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Long-term Outcomes (15 Years) After Subthalamic Nucleus Deep Brain Stimulation in Patients With Parkinson Disease

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ABSTRACT

Objective: To evaluate the effects of deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson disease (PD) patients on motor complications beyond 15 years after surgery.

Methods: Data about motor complications, quality of life (QoL), activities of daily living, the UPDRS motor scores, dopaminergic treatment, stimulation parameters, and side effects of STN-DBS were retrospectively retrieved and compared between before surgery, at 1 year and beyond 15 years after bilateral STN-DBS.

Results: Fifty-one patients with 17.06 ± 2.18 years STN-DBS follow-up were recruited. Compared to baseline, the time spent with dyskinesia and the time spent in the off state were reduced by 75% ($p<0.001$) and by 58.7% ($p<0.001$), respectively. Moreover, dopaminergic drugs were reduced by 50.6% ($p<0.001$). The PDQL total score, and the emotional function and social function domains improved of 13.8% ($p=0.005$), 13.6% ($p=0.01$) and 29.9% ($p<0.001$), respectively. Few and mostly manageable device-related adverse events were observed during the follow-up.

Conclusions: STN-DBS is still effective beyond 15 years from the intervention, notably with significant improvement in motor complications and stable reduction of dopaminergic drugs. Furthermore, despite the natural continuous progression of PD with worsening of levodopa-resistant motor and non-motor symptoms over the years, STN-DBS patients could maintain an improvement in QoL.

Classification of Evidence: This study provides Class IV evidence that, for patients with PD, STN-DBS remains effective at treating motor complications 15 years after surgery.

INTRODUCTION

In patients with advanced Parkinson disease (PD), deep brain stimulation of the subthalamic nucleus (STN-DBS) is a well-recognized effective treatment in both short- and long-term follow-up.[1, 2] The improvement of several motor and non-motor signs has been reported up to 11 years after STN-DBS, although the magnitude of this effect tends to decline over time.[3-5] Conversely, initial post-operative quality of life (QoL) improvement has been described to fall to preoperative levels after 5-year stimulation, likely due to the escalation of both levodopa- and stimulation-resistant motor and non-motor features of PD, such as impairments of gait, balance, speech and cognition.[6, 7]

Despite the worldwide increasing expectancy of life and the growing number of STN-DBS procedures yearly performed,[8] large data about patients in the second or third decade after the surgical procedure are missing. Indeed, this population with longstanding advanced PD and STN-DBS is often not regularly followed in DBS clinics because of increased difficulty in reaching the hospital or admission in long-term care facilities. Therefore, when the sustained benefits from STN-DBS are not directly confirmed in the clinic it can be challenging to decide whether to replace the stimulator device at the time of its end of life.

The few available data about motor response from STN DBS after more than 10 years focus on small populations, and do not allow to draw solid conclusions about STN DBS effects in the very long-term follow-up.

The overall objective of this study was to evaluate the effects of STN-DBS beyond 15 years after surgery, mainly focusing on PD motor complications changes.

METHODS

Study population

All consecutive PD patients operated on with bilateral STN-DBS at the Grenoble Alpes University Hospital from 1993 to 2004 were retrospectively evaluated. Patients with previous neurosurgical interventions for PD or implantation of DBS electrodes in other deep brain nuclei were excluded.

At time of surgery, all patients fulfilled the criteria of idiopathic PD according to the UK Brain Bank criteria[9] and the following inclusion criteria: presence of disabling motor complications (i.e. motor

fluctuations or levodopa induced dyskinesia) not optimized with antiparkinsonian medication, presence of levodopa responsiveness in all cardinal motor symptoms of PD, including tremor, and age at surgery lower than 75 years.[10] Exclusion criteria at time of surgery were: presence of moderate/severe cognitive impairment, ongoing severe psychiatric disorders, severe atrophy or diffuse cerebral ischemic lesions on brain MRI, and systemic comorbidities interfering with surgery.[11]

Details about the DBS surgical procedure have been previously reported in detail.[12, 13]

Standard protocol approvals, registrations, and patient consents

The Grenoble CHU research center authority reviewed and approved the study protocol. All patients signed informed consent for the study.

