Received: 18 March 2022 | Accepted: 30 May 2022

DOI: 10.1111/ene.15436

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Long-term independence and quality of life after subthalamic stimulation in Parkinson disease

Anna Castrioto[1] | Bettina Debû[1] | Emilie Cousin[2,3] | Pierre Pelissier[1] | Eugénie Lhommée[1] | Amélie Bichon[1] | Emmanuelle Schmitt[1] | Andrea Kistner[1] | Sara Meoni[1] | Eric Seigneuret[4] | Stephan Chabardes[1] | Paul Krack[5] | Elena Moro[1] | Valérie Fraix[1]

[1]Inserm, U1216, Grenoble Alpes University Hospital Center, Grenoble Institute of Neurosciences, Grenoble Alpes University, Grenoble, France

[2]CNRS LPNC UMR 5105, Grenoble Alpes University, Grenoble, France

[3]UMS IRMaGe Grenoble University Hospital Center, Grenoble Alpes University, Grenoble, France

[4]Department of Neurosurgery, Grenoble Alpes University Hospital Center, Grenoble, France

[5]Department of Neurology, Inselspital, University Hospital Bern, Bern, Switzerland

Correspondence
Anna Castrioto, Movement Disorders Center, Neurology, CHU Grenoble Alpes, Grenoble, France.
Email: acastrioto@chu-grenoble.fr

Funding information
This is an investigator-initiated study. Medtronic provided financial support. The sponsor had no role in the study design, data analysis and interpretation, and writing the manuscript.

Abstract

Background and purpose: Studies on long-term nonmotor outcomes of subthalamic nucleus stimulation in Parkinson disease (PD) are scarce. This study reports on very long-term non-motor and motor outcomes in one of the largest cohorts of people with advanced PD, treated for >10 years with subthalamic nucleus stimulation. The main outcome was to document the evolution of independence in activities of daily living. The secondary outcomes were to measure the change in quality of life, as well as non-motor and motor outcomes.

Methods: Patients were studied preoperatively, at 1 year, and beyond 10 years after subthalamic stimulation with an established protocol including motor, non-motor, and neuropsychological assessments.

Results: Eighty-five people with PD were included. Independence scores in the off-medication condition (measured with the Schwab & England Activities of Daily Living Scale) as well as quality of life (measured with the Parkinson's Disease Questionnaire [PDQ]-37) remained improved at longest follow-up compared to preoperatively (respectively, $p < 0.001$, $p = 0.015$). Cognitive scores, measured with the Mattis Dementia Rating Scale, significantly worsened compared to before and 1 year after surgery ($p < 0.001$), without significant change in depression, measured with the Beck Depression Inventory. Motor fluctuations, dyskinesias, and off dystonia remained improved at longest follow-up ($p < 0.001$), with a significant reduction in dopaminergic treatment (45%, $p < 0.001$).

Conclusions: This study highlights the long-term improvement of subthalamic stimulation on independence and quality of life, despite the progression of disease and the occurrence of levodopa-resistant symptoms.

KEYWORDS
activities of daily living, deep brain stimulation, Parkinson disease, quality of life, subthalamic nucleus

INTRODUCTION

Subthalamic nucleus (STN) deep brain stimulation (DBS) has dramatically changed the management of advanced Parkinson disease (PD), allowing an improvement of motor complications, non-motor fluctuations, quality of life, and a reduction of dopaminergic medication [1, 2]. Long-term data on STN-DBS suggest a sustained benefit on motor symptoms and complications, with a persistent reduction of dopaminergic medication [3–6, 7]. However, non-motor outcome data at very long-term follow-up are scarce [8, 9]. This is understandable, considering the difficulties of long-term follow-up for people living far away from the centers of investigation, as well as the old age and the comorbidities in patients with long disease duration. Nonetheless, documenting the very long-term non-motor outcome, including activities of daily living, cognition, mood, and quality of life, is very important for the patient and his/her caregiver, as well as for the clinician.

The emergent field of palliative care in neurodegenerative disease highlights the relevance of very long-term non-motor outcome in people with PD treated with STN-DBS. Based on a single case report, it has been claimed that STN-DBS is deleterious in late stages of PD, leading to prolonged life in an inacceptable condition for patients and caregivers [10]. On the other hand, results from a large cohort of patients followed for >15 years have provided more encouraging results [7]. Better knowledge on very long-term non-motor evolution is thus essential to address these issues and to guide patients, families, and physicians.

The purpose of this study was to assess the very long-term non-motor outcome, including independence in activities of daily life, quality of life, cognition, mood, and motor outcome in the first historical cohort of PD patients treated with STN-DBS in Grenoble.

METHODS

Study design

This is a longitudinal monocentric study assessing people with PD preoperatively, at 1 year and beyond 10 years after STN-DBS. Inclusion criteria were diagnosis of PD, complicated with motor fluctuations and dyskinesias, and treated with STN-DBS between 1993 and 2004, for at least 10 years. Criteria for undergoing STN-DBS and surgical procedure have already been described elsewhere [1]. Preoperative and 1-year postoperative data were collected retrospectively, and data beyond 10 years prospectively.

