RESEARCH ARTICLE

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

Francesco Bove, MD, Delia Mulas, MD, Francesco Cavallieri, MD, Anna Castrioto, MD, PhD, Stephan Chabardès, MD, PhD, Sara Meoni, MD, PhD, Emmanuelle Schmitt, MPsych, Amélie Bichon, MPsych, Enrico Di Stasio, MD, Andrea Kistner, PhD, Pierre Pélissier, MSc, Eric Chevrier, PT, MSc, Eric Seigneuret, MD, Paul Krack, MD, PhD, Valerie Fraix, MD, PhD, and Elena Moro, MD, PhD

Correspondence
Dr. Moro
elenamfmoro@gmail.com

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Abstract

Objective

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

Methods

Data on motor complications, quality of life (QoL), activities of daily living, Unified Parkinson's Disease Rating Scale motor scores, dopaminergic treatment, stimulation measures, and side effects of STN-DBS were retrospectively retrieved and compared 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% ($p < 0.001$). Parkinson's Disease Quality of Life Questionnaire total score and the emotional function and social function domains improved 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 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 nonmotor symptoms over the years, patients undergoing STN-DBS 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.

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From the Movement Disorders Unit, Division of Neurology (F.B., D.M., F.C., A.C., S.M., E.S., A.B., A.K., P.P., E.C., V.F., E.M.), CHU Grenoble Alpes, Grenoble, France; Neurology Unit (F.B.) and Chemistry, Biochemistry and Clinical Molecular Biology (E.D.S.), Fondazione Policlinico Universitario A. Gemelli IRCCS; Department of Neurosciences (F.B.) and Institute of Biochemistry and Clinical Biochemistry (E.D.S.), Università Cattolica del Sacro Cuore, Rome; Institute of Neurology (D.M.), Mater Olbia Hospital, Olbia; Neurology Unit, Neuromotor and Rehabilitation Department (F.C.), Azienda USL-IRCCS di Reggio Emilia; Clinical and Experimental Medicine PhD Program (F.C.), University of Modena and Reggio Emilia, Modena, Italy; Grenoble Institute of Neurosciences (A.C., S.C., S.M., E.S., A.B., A.K., P.P., E.C., E.S., V.F., E.M.), University Grenoble Alpes, Inserm, U1216, Grenoble; Division of Neurosurgery (S.C., E.S.), Centre Hospitalier Universitaire (CHU), Grenoble Alpes University, France; Department of Health Sciences (S.M.), University of Milan, Italy; and Department of Neurology (P.K.), Bern University Hospital, Switzerland.

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Glossary

ADL = activities of daily living; **AE** = adverse event; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **IPG** = implantable pulse generator; **LEDD** = levodopa equivalent daily dose; **MDS** = Movement Disorders Society; **PD** = Parkinson disease; **PDQL** = Parkinson's Disease Quality of Life Questionnaire; **QoL** = quality of life; **STN-DBS** = deep brain stimulation of the subthalamic nucleus; **UPDRS** = Unified Parkinson's Disease Rating Scale.

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 nonmotor 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 postoperative 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 nonmotor features of PD, such as impairments of gait, balance, speech, and cognition.[6,7]

Despite the worldwide increasing life expectancy and the growing number of STN-DBS procedures performed yearly,[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 end of its life.

The few available data about motor response from STN-DBS after more than 10 years focus on small populations and do not allow one to draw solid conclusions about STN-DBS effects in 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

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.

Study Population

All consecutive patients with PD 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 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]