Outcomes and measures

Main outcome of the study was the change in the UPDRS-IV items at long-term follow-up (beyond 15 years) after STN-DBS compared to baseline (before surgery). Changes in the time spent with dyskinesia (item 32 of UPDRS[14] or 4.1 of MDS-UPDRS[15]), and in the time spent in the off state (item 39 of UPDRS or 4.3 of MDS-UPDRS) were evaluated over time.

Secondary outcomes included changes in QoL, activities of daily living (ADLs), the UPDRS motor scores, dopaminergic treatment, stimulation parameters and overall safety of STN-DBS at both the short- and long-term follow-up (one year and beyond 15 years postoperatively, T1 and T2 respectively) compared to baseline (T0).

Changes in QoL were evaluated with the Parkinson's Disease Quality of Life Questionnaire (PDQL)[16], also analyzing its four domains: parkinsonian symptoms, systemic symptoms, emotional function, and social function. ADLs were assessed by the UPDRS and MDS-UPDRS part II. Because our center started to use the MDS-UPDRS to evaluate patients after 2011, the MDS-UPDRS part II total scores were regressed to the corresponding UPDRS II scores using the available conversion formula that allowed to standardize the entire cohort to the UPDRS.[17] The presence of dementia (major neurocognitive disorder) was evaluated according to the diagnostic criteria of the DSM-V.[18] Changes in motor scores were evaluated comparing the preoperative on-medication UPDRS-III score to the UPDRS-III score in the on-stimulation/on-medication condition at both short- and long-term follow-up (in the long-term assessments the patients were evaluated only in the on-medication condition with chronic anti-PD treatment). To allow the comparisons, the MDS-UPDRS part III total scores were regressed to the corresponding UPDRS-III.[17] Changes in dopaminergic treatment were determined using the levodopa equivalent daily dose (LEDD).[19] Stimulation parameters were registered at all

follow-up visits. Finally, all adverse events (AEs) occurring during the study period, including surgery-related, device-related and stimulation-/treatment-related AEs, were collected.

Statistical analysis

For both main and secondary outcomes, the Friedman test and the Wilcoxon signed-rank test were used to compare follow-up data within the same group. All statistical computations were two-tailed, and a *P* value <0.05 was considered significant. Continuous variables are presented as mean ± standard deviation (SD). The statistical analyses were performed using the Statistica 7.0 software (StatSoft, Tulsa, OK, USA), considering all follow-up data available at September 1st, 2019.

Data availability

Anonymized data of this study will be available from the corresponding author on reasonable request from any qualified researcher, following the EU General Data Protection Regulation.

Classification of Evidence

This study provides Class IV evidence that, for patients with PD, STN-DBS remains effective at treating motor complications (time spent with dyskinesia and in the off state) 15 years after surgery.

RESULTS

A total of 138 PD patients with bilateral STN-DBS operated between 1993 and 2004 were retrieved from the Movement Disorders Center database of the CHU of Grenoble. Data from 51 out of these 138 patients were available at the long-term follow-up. Mean long-term follow-up time was 17.06 ± 2.18 years, with a median of 16 years (range 15-24) (Figure 1). Of the missing 87 patients, 56 were lost at follow-up and 31 were dead before the 15th year of follow-up (23 of unknown causes, four of aspiration pneumonia, two of complications of accidental fall, one of cardiac arrest, and one of eye tumor). Some of the included patients were also part of the 5-year prospective cohort study previously published by our group.[13]

Table 1 describes the baseline demographic and clinical data of the included 51 patients.

Primary outcome

Long-term STN-DBS effects on motor complications

STN-DBS was effective in improving motor fluctuations and dyskinesia in 39 patients having complete long-term data (Figure 2). Compared to baseline, the time spent with dyskinesia was reduced by 75% (1.64 ± 0.87 at T0 vs. 0.41 ± 0.68 at T2; $P < 0.001$), and the time spent in the off state diminished by 58.7% (1.85 ± 0.74 at T0 vs. 0.74 ± 0.68 at T2; $P < 0.001$).