Assessments included the Unified Parkinson's Disease Rating Scale (UPDRS) for non-motor symptoms (Part I), activities of daily living (ADL; Part II), motor examination (Part III), motor fluctuations and dyskinesias (Part IV), stage of disease (Hoehn & Yahr stage or Part V), and independence (Schwab & England Activities of Daily Living [ADL] Scale or Part VI) [11]. Patients were assessed in the off- and on-medication conditions before and 1 year after surgery (to "quantify" the response to STN-DBS) and under the chronic medication and stimulation condition at last follow-up visit (to reduce the burden and the duration of the assessment, considering they have minimal motor fluctuations, and, as such, very little difference between the two conditions). Levodopa equivalent daily dose (LEDD), calculated according to Tomlinson et al. [12] was collected at each assessment. Quality of life was assessed using the Parkinson's Disease Questionnaire (PDQ)-37 [13] and PDQ-39 [14]. Neuropsychological evaluation was performed before and after surgery in the on-medication condition. Depression was assessed with the Beck Depression Inventory (BDI) version 1 [15] and version 2 [16], and cognition with the Mattis Dementia Rating Scale (MDRS) [17].

All patients gave their written informed consent, and the study conformed with the World Medical Association Declaration of Helsinki [18]. The protocol was registered and approved by the institutional review board, Comité d'Ethique des Centres d'Investigation Clinique de l'inter-région Rhône-Alpes-Auvergne (number of registration: 5891).

Statistical analysis

The primary outcome was the evolution of patients' independence at last follow-up, based on the Schwab & England ADL Scale (UPDRS VI).

Secondary outcomes were changes over time in cognition, depression, and quality of life, motor severity, severity of dyskinesias (sum of the items 32–34 of the UPDRS), off dystonia (item 35 of the UPDRS) and motor fluctuations (sum of items 36–39 of the UPDRS), activities of daily life (UPDRS II), LEDD, and complications.

Analyses included analyses of variance (ANOVAs) and multiple linear regressions.

For each variable (UPDRS scores and subscores, MDRS, BDI I, BDI II, and PDQ-37), we performed ANOVA with repeated measures using JASP (JASP Team, 2021). We examined the influence of time (pre-op vs. post-op 1 year vs. post-op 10 years) and medication (off-medication, on-medication) on the UPDRS VI and UPDRS II scores. For all other variables, only the effect of time could be examined, as the 10-year follow-up was carried out on-medication only. Greenhouse–Geisser corrections were applied in cases of violation of the sphericity assumption. Significant effects, interactions, and corrections for multiple comparisons were further examined using the Holm post hoc test. Significance level was set at $p < 0.05$.

Factors predictive of long-term independence (post-op 10 years UPDRS VI score) were examined using a multiple regression analysis of baseline characteristics of patients (gender, disease duration, severity of motor and nonmotor symptoms, measured with UPDRS score, severity of motor fluctuations, dyskinesias and dystonia [calculated with the UDPRS IV respective items], BDI II, MDRS score, levodopa response, LEDD), using Statistica 7.9 (https://www.tibco.com/products/data-science).

Similarly, a multiple regression analysis was performed to find predictors of long-term outcome of quality of life, using 10-year post-op PDQ-37 total score and subscores.

RESULTS

Between 1993 and 2004, 243 people with PD underwent STN-DBS at the University Hospital Center of Grenoble, France. Data for 85 patients were available and included in the analysis. Among patients that could not be included, 60 were dead (four of complication of accidental fall, four of cancer, two of ischemic heart disease, one of stroke, one of pulmonary embolism, four of aspiration pneumonia, three of infections, 12 following disease evolution, the others of unknown cause), 97 were lost at follow-up, and one was no longer treated with STN-DBS, because his stimulator had been removed following an infection.

Among patients included in the study, all but one had bilateral STN-DBS. The patient with unilateral STN-DBS had previously had contralateral thalamotomy for resting tremor. One patient had previously had bilateral pallidal stimulation and one bilateral thalamic stimulation, which were switched off after STN-DBS. One patient with parkin mutation underwent bilateral pallidal stimulation 7 years after bilateral STN-DBS because of severe dyskinesias, without further improvement. Six patients underwent bilateral pedunculopontine nucleus (PPN) stimulation because of severe levodopa-resistant freezing of gait. In four of them, PPN stimulation was ON at the time of the last follow-up.

For the entire cohort of 85 patients, the mean follow-up was 12.5 years (±2.5 SD, range = 10–20, median = 12). Demographics are reported in Table 1, scores at the different scales in Table 2, and parameters of stimulation in Table 3.