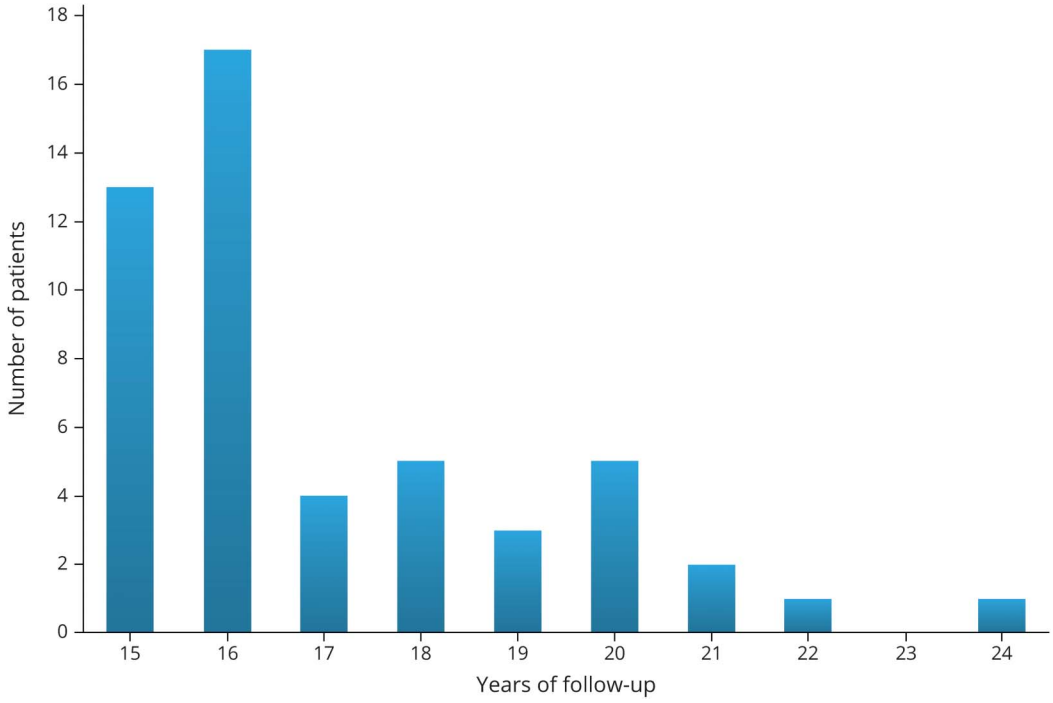
Outcomes and Measures

The main outcome of the study was the change in the Unified Parkinson's Disease Rating Scale (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 Movement Disorders Society [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 measures, and overall safety of STN-DBS at both the short- and long-term follow-up (1 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 4 domains: parkinsonian symptoms, systemic symptoms, emotional function, and social function. ADLs were assessed by the UPDRS and MDS-UPDRS-II. Because our center started to use the MDS-UPDRS to evaluate patients after 2011, the MDS-UPDRS-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

Figure 1 Distribution of Patients With Parkinson Disease by Follow-up Duration



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-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 measures were registered at all follow-up visits. 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 2-tailed, and a p value < 0.05 was considered significant. Continuous variables are presented as mean ± SD. Statistical analyses were performed using Statistica 7.0 software (StatSoft), considering all follow-up data available on September 1, 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 patients with PD 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 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 to follow-up and 31 were dead before the 15th year of follow-up (23 of unknown causes, 4 of aspiration pneumonia, 2 of complications of accidental fall, 1 of cardiac arrest, and 1 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 51 included 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; $p < 0.001$).

Table 1 Demographic and Clinical Data of Patients With Parkinson Disease With Deep Brain Stimulation of the Subthalamic Nucleus (n = 51) at Baseline

Characteristics	Values
Sex, male/female	33/18
Age, y	51.03 ± 8.53 (34–72)
Disease duration, y	11.35 ± 3.77 (4–20)
Motor subtype (PIGD/tremor-dominant/ indeterminate)	24/20/7
UPDRS-I	1.95 ± 1.36
UPDRS-II "on" medication	4.61 ± 4.25
UPDRS-II "off" medication	23.9 ± 6.46
UPDRS-III "on" medication	10.86 ± 6.94
UPDRS-III "off" medication	43.91 ± 12.95
UPDRS-IV	10.55 ± 3.05
Levodopa responsiveness (% of improvement)	75.3
Hoehn & Yahr "on" medication	1.55 ± 0.78
Hoehn & Yahr "off" medication	3.31 ± 0.86
LEDD	1,305.62 ± 427.23

Abbreviations: LEDD = levodopa equivalent daily dose; PIGD = postural instability/gait disturbance; UPDRS = Unified Parkinson's Disease Rating Scale.
Data are reported as mean ± SD (range) unless otherwise indicated.