Secondary outcomes

Short-term STN-DBS effects on motor complications

In the 51 patients, STN-DBS was effective in improving motor fluctuations and dyskinesias at short-term follow-up (Figure 2). One year after the intervention, the time spent with dyskinesia was lessened by 78.7% (1.75 ± 0.93 at T0 vs. 0.42 ± 0.65 at T1; $P < 0.001$), and the time spent in the off state decreased by 71.4% (1.76 ± 0.76 at T0 vs. 0.46 ± 0.68 at T1; $P < 0.001$) compared to baseline.

Short-and long-term STN-DBS effects on QoL

In 27 patients having full long-term follow-up data, there was an improvement of the PDQL scores at both short- and long-term follow-up (Figure 3). The PDQL total score significantly improved of 26.7% at short-term and of 13.8% at long-term follow-up (107.22 ± 18.56 at T0 vs. 135.81 ± 25.39 at T1 vs. 122.04 ± 20.63 at T2; $P < 0.001$). Analyzing the PDQL single subscores, there was significant improvement of the emotional function domain (21.7% and 13.6% of improvement at short- and long-term follow-up, respectively; 27.3 ± 5.08 at T0 vs. 33.23 ± 5.94 at T1, vs. 31.0 ± 6.23 at T2; $P = 0.001$) and of the social function domain (33.3% and 29.9% of improvement at short- and long-term follow-up, respectively; 19.85 ± 5.41 at T0 vs. 26.46 ± 6.44 at T1, vs. 25.78 ± 5.73 at T2; $P < 0.001$). Conversely, for the parkinsonian symptoms domain there was a significant improvement at short-term (38.22 ± 6.84 at T0 vs. 49.62 ± 8.07 at T1; $P < 0.001$) but not at long-term follow-up (38.22 ± 6.84 at T0 vs. 38.3 ± 6.87 at T2; $P = 0.95$). Similarly, the systemic symptoms domain improved significantly at the short-term (20.04 ± 3.97 at T0 vs. 24.0 ± 5.94 at T1; $P = 0.001$) but not at the long-term follow-up (20.04 ± 3.97 at T0 vs. 22.0 ± 5.14 at T2; $P = 0.07$).

Long-term STN-DBS effects on ADLs

In the long-term follow-up, 19 patients (37.3%) were completely independent in their ADLs, 27 patients (52.9%) needed some help, and five (9.8%) were institutionalized; 18 of 51 patients (35.3%) were demented. In 40 patients having complete long-term data of the UPDRS-II in the on condition, a significant worsening was observed (4.02 ± 3.97 at T0 vs. 5.54 ± 4.71 at T1, vs. 21.55 ± 9.86 at T2; $P < 0.001$). Conversely, when considering the baseline UPDRS-II in the off condition, the UPDRS-II in the on condition at long-term follow-up was slightly reduced, although not significantly (23.16 ± 6.39 at T0 vs. 21.55 ± 9.86 at T2; $P = 0.58$), while it was greatly reduced at 1-year follow-up (23.16 ± 6.39 at T0 vs. 5.54 ± 4.71 at T1; $P < 0.001$).

Long-term STN-DBS effects on motor scores

In the total sample of 51 patients at long-term follow-up, there was a significant worsening of the UPDRS-III in the on-stimulation/on-medication condition during chronic medication compared to the preoperative on condition (10.86 ± 6.94 at T0 vs. 10.53 ± 7.62 at T1 vs. 32.95 ± 15.47 at T2; $P < 0.001$).

Dopaminergic therapy and stimulation parameters

Compared to baseline, LEDD was significantly reduced by 73.4% at the short-term and by 50.6% at the long-term follow-up (1,305.62 ± 427.23 at T0 vs. 347.41 ± 277.94 at T1, vs. 644.91 ± 334.26 at T2; $P < 0.001$) in the total sample.

In the long-term follow-up, monopolar stimulation was applied bilaterally in 41 patients, double monopolar stimulation bilaterally in four patients, monopolar at one side and double monopolar at the other side in four patients, bipolar at one side and monopolar at the other side in one patient, and bipolar stimulation bilaterally in another patient. Voltage and pulse width did not change significantly, while frequency was significantly reduced bilaterally when compared to the parameters at 1-year follow-up (141.2 ± 20.37 Hz at T1 vs. 130.59 ± 23.27 Hz at T2 on the left side, $P = 0.018$; 140.4 ± 20.0 Hz at T1 vs. 130.39 ± 23.23 Hz at T2 on the right side; $P = 0.015$) (Table 2).