Primary outcome

Schwab & England ADL Scale (UPDRS VI)

Complete data were available for 76 patients. Analysis of the independence scores showed that the effects of time ($F_{2,150}$ = 43.71, p < 0.001), medication ($F_{1,75}$ = 314.05, p < 0.001), as well as the interaction between time and medication ($F_{2,150}$ = 148.26, p < 0.001) were significant. In the off-medication condition, the 1-year improvement compared to before surgery persisted beyond 10 years (ps < 0.001). In the on-medication condition, there was no difference between the pre-op and 1-year scores (p = 0.61), whereas the score beyond 10 years had significantly worsened (ps < 0.001).

TABLE 1 Baseline demographics of patients

Patients, *N*	85
Gender, M/F, *n*	56/29
Age at disease onset, years	40 ± 7.9 (22–59)
Age at surgery, years	52.4 ± 9 (31–70)
Disease duration at surgery, years	12 ± 4.4 (4–27)
Disease duration at last follow-up, years	24 ± 5.2 (15–39)

Note: Data are given as mean ± SD (range), unless otherwise specified.
Abbreviations: F, female; M, male.

Secondary outcomes

Quality of life

The PDQ-37 was available at the three time-point evaluations for 55 patients, which were included in the analysis. The PDQ-39 was available at the three time-point evaluations for two patients only. Statistical analysis was therefore not possible for these two patients.

There was an effect of time on PDQ-37 ($F_{2,102}$ = 43.848, p < 0.001), which was significantly improved postoperatively both at 1-year (p < 0.001) and beyond 10 years (p = 0.015) compared to before surgery. Nevertheless, at 10 years there was a significant worsening compared to 1 year after surgery (p < 0.001).

Looking at the PDQ-37 subscales (Figure 1), parkinsonian symptoms significantly improved ($F_{2,102}$ = 57.467, p = 0.001), the effect of time being significant both at short and at long term after surgery compared to before surgery (ps < 0.001), despite a significant worsening at last follow-up compared to the short-term follow-up (p = 0.001). Regarding systemic symptoms, the effect of time was also significant ($F_{2,102}$ = 14.829, p < 0.001). The improvement observed 1 year after surgery compared to presurgery (p < 0.001) was no longer significant at last follow-up (p = 0.23), with a significant worsening between 1- and 10-year follow-ups (p < 0.001). The same was true for social functioning ($F_{2,102}$ = 30.683, p < 0.001; pre-op vs. 10 years, p = 0.12; 1 year vs. 10 years, p < 0.001). Finally, analysis of emotional functioning scores also revealed an effect of time ($F_{2,102}$ = 17.232, p < 0.001). The significant improvement observed 1 year after surgery (p < 0.001) was still significant at last follow-up (p < 0.03), although there was a worsening between the 1- and 10-year follow-ups (p = 0.001).

Cognition

Data were available at the three time points for 66 patients. There was an effect of time on the scores of the MDRS ($F_{2,130}$ = 31.08, p < 0.001). Although there was no significant difference in scores between before and 1 year after surgery, there was a significant worsening beyond 10 years of follow-up (p < 0.001). Looking at the MDRS subscales (Attention, Initiation-Perseveration, Construction, Conceptualization, and Memory), the effect of time was significant for all subscales (Attention, $F_{2,130}$ = 7.32, p < 0.001; Initiation-Perseveration, $F_{2,130}$ = 27.698, p ≤ 0.001; Construction, $F_{2,130}$ = 8.299, p < 0.001; Conceptualization, $F_{2,130}$ = 3.79, p = 0.025; Memory, $F_{2,130}$ = 28.935, p < 0.001). There