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 26.7% at short-term and 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 independent in their ADLs, 27 patients (52.9%) needed some help, and 5 (9.8%) were institutionalized; 18 of 51 patients (35.3%) had dementia. 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"-

Figure 2 Long-term Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) Efficacy on Motor Complications

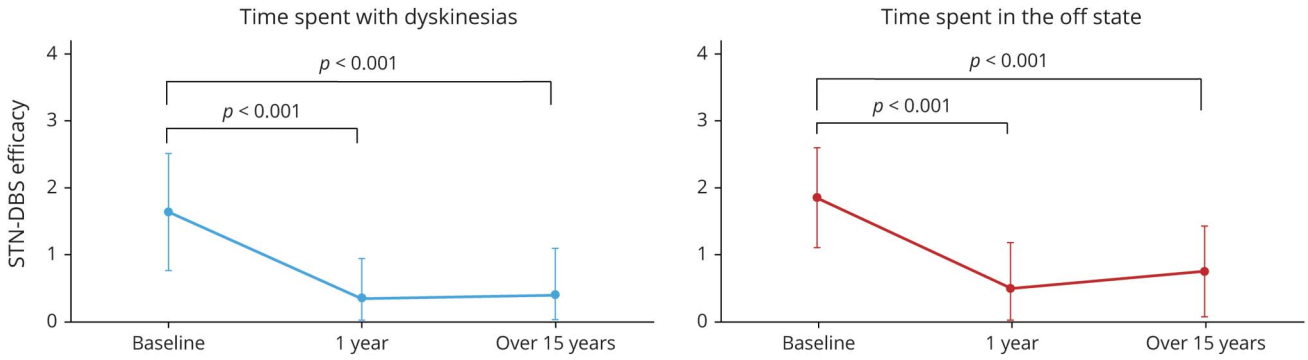
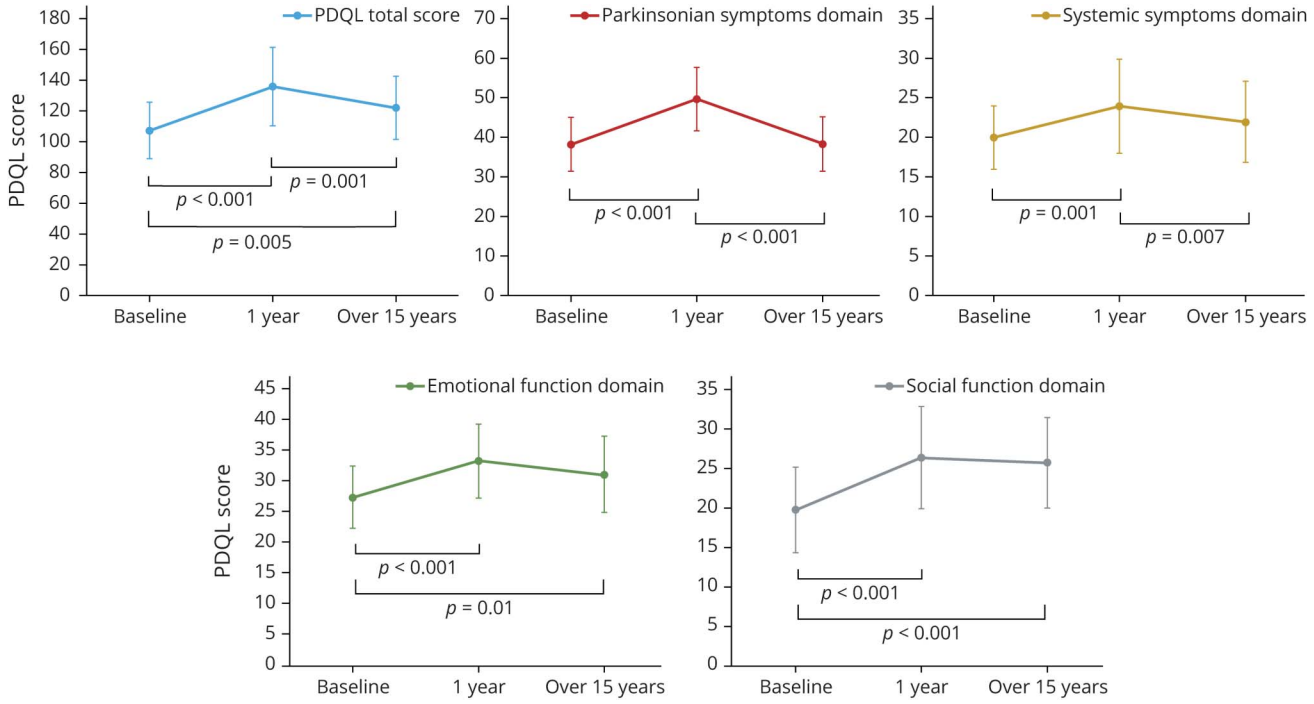


