment and a clinical interview, aimed at detecting the presence of behavioral abnormalities or psychiatric disorders, were performed preoperatively (during the week preceding electrode implantation) and postoperatively between 12 and 18 months after implantation. All cognitive and behavioral assessments before and after surgery were performed while the patients were on an antiparkinsonian medication. Postoperative cognitive and behavioral assessments were performed with stimulators turned on.

Statistical analysis
Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 13.0). The Wilcoxon rank sum test was applied for comparison between the mean scores preoperatively and at the postoperative assessment. A level of $P < 0.05$ was considered significant.

Ethics
Written informed consent was obtained from each subject. The local ethics committee of the university approved this study.

RESULTS
There was a worsening of verbal fluency and verbal digit span after DBS. Verbal memory declined compared with preoperative scores and deteriorated in two out of six items. The general cognitive screening and visuospatial abilities remained unchanged. Mood was not altered [Table 2]. No serious adverse events (e.g., hemorrhage, infection, or infarction) occurred during surgery. Postoperative imaging revealed no dislocation of the electrodes.

DISCUSSION
Our results and the most consistent findings from the literature [Table 3] revealed declines in verbal fluency. Additionally, our results also confirmed previous results, which demonstrated more decline of verbal memory relative to nonverbal memory. Otherwise, executive functions and visuospatial abilities were less affected following STN DBS.

The variable frequencies of cognitive decline after STN DBS in the literature were caused by different ascertainment methods, patient selection criteria,

| Table 3: Review of case series regarding cognitive decline after STN DBS for PD |
| Series | No. of patients | Follow-up in months | Improvements | Unchanged | Declines |
|---------|-----------------|---------------------|--------------|-----------|----------|
| Ardouin et al.[1] | 24 | 12 | EF | GCS | L |
| Pillon et al.[37] | 63 | 6-12 | EF | M | L |
| Perozzo et al.[36] | 20 | 6 | - | L, M, EF | - |
| Daniele et al.[10] | 20 | 12-18 | GCS, EF | M | L |
| Krack et al.[26] | 49 | 60 | - | GCS | EF |
| Funkiewiez et al.[18] | 50 | 12-36 | - | EF, GCS | L |
| Castelli et al.[7] | 72 | 15 | EF | M | L |
| De Gaspari et al.[11] | 26 | 15 | - | GCS | L |
| Deuschl et al.[12] | 78 | 6 | - | GCS | - |
| Erola et al.[14] | 29 | 12 | - | EF | L |
| Smeding et al.[42] | 103 | 6 | - | - | L, EF, M |
| Aybek et al.[36] | 57 | 34 | - | L, VS | M, EF |
| Ory-Magne et al.[35] | 45 | 24 | - | EF, L, M | - |
| Heo et al.[19] | 46 | 12 | - | GCS, EF, M (nonverbal) | L, M (verbal) |
| Ellrichmann et al.[13] | 19 | 12 | EF | - | - |
| York et al.[51] | 23 | 6 | - | GCS, EF, VS | L, M |
| Witt et al.[48] | 60 | 6 | - | GCS, M, VS | L, EF |
| Okun et al.[34] | 26 | 7 | - | L (phonematic VF) | L (semantic VF) |
| Zangaglia et al.[34] | 32 | 36 | - | GCS, M | L, EF |
| Fasano et al.[18] | 20 | 96 | - | GCS | L, M, EF |
| Kishore et al.[25] | 45 | 60 | - | GCS, EF, L, M, VS | - |
| Smeding et al.[42] | 105 | 12 | - | - | L, M, EF, GCS |
| Merola et al.[29] | 19 | 95 | - | - | L, M, EF |
| Saez-Zea et al.[36] | 21 | 6 | - | GCS, EF, M | L |
| Kim et al.[24] | 36 | 6-36 | - | - | GCS |
| Current series | 20 | 6-12 | - | GCS, EF, VS | L, M (verbal) |

EF: Executive function, GCS: General cognitive screening, L: Language, M: Memory, VS: Visuospatial abilities, STN: Subthalamic nucleus, DBS: Deep brain stimulation, PD: Parkinson’s disease
operative techniques, and pre- and postoperative patient management strategies. Studies using formal and substantial neuropsychological evaluation were more likely to find changes than studies using undefined methods or simple cognitive screening instruments such as the MMSE.

Despite use of different assessment tools, STN DBS in most series was associated with decline of verbal fluency. Performance on verbal fluency might be disrupted in PD and consecutively predict incipient dementia.[21,50] Otherwise, the finding that STN DBS patients declined in verbal fluency and related functions more than in other cognitive tasks might reflect a different mechanism underlying cognitive deterioration following surgery. Declines in verbal fluency were usually associated with left-sided DBS.[53,54] In a positron emission tomography (PET) study STN stimulation resulted in decreased activation of the inferior frontal and temporal cortex in the left cerebral hemisphere, resulting in decreased verbal fluency.[40] The effects of STN DBS might be attributable to the electrical stimulation of specific structures or inhibition of over activity in the thalamic region. However, since the decline in verbal fluency was mostly detected shortly after surgery, it might be due to surgical micro lesions affecting cortical-basal circuits involved in word retrieval processes.[41-47] Several studies assessed language function in PD patients following STN DBS on and off stimulation. With the exception of two, all studies failed to observe a significant improvement or decline in verbal fluency in the on-stimulation compared with the off-stimulation condition.[22,77]

In conclusion, STN DBS independently affects verbal and nonverbal cognitive function.

STN DBS in the treatment of PD has resulted in a significant reduction of motor symptoms and improved independence and quality of life for most carefully selected patients. This procedure is associated with some risk for cognitive side effects beyond the expected rate of usual surgical complications such as hemorrhage or infection. The neuropsychological assessment must be considered essential to minimize such risks and to further our understanding of the underlying neurobiology and neuropsychological impact of these treatments.

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