TABLE 2 Motor and non-motor outcomes

Outcome	Pre-op	1 year post-op	>10 years post-op
Schwab & England Activities of Daily Living Scale off-medication, range = 0–100[a]	51.3 ± 20.3	83.9 ± 10.8	63.2 ± 24.6
Schwab & England Activities of Daily Living Scale on-medication, range = 0–100[a]	89.6 ± 9	90.9 ± 9.1	70.4 ± 23.7
PDQ-37, maximum = 185[a]	101.3 ± 16.1	131.2 ± 23.6	110.6 ± 23.8
MDRS, maximum = 144[a]	136.5 ± 7.2	136.4 ± 7.1	126.3 ± 15.5
BDI I, maximum = 63[b]	14.1 ± 7.4	9.6 ± 6.9	11.6 ± 7.2
BDI II, maximum = 63[b]	12.5 ± 6.3	12.5 ± 10.3	14.9 ± 10.5
UPDRS II off medication, maximum = 52[b]	24.8 ± 6.7	9.2 ± 5.8	21.6 ± 9.0
UPDRS II on medication, maximum = 52[b]	5.5 ± 4	6.0 ± 3.8	18.9 ± 8.4
Dyskinesias score, maximum score 12[b]	4.5 ± 2.6	0.8 ± 1.4	1.7 ± 2.6
Off dystonia score, maximum = 1[b]	0.7 ± 0.5	0.3 ± 0.4	0.3 ± 0.5
Motor fluctuations, maximum = 7[b]	3.8 ± 1.1	0.6 ± 1.0	1.4 ± 1.5
UPDRS III off medication, maximum = 108[b]	48.1 ± 15.7	42.1	
UPDRS III on medication/stimulation, maximum = 108[b]	12.5 ± 7.4	10.4 ± 7.7	30.3 ± 15.6
Bradykinesia off medication/stimulation, maximum = 36[b]	20.1 ± 7.1	19.3 ± 8.3	
Bradykinesia on medication/stimulation, maximum = 36[b]	5.2 ± 4.2	4.5 ± 3.6	13.7 ± 7.9
Rigidity off medication/stimulation, maximum = 20[b]	10.5 ± 4.3	9.3 ± 4.2	
Rigidity on medication/stimulation, maximum = 20[b]	3.3 ± 2.6	1.9 ± 2.1	4.1 ± 4.1
Tremor off medication/stimulation, maximum = 16[b]	7.7 ± 6.3	6.8 ± 5.9	
Tremor on medication/stimulation, maximum = 16[b]	0.6 ± 1.5	0.5 ± 1.1	1.9 ± 2.9
Axial signs off medication/stimulation, maximum = 16[b]	10 ± 4.4	8.1 ± 3.9	
Axial signs on medication/stimulation, maximum = 16[b]	3.2 ± 2.3	2.9 ± 2.4	9.6 ± 5.3
LEDD	1282.1 ± 544.2	361.7 ± 282.9	694.6 ± 418.2
Dopamine agonists	360 ± 301.3	187.0 ± 140.9	161.2 ± 133.6
Patients on benzodiazepine, *n*	45	32	30
Patients on antidepressant, *n*	23	32	33
Patients clozapine, *n*	3	2	15
Patients on acetylcholine-esterase inhibitors, *n*	0	0	7

Note: Data are given as mean ± SD, unless otherwise specified.

Abbreviations: BDI, Beck Depression Inventory; LEDD, levodopa equivalent daily dose; MDRS, Mattis Dementia Rating Scale; PDQ, Parkinson's Disease Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale.

[a]For the Schwab & England, PDQ-37, and MDRS, the higher the score, the better the outcome.

[b]For the BDI I, BDI II, UPDRS II, UPDRS III, and UPDRS subscores, the higher the score the worse the outcome.

was no significant change between the preoperative and the 1-year postoperative assessment for any of the subscales. Beyond 10 years, there was a significant worsening of all subscales compared to both preoperative and 1-year postoperative follow-up (Attention, $p = 0.01$ and $p = 0.001$; Initiation-Perseveration, $ps < 0.001$; Construction, $p = 0.002$ and $p < 0.001$; Memory, $ps < 0.001$), except for the Conceptualization subscale, which remained unchanged at last follow-up compared to before surgery ($p = 0.32$), although it deteriorated compared to 1 year after surgery ($p = 0.02$).

Regarding patients with an MDRS score < 131, they were seven of 76 (9%) before surgery (mostly with a lower education and/or not being French native speakers; the scores of five of them improved to >131 at 1 year after surgery), 11 of 72 (15%) 1 year after surgery, and 38 of 78 (49%) beyond 10 years.

Beck Depression Inventory

Depression scores at the three time points were available for 63 patients, 28 assessed using the BDI I scale, and 35 assessed using the BDI II scale. The effect of time was significant on BDI I scores ($F_{2,54} = 4.755$, $p < 0.05$). Postoperative BDI I scores at 1 year were significantly reduced compared to the preoperative scores ($p < 0.01$). Scores beyond 10 years were not significantly different from those at 1-year follow-up or those before surgery.

TABLE 3 Parameters of stimulation

	1 year post-op		>10 years post-op	
	R	L	R	L
Amplitude, V	2.9 ± 0.6	3.3 ± 3	2.8 ± 0.6	3.0 ± 0.6
Rate, Hz	142.3 ± 21.9	139.9 ± 21.4	136.2 ± 18.8	136.0 ± 18.7
Pulse width, μs	60.6 ± 3.7	61.1 ± 5.6	63.2 ± 9.3	63.3 ± 9.4
Patients with nonmonopolar configuration, *n*	8 double monopolar, 4 bipolar	6 double monopolar, 3 bipolar	9 double monopolar	9 double monopolar, 1 bipolar

Note: Data are given as mean ± SD, unless otherwise specified.
Abbreviations: L, left; R, right.

For patients assessed using the BDI II, postoperative depression scores were not different from preoperative ones ($F_{2,68} = 1.43$, not significant).

Activities of daily living (UPDRS II)

Data were available for 76 patients. Analysis revealed significant effects of both time ($F_{2,150} = 131.695$, $p < 0.001$) and medication ($F_{1,75} = 394.99$, $p < 0.001$) on the UPDRS II scores (activities of daily life). The interaction between time and medication was also significant ($F_{2,150} = 271.24$, $p < 0.001$). Examination of the interaction revealed that scores beyond 10 years were significantly improved compared to before surgery in the off-medication condition ($p < 0.01$), although significantly worsened compared to 1 year postoperatively ($p < 0.001$, Table 2). In the on-medication condition, scores were stable at 1 year but had markedly deteriorated at the last follow-up ($p < 0.001$).