STN-DBS adverse events

All adverse events (AEs) after STN-DBS implantation in the 51 patients are listed in the Table 3. Patients with intraventricular hemorrhage had transient confusion without neurological sequelae. Subdural hematomas and intracerebral edemas were asymptomatic in all cases. In three cases, infection required lead explant with following replacement. Among stimulation-/treatment-related AEs, mean weight gain was 9.0 ± 3.6 kg after the first year from DBS implant. Weight gain remained stable over time (8.9 ± 9.96 kg at the last follow-up). During the observation, patients underwent 2.63 ± 1.04 (range 1-7) IPG replacements.

DISCUSSION

In this retrospective single-center study, STN-DBS was effective in improving motor complications in the very long-term follow-up of advanced PD patients. In this population, QoL improvement and dopaminergic drugs reduction were sustained beyond 15 years from surgery, despite the underlying

disease progression. To our knowledge, this is the longest and largest follow-up described in patients with DBS.

In PD natural history, motor fluctuations and dyskinesia highly affect patients' QoL, thus representing the major criteria for eligibility to advanced treatments when they are not satisfactorily managed with standard oral therapy.[10] Several randomised clinical trials have demonstrated that STN-DBS improves motor fluctuations and dyskinesia.[20-23] Furthermore, these benefits have been shown to persist beyond 5 years from the intervention in large retrospective studies.[3, 4, 7, 24-27] In our study, the reduction of time spent with dyskinesia and daily off time was persistent beyond 15 years after STN-DBS, with an improvement of more than 50% in all items compared to baseline. These effects may be partially explained by the important post-operative dopaminergic drugs reduction. Indeed, DBS itself is supposed to provide an overall stabilization of the cortico-basal ganglia network, and changes in striatal synaptic plasticity could exert antidyskinetic and stable antiparkinsonian effects.[27]

The improvement of parkinsonian motor and non-motor symptoms after STN-DBS has been associated to QoL improvement by several authors.[6, 20-24, 28-30] If QoL improvement has been widely described in the first years after DBS, only few studies have reported a QoL improvement persistent at 5-year follow-up.[24, 30] Some authors have described that QoL scores returned to baseline at the 5- and 8-year follow-up, probably due to levodopa-refractory and stimulation-resistant motor and non-motor features of PD.[7, 31] In our sample, we found a significant QoL improvement at both the short- and long-term follow-up. One year after DBS, the PDQL scale improved in all its subdomains. Beyond 15 years, parkinsonian and systemic symptoms returned to preoperative baseline, probably due to the disease progression, whereas emotional and social function domains remained significantly improved. The sustained improvement in these domains, as well as in the PDQL total score, at least partially might depend on the long-term effects of STN-DBS on motor complications, persistent over time in our sample. Accordingly, the cumulative daily off time has been found to be the strongest predictor for improvement in QoL after STN-DBS, as a higher increase in the time spent in on condition correlates with a better QoL improvement.[28] Moreover, the sustained improvement of emotional functions might reflect beneficial effects of DBS on mood and other psychiatric symptoms, which largely influence QoL in PD patients, often more than motor symptoms.[32] Different results in QoL outcome at long-term follow-up may depend on different selection criteria of patients for DBS among various centers. In particular, younger age at PD onset and at surgery, as well as better cognitive performances (especially on frontal score) and levodopa responsiveness at baseline, have been associated to better motor and

non-motor outcomes.[33-36] In our cohort, mean age at PD onset was 40 years, mean age at surgery was 51 years, levodopa responsiveness was 75% at baseline, and patients with moderate/marked cognitive impairment were excluded from DBS. Therefore, a rigorous selection for DBS might provide positive outcomes in term of QoL improvement at both short- and long-term follow-up.