Figure 3 Parkinson's Disease Quality of Life Questionnaire (PDQL) Scores and Related Subscores in Patients With Parkinson Disease Undergoing Deep Brain Stimulation of the Subthalamic Nucleus



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 Measures

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 4 patients, monopolar at 1 side and double monopolar at the other side in 4 patients, bipolar at 1 side and monopolar at the other side in 1 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 measures 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 AEs after STN-DBS implantation in the 51 patients are listed in table 3. Patients with intraventricular hemorrhage had transient confusion without neurologic sequelae. Subdural hematomas and intracerebral edemas were asymptomatic in all cases. In 3 cases, infection required lead explant with 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) implantable pulse generator (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 patients with advanced PD. 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 randomized 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

Table 2 Subthalamic Nucleus (STN) Stimulation Measures at 1-Year and Over 15-Year Follow-up in 51 Patients With Parkinson Disease

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

Data are reported as mean ± SD (range).

explained by the important postoperative dopaminergic drugs reduction. Indeed, DBS itself is supposed to provide an overall stabilization of the corticobasal ganglia network, and changes in striatal synaptic plasticity could exert antidyskinetic and stable antiparkinsonian effects.[27]

The improvement of parkinsonian motor and nonmotor symptoms after STN-DBS has been associated with QoL improvement by several authors.[6,20-24,28-30] QoL improvement has been widely described in the first years after DBS, but 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 nonmotor features of PD.[7,31] In our sample, we found 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 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 patients with PD, 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 with better motor and nonmotor 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 from 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.

UPDRS-III score in the "off"-medication condition at long-term follow-up not being available, 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 73.4% at 1 year and 50.6% at more than 15 years after DBS. These findings are a good indication of how effectively STN-DBS improves PD

Table 3 Adverse Effects (AEs) After Deep Brain Stimulation of the Subthalamic Nucleus in the Short- and Long-term Follow-up

AEs	No. of events
Surgery-related	
Intraventricular hemorrhage	1
Subdural hematoma	1
Intracerebral edema	7
Transient neurologic symptoms during the intervention[a]	1
General health complications[b]	2
Peri- or postoperative confusion	7
Device-related	
Connector cable fracture	7 (6 patients)
Lead malfunction	2
Lead reimplantation[c]	6 (5 patients)
IPG battery failure	13 (12 patients)
Infection[d]	8 (6 patients)
Skin erosion	4 (3 patients)
Fibrosis around connector cable	3
IPG pocket hematoma	4
Stimulation-/treatment-related	
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)

Abbreviation: IPG = implantable pulse generator.
[a] Transient aphasia.
[b] A pneumonia and a cardiac arrhythmia during the surgical procedure.
[c] Lead reimplantations were due to intracranial infections (3 cases), lead malfunctions (2 cases), and lead suboptimal placement (1 case).
[d] Infections were in 3 cases cranial (intracerebral and extracerebral), in 3 cases cranial (extracerebral), and in 2 cases localized at the IPG pocket.

symptoms. The reduction usually minimizes the AEs of PD drugs, such 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 stimulation measures management, a significant increase in voltage during the first years after the intervention is usually described, but no further modifications thereafter.[4,7] In line with these studies, we did not find significant changes in voltage or pulse width between the short- and long-term follow-up. The only measure 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 an AE profile in line with what has been reported by randomized clinical trials and other large retrospective studies.[4,20-25,38] We reported only 1 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, 5 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, such as motor and psychiatric complications, were mainly related to PD itself. Conversely, whereas patients with PD 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 an inevitable limit of long-term retrospective studies, as a dropout rate between 37.5% and 70.2% has been reported.[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 us 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 nonmotor symptoms at the long-term follow-up, because the UPDRS-I section or other scales specifically designed to assess nonmotor 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, such as PDQL, at various time points with many years of difference may be affected by several biases, such as new comorbidities, aging, and different acceptance levels of chronic state of disability deriving from PD. 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.

Our findings confirm that STN-DBS is 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 nonmotor symptoms in the late stages of PD, patients with STN-DBS maintained an improvement in QoL. Few and mostly manageable device-related AEs were found during the follow-up. This information on long-term outcomes after DBS surgery can be useful to patients, caregivers, and treating physicians when counseling about surgery.

Study Funding

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Disclosure

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Appendix 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 Schmitt, 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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Francesco Bove, Delia Mulas, Francesco Cavallieri, et al.

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