Motor complications

Dyskinesias and motor fluctuation scores were available at three time points for 76 patients, off dystonia scores for 77 patients. The effect of time was significant on the scores of the three types of motor complications (dyskinesias, $F_{2,130} = 70.412$, $p < 0.001$; motor fluctuations, $F_{2,150} = 174.95$, $p < 0.001$; off dystonia, $F_{2,152} = 30.433$, $p < 0.001$). Scores remained significantly improved at >10 years compared to before surgery (all $ps < 0.001$), although motor fluctuations and dyskinesia had worsened compared to 1 year after surgery ($p < 0.001$ and $p < 0.01$, respectively). There was no significant change of off dystonia scores between 1 year after surgery and long-term follow-up ($p = 0.708$).

Motor severity

Motor UPDRS III scores and subscores are reported in Table 2 (complete data at the three evaluations for 78 patients). The direct comparison could not be performed, because at last follow-up patients were assessed in their chronic condition. Compared to the best ON condition before surgery and 1 year after surgery, at last follow-up under chronic conditions there was a worsening of scores ($F_{2,154} = 136.71$, $p < 0.001$).

Dopaminergic medication

Dopaminergic medication was significantly reduced at 1 year and 10 years postoperatively compared to preoperatively (Table 2; $F_{2,170} = 115.80$, $p < 0.001$). At last follow-up, although still significantly reduced compared to before surgery, LEDD was significantly increased compared to the 1-year postoperative daily dose

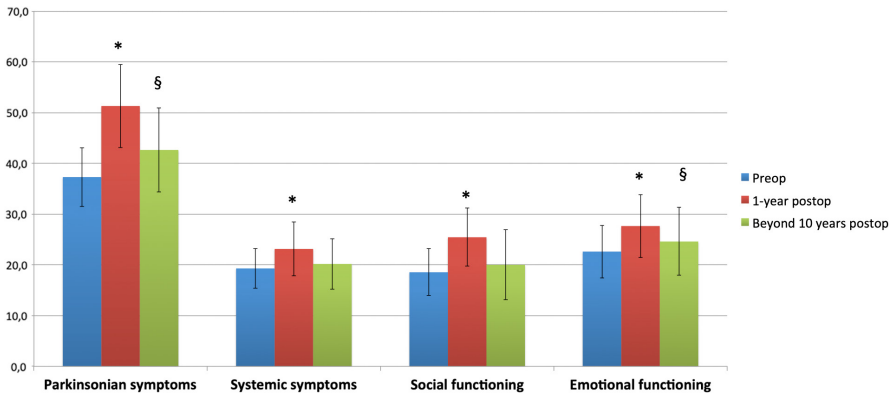

FIGURE 1 Parkinson's Disease Questionnaire-37 subscores at different follow-up visits. *Comparison of preoperative versus 1 year postoperative values is statistically significant. §Comparison of preoperative versus 1 year postoperative values is statistically significant [Colour figure can be viewed at wileyonlinelibrary.com]

($p < 0.001$). When looking at the dopamine agonist alone, there was a significant reduction at 1 year and 10 years postoperatively (Table 2; $F_{2,168} = 26.564$, $p < 0.001$), without any significant change between 1 year and 10 years after surgery ($p = 0.56$).

Preoperative predictor of independence and quality of life at long term

Younger age at surgery, lower preoperative UPDRS I (non-motor symptoms) score, and male gender were identified as predictors of long-term independence (overall model summary on UPDRS VI: $R^2 = 0.39817783$ and, respectively, beta [β] = −0.447413, $p < 0.0005$; beta = −0.272076, $p < 0.05$; beta = 0.260260, $p < 0.05$).

Multiple regression analysis failed to identify any predictive factor of long-term quality of life. When looking at quality of life subdomains, the preoperative MDRS score was recognized as predictive of the emotional subscore of quality of life (overall model summary on PDQ-37 emotional subdomain: $R^2 = 0.37883783$, beta = −0.454021, $p = 0.05$).

Complications

Of the 85 patients included in the analysis, at >10 years three patients presented skin erosion; two had erosion of the scalp (one retroauricular, one cranial at site of insertion of the left electrode, both managed conservatively with surgical cleansing) and one at the level of the neurostimulator, requiring stimulator replacement. One patient underwent a unilateral subthalamic electrode replacement 8 years after surgery, because the first one was too medial. Two patients had a replacement of the connection cable, due to its fracture. One patient had a surgical cleansing and later on a replacement of the connection cable because of a dysfunction revealed by a current leakage.

One patient, with bilateral PPN stimulation, presented an infection of the PPN stimulator and its electrodes, requiring an ablation of the system.

Finally, five patients presented a severe akinetic crisis, following unexpected interruption of stimulation, because of stimulator arrest, requiring prompt replacement. Motor function improved again after stimulation was resumed.

At last follow-up, two patients lived in a nursing home, whereas the remaining 80 still lived at home.