STN-DBS also improves ADLs, as widely demonstrated.[20, 22] Improvement has been consistently seen up to 5 years from the intervention, but longer-term results have mostly shown a progressive worsening beyond 5 years form DBS.[3, 4, 25] We found a significant deterioration of ADLs after more than 15 years of stimulation in the on condition compared to baseline, likely due to disease progression, worsening of axial symptoms and cognitive impairment. However, considering that the on periods were significantly increased by STN-DBS and that patients spent most time in the on condition after surgery, the UPDRS II score in the on condition at long-term follow-up appeared slightly improved compared with the UPDRS II score in the off condition before DBS.

Not being available the UPDRS III score in the off-medication condition at long-term follow-up, we could compare only the score in the on-stimulation/on-medication condition during chronic medication to the score in the preoperative on condition. We found a marked increase in the UPDRS III total score at long-term follow-up, as expected for disease progression.[37] Accordingly, in other studies, the UPDRS III total score in the on-medication condition worsened beyond 5 years of stimulation.[3, 4, 7, 38] This observation may be explained by the fact that STN-DBS is a symptomatic treatment of the off medication period but it does not usually significantly improve symptoms during the on medication period, reflecting the levodopa sensitivity of symptoms at this stage of the disease.[2]

As extensively demonstrated, STN-DBS allows dopaminergic drugs reduction over time.[3, 4, 7, 13, 20-22, 24-26] In our population, dopaminergic drugs reduction was of 73.4% one year and of 50.6% at more than 15 years after DBS. These findings are a good indication of how effectively STN-DBS improves PD symptoms. The reduction usually minimizes the AEs of PD drugs, as dyskinesia and hyperdopaminergic behaviors.[39] Moreover, the progressive desensitization of the dopaminergic receptors that complements the LEDD reduction can be confirmed by the poor response to sustained doses of levodopa that can be needed in case of sudden battery failure.[40, 41]

Concerning the stimulation parameters management, it is usually described a significant increase in voltage during the first years after the intervention, but no further modifications thereafter.[4, 7] In line with these studies, we did not found significant changes in voltage or pulse width between the short- and long-term follow-up. The only parameter significantly changed at long-term follow-up was the

frequency, which was reduced to 80 or 60 Hz in some patients to better manage speech or axial disturbances. As in other long-term studies, most patients received monopolar stimulation through a single contact on each electrode, but some received bipolar or double monopolar stimulation.[2]

In our study, STN-DBS showed a AEs profile in line with what reported by randomized clinical trials and other large retrospective studies.[4, 20-25, 38] We reported only one life-threatening AE during surgery (cardiac arrhythmia); other minor AE were recorded, mostly asymptomatic events and all without sequelae. During the long-term follow-up, five patients needed lead reimplantation, due to intracranial infections, lead malfunctions or lead suboptimal placement. All patients underwent IPG replacements, mainly for battery end of life, on average 2.63 ± 1.04 times during a mean observation of 17.06 ± 2.18 years. Among the stimulation-/treatment-related AEs, many reported events, as motor and psychiatric complications, mainly related on PD itself. Conversely, whereas PD patients with only medical treatment show a progressive weight decline, stimulated patients have gain weight after the intervention[38] We found a mean weight gain of 9 kg in the first year of follow-up, which remained substantially stable during the whole follow-up. Eyelid-opening apraxia was found in 29% of our sample.[4, 25, 38]

Our study has several limitations. The first is the high percentage of patients lost at long-term follow-up (40.6% of total sample at over-15-year follow-up), with a risk of bias, as those patients on whom longer term follow-up is available are likely to be the ones who are doing well. However, this is the inevitable limit of long-term retrospective studies, as it has been reported a dropout rate between 37.5% and 70.2%.[3, 4, 38] A second limit of this study is the lack of motor symptoms evaluation in the off-medication condition at the long-term follow-up, thus not allowing to measure the precise motor effects of stimulation alone. Nevertheless, our data strongly support a long-term motor effect of STN-DBS, as it allowed a significant reduction of motor complications and dopaminergic drugs. Likewise, missing the evaluation of ADLs in the off-medication condition, the effect of DBS at long-term follow-up might have been underestimated. A third limit of this study is the lack of data about non-motor symptoms at the long-term follow-up, because the UPDRS I section or other scales specifically designed to assess non-motor symptoms were not available for all patients beyond 15 years of stimulation. Another limit of the study is the lack of long-term follow-up data for some patients: 12 of 51 patients lacked the UPDRS-IV evaluation, and 24 of 51 patients lacked the PDQL scale. Finally, it has to be taken into account that comparing a subjective scale, as PDQL, at various time point with many years of difference may be affected by several bias, as new comorbidities, aging and different