DISCUSSION

This is the largest longitudinal study on non-motor outcome in people with PD treated with STN-DBS, including 85 people followed up for a mean of 12.5 years.

Independence

Despite disease evolution, the Schwab & England scores measuring independence were still improved in the off-medication condition beyond 10 years compared to before surgery, reflecting the long-lasting improvement in fluctuations. Furthermore, patients with disease duration >20 years at last follow-up were still mostly independent in the on-medication condition. Even in the off-medication condition, they were somewhat independent, with 98% still living at home at the last follow-up. Although this was not a controlled study, without an arm of age- and sex-matched patients with best medical treatment instead of surgery, in the Sydney cohort, the largest cohort of parkinsonian patients followed up to 20 years, only one patient of 30 lived independently after 20 years of disease evolution [19]. However, the younger age at onset in our cohort compared to the Sydney one could be, at least in part, responsible for such a different outcome.

Younger age, male gender, and lower preoperative non-motor symptoms score were identified as positive predictive factors of long-term independence, suggesting that younger patients with a pure motor phenotype might be the ideal candidates for surgery. A better outcome in younger patients, with less levodopa-resistant symptoms, has been described in the past [20]. The better outcome in male patients may appear somewhat contradictory to data showing a slower progression in women with PD [21]. However, it has already been reported that women with PD experience more depressive and anxiety symptoms [22], with worse scores when using

self-reported measures of disease severity [23]. Those findings as well as social and lifestyle gender differences are likely to play a role in contributing to a better outcome in men.

Quality of life

Studies on quality of life in patients with STN-DBS have reported an overall improvement up to 3–5 years [24–27]. Data on quality of life beyond 5 years are very scarce, with only one study showing a decline after 5 years of follow-up [28], whereas more recently a study coming from our group reported an improvement up to 15 years [7]. Different selection criteria for surgery, different electrode placement, and optimal stimulation and medication management [29], as well as different baseline and cultural characteristics of patients, could explain different outcomes on quality of life at long-term follow-up.

In our study, quality of life beyond 10 years after surgery was still improved compared to before surgery. On further examination of quality of life subscales, all subscales remained improved compared to before surgery, although the effect was no longer significant for the systemic and social subscales. Axial levodopa-resistant symptoms, which are also resistant to STN-DBS, have been shown to become the major complaints of the patients in late stages of disease [30]. Together with systemic symptoms, they are likely to interfere with autonomy and social functioning. This may explain the loss of significance for these subdomains. Such impact of axial symptoms, which become more severe with disease evolution and are mainly resistant to both dopaminergic medication and STN-DBS, may explain why we could not confirm the benefit in the social domain reported by Bove et al. [7]. On the other hand, our results confirm, on a larger sample, the maintained benefit in the emotional domain, as also reported by Bove et al. [7]. The discrepancy between their and our results could be related to the larger population assessed in our study and the greater statistical power. Moreover, we cannot exclude a bias selection for those patients who are still available at very long-term follow-up, with a better non-motor outcome.

We could not identify any predictor of long-term quality of life in our study, contrary to what was found recently in a 36-month follow-up study [31].

Non-motor symptoms

As expected, we found a significant worsening of cognitive function over time. At last follow-up, the number of patients treated with clozapine or acetylcholine-esterase increased as well, underlying this progression. About 48% of patients with disease duration >20 years and treated for >10 years with STN-DBS were demented, similar to what was found in a Danish cohort of patients, where dementia was defined with a Mini-Mental State Examination score <24 or with the use of acetylcholine-esterase inhibitors [32]. However, the prevalence of dementia in our cohort is far lower than that of the Sydney study, which showed a prevalence of dementia of 80% in PD after 20 years of disease duration [19]. Such better cognitive outcome may in part reflect the bias of preoperative selection, including a different phenotype of patient (younger age at onset and with levodopa-responsive symptoms, without cognitive decline and limited axial symptoms). In previous studies on long-term effects of STN-DBS [1, 3, 5, 6, 25, 26, 33], the reported percentage of patients with dementia was much lower, probably because of shorter follow-up (5–10 years). Interestingly, in our cohort, only two patients lived in a nursing home. This proportion of patients is much lower than what could be expected from the natural course of the disease [19]. It is also much smaller than that reported for the Danish cohort [32]. This latter discrepancy may reflect cultural and social differences and not only differences of management.

Depression scores were quite stable over time, as already shown in other long-term studies. The use of antidepressants did not change between 1-year and last follow-up either. The lack of depression in these patients is particularly noteworthy given the progressive worsening of the disease, and probably contributes to preserving quality of life at very long-term follow-up.

Motor symptoms

As published by Bove et al. [7], the benefit of stimulation on motor fluctuations, dyskinesias, and off dystonia remained significant at very long-term follow-up. This is in line with the reduction in dopaminergic medication, which remained significantly low at the last follow-up, with an increase in mean levodopa daily dose at last follow-up compared to 1 year after surgery, but not in dopamine agonists. Consequently, in addition to the improved overall motor functioning, and therefore independence, STN-DBS also enabled limiting the adverse effects related to antiparkinsonian drugs. This is likely to have contributed to the slowed degradation of quality of life.

The main limitation of this study is the considerable proportion of patients lost at follow-up, which might represent a selection bias, because these patients are those likely to have a worse outcome. On the other hand, our center attracted many people from far away, explaining the high rates of patients lost at follow-up. The other shortcoming is the lack of a control group.

CONCLUSIONS

Our study shows that, despite the evolution of disease, STN-DBS provides an improvement in independence score in the off-medication condition, measured with the Schwab & England ADL Scale at very long-term follow-up, compared to preoperatively. Altogether, STN-DBS not only improved bothersome motor symptoms in the long term, but also non-motor symptoms. Therefore, STN-DBS can be a very beneficial procedure in the long term for carefully and rigorously selected patients. A long-term study comparing a cohort with

STN-DBS and one age- and sex-matched with best medical treatment is needed, considering the current lack of comparative long-term studies.

All these results are very important, in light of the recent ethical debate concerning late stage PD and more specifically advanced PD with STN-DBS [10]. It has been claimed that STN-DBS might expand life while failing to improve, or to maintain, quality of life, prolonging agony for the patient and an inacceptable burden for the caregiver. Our study demonstrates that STN-DBS can improve functional independence and quality of life even at very advanced stages of PD. The progression of axial levodopa-unresponsive symptoms, including dementia, is not accelerated, although not prevented, by stimulation.

AUTHOR CONTRIBUTIONS

Anna Castrioto: Conceptualization (equal); formal analysis (equal); funding acquisition (supporting); investigation (equal); methodology (equal); writing – original draft (lead); writing – review and editing (equal). **Bettina Debut:** Conceptualization (supporting); data curation (supporting); formal analysis (lead); methodology (lead); writing – review and editing (equal). **Emilie Cousin:** Formal analysis (equal); methodology (supporting); validation (equal); writing – review and editing (equal). **Pierre PELISSIER:** Data curation (lead); methodology (equal); project administration (lead); resources (equal); supervision (equal). **E. Lhomme:** Conceptualization (equal); data curation (equal); investigation (equal); validation (equal); writing – review and editing (equal). **Amlie Bichon:** Data curation (equal); investigation (equal); validation (equal); writing – review and editing (equal). **Emmanuelle SCHMITT:** Data curation (equal); investigation (equal); validation (equal); writing – review and editing (equal). **A. Kistner:** Data curation (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal). **Sara Meoni:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Eric Seigneuret:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Stephan Chabardes:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Paul Krack:** Conceptualization (lead); data curation (equal); funding acquisition (lead); investigation (supporting); writing – review and editing (equal). **Elena Moro:** Conceptualization (supporting); data curation (supporting); investigation (equal); writing – review and editing (equal). **Valrie FRAIX:** Conceptualization (equal); data curation (lead); investigation (lead); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal).

ACKNOWLEDGMENTS

We thank Pierre Pollak, Claire Ardouin, and Alim-Louis Benabid for their essential contribution to the field of subthalamic stimulation and the management of patients. Open access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST

A.C. declares research grants from France Parkinson Association and Medtronic, and lecturing fees from AbbVie. S.M. declares research grants from Medtronic. S.C. serves as a consultant for Medtronic and Boston Scientific. P.K. declares grants from the Swiss National Science Foundation, Roger de Spoelberch Foundation, Bertarelli Foundation, Annemarie Opprecht Foundation, Parkinson Schweiz, Michael J. Fox Foundation, Aleva Neurotherapeutics, and Boston Scientific, and personal fees (lecturing fees to employing institution/travel expenses to scientific meetings) from Boston Scientific, Bial, and Zambon outside the submitted work. E.M. has received honoraria from Abbott, Medtronic, and Kyowa. V.F. hs received honoraria from AbbVie, and lecturing fees from Medtronic and Boston Scientific. None of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

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.

ORCID

Anna Castrioto https://orcid.org/0000-0002-2385-7096

REFERENCES

1. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*. 2003;349(20):1925-1934.
2. Lhommée E, Klinger H, Thobois S, et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. *Brain J Neurol*. 2012;135(Pt 5):1463-1477.
3. Fasano A, Romito LM, Daniele A, et al. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain J Neurol*. 2010;133(9):2664-2676.
4. Castrioto A, Lozano AM, Poon Y-Y, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol*. 2011;68(12):1550-1556.
5. Zibetti M, Merola A, Rizzi L, et al. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord*. 2011;26(13):2327-2334.
6. Rizzone MG, Fasano A, Daniele A, et al. Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: from the advanced phase towards the late stage of the disease? *Parkinsonism Relat Disord*. 2014;20(4):376-381.
7. Bove F, Mulas D, Cavallieri F. Long-term outcomes (15 years) after subthalamic nucleus deep brain stimulation in patients with Parkinson disease. *Neurology*. 2021. 10.1212/WNL.0000000000012246. Online ahead of print.
8. Jost ST, Sauerbier A, Visser-Vandewalle V, et al. A prospective, controlled study of non-motor effects of subthalamic stimulation in Parkinson's disease: results at the 36-month follow-up. *J Neurol Neurosurg Psychiatry*. 2020;91(7):687-694.
9. Bjerknes S, Toft M, Brandt R, et al. Subthalamic nucleus stimulation in Parkinson's disease: 5-year extension study of a randomized trial. *Mov Disord Clin Pract*. 2022;9(1):48-59.
10. Gilbert F, Lancelot M. Incoming ethical issues for deep brain stimulation: when long-term treatment leads to a "new form of the disease". *J Med Ethics*. 2020;47(1):20-25.
11. Fahn S, Elton R. Members of the UPDRS development committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent Developments in Parkinson's Disease*. Macmillan Healthcare Information; 1987:153-163.

12. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord off J Mov Disord Soc*. 2010;25(15):2649-2653.
13. de Boer AG, Wijker W, Speelman JD, de Haes JC. Quality of life in patients with Parkinson's disease: development of a questionnaire. *J Neurol Neurosurg Psychiatry*. 1996;61(1):70-74.
14. Fitzpatrick R, Peto V, Jenkinson C, Greenhall R, Hyman N. Health-related quality of life in Parkinson's disease: a study of outpatient clinic attenders. *Mov Disord*. 1997;12(6):916-922.
15. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961 Jun;4:561-571.
16. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. Psychological Corporation; 1996.
17. Mattis S. *Dementia rating scale*. Psychological Assessment Resources; 1988.
18. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.
19. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord*. 2008;23(6):837-844.
20. Merola A, Zibetti M, Artusi CA, et al. Subthalamic nucleus deep brain stimulation outcome in young onset Parkinson's disease: a role for age at disease onset? *J Neurol Neurosurg Psychiatry*. 2012;83(3):251-257.
21. Iwaki H, Blauwendraat C, Leonard HL, et al. Differences in the presentation and progression of Parkinson's disease by sex. *Mov Disord*. 2021;36(1):106-117.
22. Crispino P, Gino M, Barbagelata E, et al. Gender differences and quality of life in Parkinson's disease. *Int J Environ Res Public Health*. 2020;18(1):198.
23. Abraham DS, Gruber-Baldini AL, Magder LS, et al. Sex differences in Parkinson's disease presentation and progression. *Parkinsonism Relat Disord*. 2019;69:48-54.
24. Jiang L-L, Liu J-L, Fu X-L, et al. Long-term efficacy of subthalamic nucleus deep brain stimulation in Parkinson's disease: a 5-year follow-up study in China. *Chin Med J (Engl)*. 2015;128(18):2433-2438.
25. Lezcano E, Gómez-Esteban JC, Tijero B, et al. Long-term impact on quality of life of subthalamic nucleus stimulation in Parkinson's disease. *J Neurol*. 2016;263(5):895-905.
26. Aviles-Olmos I, Kefalopoulou Z, Tripoliti E, et al. Long-term outcome of subthalamic nucleus deep brain stimulation for Parkinson's disease using an MRI-guided and MRI-verified approach. *J Neurol Neurosurg Psychiatry*. 2014;85(12):1419-1425.
27. Kishore A, Rao R, Krishnan S, et al. Long-term stability of effects of subthalamic stimulation in Parkinson's disease: Indian experience. *Mov Disord*. 2010;25(14):2438-2444.
28. Krishnan S, Prasad S, Pisharady KK, Sarma G, Sarma SP, Kishore A. The decade after subthalamic stimulation in advanced Parkinson's disease: a balancing act. *Neurol India*. 2016;64(1):81-89.
29. Okun MS, Tagliati M, Pourfar M, et al. Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers. *Arch Neurol*. 2005;62(8):1250-1255.
30. Ferraye MU, Ardouin C, Lhommée E, et al. Levodopa-resistant freezing of gait and executive dysfunction in Parkinson's disease. *Eur Neurol*. 2013;69(5):281-288.
31. Jost ST, Visser-Vandewalle V, Rizos A, et al. Non-motor predictors of 36-month quality of life after subthalamic stimulation in Parkinson disease. *NPJ Pack Dis*. 2021;7(1):48.
32. Bang Henriksen M, Johnsen EL, Sunde N, Vase A, Gjelstrup MC, Østergaard K. Surviving 10 years with deep brain stimulation for Parkinson's disease--a follow-up of 79 patients. *Eur J Neurol*. 2016;23(1):53-61.
33. Lau B, Meier N, Serra G, et al. Axial symptoms predict mortality in patients with Parkinson disease and subthalamic stimulation. *Neurology*. 2019;92(22):e2559-e2570.

How to cite this article: Castrioto A, Debû B, Cousin E, et al. Long-term independence and quality of life after subthalamic stimulation in Parkinson disease. *Eur J Neurol*. 2022;29:2645-2653. doi: 10.1111/ene.15436