acceptation of chronic state of disability deriving from PD. In fact, some patients might better accept their disability many years after DBS surgery compared to younger surgical candidates with high demand for work and social functioning.

In conclusion, our findings confirm that STN-DBS is still effective beyond 15 years from the intervention, with a significant improvement in motor complications and a stable reduction of dopaminergic drugs. Despite the inevitable progression of levodopa-resistant motor and non-motor symptoms in the late stages of PD, STN-DBS patients maintained an improvement in QoL. Few and mostly manageable device-related AEs were found during the follow-up. This information about the long-term outcomes after DBS surgery can be useful to patients, caregivers and treating physicians when counseling about surgery.

Appendix 1: Authors

Name	Location	Contribution
Francesco Bove, MD	Università Cattolica del Sacro Cuore, Rome	Design and conceptualization of the study, analysis of the data, drafting the manuscript
Delia Mulas, MD	Mater Olbia Hospital	Design and conceptualization of the study, major role in the acquisition of data, drafting the manuscript
Francesco Cavallieri, MD	University of Modena and Reggio Emilia	Major role in the acquisition of data
Anna Castrioto, MD, PhD	CHU Grenoble Alpes	Major role in the acquisition of data
Stephan Chabardès, MD, PhD	CHU Grenoble Alpes	Major role in the acquisition of data
Sara Meoni, MD, PhD	CHU Grenoble Alpes	Major role in the acquisition of data
Emmanuelle Schimtt, MPsych	CHU Grenoble Alpes	Major role in the acquisition of data
Amélie Bichon, MPsych	CHU Grenoble Alpes	Major role in the acquisition of data
Enrico Di Stasio, MD	CHU Grenoble Alpes	Analysis of the data
Andrea Kistner, PhD	CHU Grenoble Alpes	Major role in the acquisition of data
Pierre Pélissier, MSc	CHU Grenoble Alpes	Major role in the acquisition of data
Eric Chevrier, PT, MSc	CHU Grenoble Alpes	Major role in the acquisition of data

Eric Seigneuret, MD	CHU Grenoble Alpes	Major role in the acquisition of data
Paul Krack, MD, PhD	University Hospital Bern	Interpretation of the data, revising the manuscript for intellectual content
Valerie Fraix, MD, PhD	CHU Grenoble Alpes	Major role in the acquisition of data, revising the manuscript for intellectual content
Elena Moro, MD, PhD	CHU Grenoble Alpes	Design and conceptualization of the study, interpretation of the data, revising the manuscript for intellectual content

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Table 1. Demographic and clinical data of PD patients with STN-DBS (n=51) at baseline.

Sex (male/female)	33/18
Age (years)	51.03 ± 8.53 (range 34-72)
Disease duration (years)	11.35 ± 3.77 (range 4-20)
Motor subtype (PDIG/tremor-dominant/indeterminate)	24/20/7
UPDRS-I	1.95 ± 1.36
UPDRS-II on-med	4.61 ± 4.25
UPDRS-II off-med	23.9 ± 6.46
UPDRS-III on-med	10.86 ± 6.94
UPDRS-III off-med	43.91 ± 12.95
UPDRS-IV	10.55 ± 3.05
Levodopa responsiveness (% of improvement)	75.3%
Hoehn & Yahr on-med	1.55 ± 0.78
Hoehn & Yahr off-med	3.31 ± 0.86
LEDD	1305.62 ± 427.23

Abbreviations: PDIG = postural instability/gait disturbance; UPDRS = Unified Parkinson's Disease Rating Scale; med = medications; LEDD = levodopa equivalent daily dose.

Data are reported as mean ± SD unless otherwise indicated.

Table 2. STN stimulation parameters at 1-year and over 15-year follow-up in 51 PD patients.

Variable	T1	T2	*P* value
Left STN voltage (V)	2.84 ± 0.55 (range 1.5-4.0)	3.05 ± 0.58 (range 1.2-4.3)	0.05
Right STN voltage (V)	2.88 ± 0.57 (range 1.5-4.1)	2.97 ± 0.74 (range 0.6-4.9)	0.35
Left STN pulse width (μs)	61.2 ± 5.94 (range 60-90)	63.53 ± 9.76 (range 60-90)	0.21
Right STN pulse width (μs)	61.2 ± 5.94 (range 60-90)	62.35 ± 8.15 (range 60-90)	0.46
Left STN frequency (Hz)	141.2 ± 20.37 (range 130-185)	130.59 ± 23.27 (range 60-180)	0.018
Right STN frequency (Hz)	140.4 ± 20.0 (range 130-185)	130.39 ± 23.23 (range 60-180)	0.015

Abbreviations: STN = subthalamic nucleus; V = Volt; μs = microsecond; Hz = Hertz.

Data are mean ± SD (range).

Table 3. Adverse effects (AEs) after STN-DBS in the short- and long-term follow-up.

Surgery-related AEs	**N. of events**
Intraventricular hemorrhage	1
Subdural hematoma	1
Intracerebral edema	7
Transient neurologic symptoms during the intervention*	1
General health complications**	2
Peri- or post-operative confusion	7
Device-related AEs	**N. of events**
Connector cable fracture	7 (6 patients)
Lead malfunction	2
Lead reimplantation***	6 (5 patients)
IPG battery failure	13 (12 patients)
Infection****	8 (6 patients)
Skin erosion	4 (3 patients)
Fibrosis around connector cable	3
IPG pocket hematoma	4
Stimulation-/treatment-related AEs	**N. of patients**
Weight gain	27
Eyelid-opening apraxia	15
Severe dysarthria	38
Freezing of gait	46
Depression	34
Apathy	36
Anxiety	19
Impulse control disorders	24
Hallucinations	37
Psychosis	13
Suicide attempts	5 (8 events)

Abbreviations: AEs = adverse effects; IPG = implantable pulse generator.

*Transient aphasia.

**A pneumonia and a cardiac arrhythmia during the surgical procedure.

***Lead reimplantations were due to intracranial infections (three cases), lead malfunctions (two cases) and lead suboptimal placement (one case).

****Infections were in three cases cranial (intra- and extracerebral), in three cases cranial (extracerebral), in two cases localized at the IPG pocket.

Figure Legends

Figure 1. PD patients' distribution by follow-up duration.

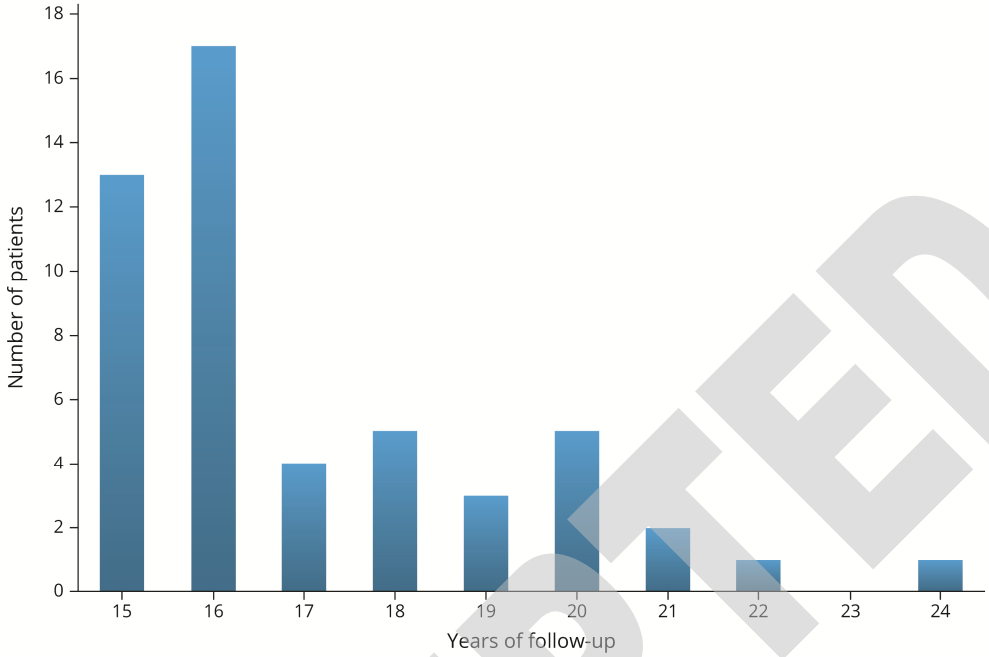


Figure 2. Long-term STN-DBS efficacy on motor complications.

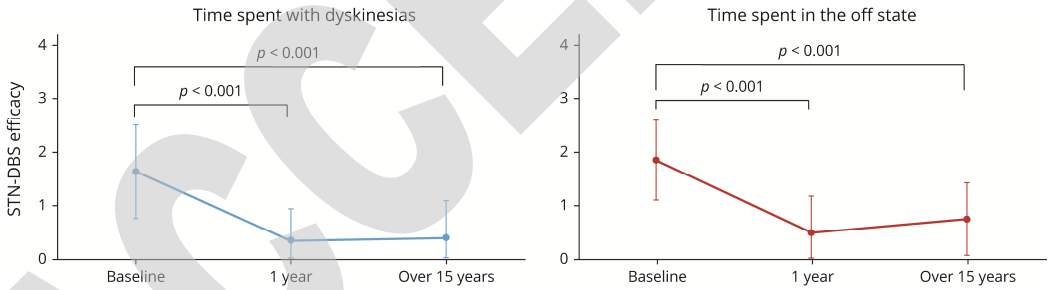
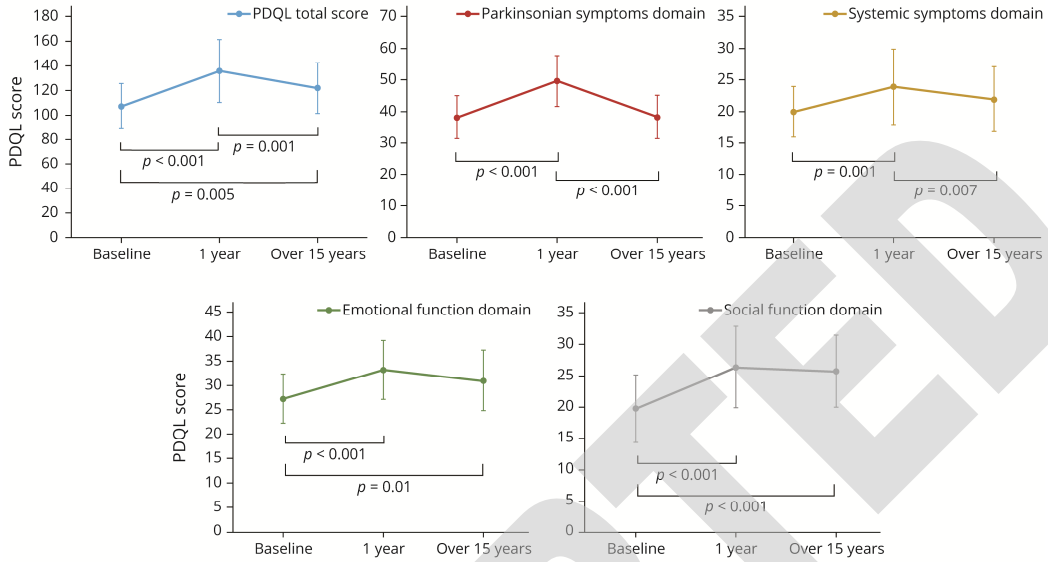


Figure 3. Parkinson's disease Quality of Life Questionnaire (PDQL) scores and related subscores in PD patients undergoing STN-DBS.



Long-term Outcomes (15 Years) After Subthalamic Nucleus Deep Brain Stimulation in Patients With Parkinson Disease

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