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ORIGINAL COMMUNICATION

Long term follow-up in advanced Parkinson's disease treated with DBS of the subthalamic nucleus

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Abstract

Background Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting both motor and non-motor systems. Deep brain stimulation of the subthalamic nucleus (STN-DBS) has been an approved treatment for PD for more than 30 years, but few data are available regarding its long-term effectiveness.

Objective The aim of this study is to evaluate patients' outcome, both from a motor and non-motor perspective, 9 to 14 years after DBS implantation. We have investigated patients with advanced PD and treated with STN-DBS, in relation to key clinical features of PD.

Methods 18 patients were assessed both retrospectively and prospectively. They underwent motor examination, neuropsychological evaluation and questionnaires on the quality of life, preoperatively, as well as 1, 9 and 14 years after DBS surgery. All patients were implanted with STN-DBS at San Raffaele Hospital between 2004 and 2010.

Results 13 males and five females underwent DBS implantation with a mean PD duration of 11 years. Stimulation significantly improved med-off/stim-on condition up to 9 years, compared to the preoperative off state, and med-on/stim-on condition at 14 years, compared to med-on/stim-off state. Long term improvement specifically involved tremor and rigidity, as well as dopaminergic daily dose. At the same time, STN-DBS had no long-lasting effect on axial symptoms and cognitive functions.

Conclusions STN-DBS remains an effective therapy for advanced PD, also over the years. Despite the underlying progression of the disease, this treatment extends the period in which the overall quality of life is still acceptable.

Keywords Subthalamic nucleus · Deep brain stimulation · Parkinson's disease · Follow-up studies

Background

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective treatment for patients with Parkinson's disease (PD) suffering from suboptimal motor control and motor fluctuations despite optimal peroral medication, but it does not halt the disease progression. After successful surgery, STN-DBS improves both motor and some non-motor symptoms and makes possible a reduction of the total dopaminergic medication load, thus reducing pharmacological side effects [1]. However, over the years, the underlying disease progresses unhindered and leads to deterioration of non-motor and axial functions. In addition, it has been observed that STN-DBS may adversely impact cognition and other neuropsychiatric features [2].

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DBS has been an available treatment for more than 30 years, many clinical studies have shown that it is safe and effective in the short and medium term. However, while STN-DBS was FDA approved for PD in 2003, studies on long-term outcomes have been limited and few studies have reported a series with follow-up of greater than 5 years [3–7].

In this framework, this study aims to evaluate advanced PD patients with STN-DBS up to 15 years of follow-up, to establish the long-term outcomes of this procedure, from a motor, non-motor and neuropsychological perspective.

Materials and methods

Fifty patients affected by advanced PD, according to inclusion and exclusion criteria proposed by the core assessment program for surgical interventional therapies in PD (CAPSIT-PD) [8], have been implanted with STN-DBS since January 2004 in our hospital. Thirty-two out of 50 patients had a follow-up time of at least 8 years, ranging from 8 to 15 years. Eighteen out of these 32 patients were enrolled in the study. Exclusion criteria were death and serious comorbidities like tumors, cerebrovascular or cardiologic disorders, as well as difficulty in reaching our hospital. All included patients were implanted with STN-DBS at San Raffaele Hospital between January 2004 and September 2010.

Patients were clinically evaluated at our center by neurologists (M.A. Volontè, S. Galantucci, P. Scamarcia) and a neuropsychologist (R. Cardamone) with long expertise in PD and, when necessary, through a phone call; retrospective data were collected from medical records. Each evaluation included motor examination with and without Levodopa and/or active stimulation, neuropsychological tests and assessment of the overall function in daily living. The chosen clinical milestones of PD were:

- Motor issues, evaluated by Unified Parkinson's Disease Rating Scale (UPDRS) III [9] and Hoehn and Yahr (H&Y) staging [10];
- Weight and Levodopa Equivalent Daily Dose (LEDD) [11];
- Quality of life (QoL), evaluated by Parkinson's Disease Questionnaire (PDQ-39) [12];
- Global cognitive performance, evaluated by Mini-Mental Scale Examination (MMSE) and specific neuropsychological tests;
- Mood, evaluated by Beck Depression Inventory–Second Edition (BDI-II) [13].

Non-motor tests were done in the ON-medication state preoperatively and in the ON-stimulation and ON-medication state postoperatively.

Patients were assessed prior to DBS surgery, as well as at 1, 9 and 14 years after the implantation. Then, we have compared each follow-up to the baseline.

Motor examination

Preoperative evaluations were performed in the "med OFF" condition (after a 12-h overnight withdrawal of all antiparkinsonian drugs) and in the "med ON" condition (levodopa dose above the threshold of the usual morning dose of dopaminergic treatment). Postoperative assessments were performed in four conditions: med-OFF/stim-ON (stimulator ON, without medication), med-OFF/stim-OFF (stimulator OFF, without medication), med-ON/stim-OFF (stimulator OFF, 1 h after the administration of the levodopa dose above the threshold of the usual morning dose of dopaminergic treatment) and med-ON/stim-ON (1 h after switching on the stimulator, 2 h after the administration of the levodopa dose above the threshold of the usual morning dose of dopaminergic treatment). In addition to UPDRS III score (items 18–31), specific subscores were considered: bradykinesia, tremor, rigidity, and axial score. Motor assessment was completed with the Modified H&Y staging.

Non-motor assessment

LEDD was expressed in mg and computed according to standard conversion factors.

PDQ-39 sub-scores and summary index represent the global QoL, with higher scores representing worse QoL [14].

Cognitive and neuropsychological evaluation

A MMSE score of less than 24 was considered indicative of cognitive impairment [15]

Domains assessed by neuropsychological tests include:

- Attention and executive functions (Attentional Matrices [16], Trail Making Test [17], Stroop Test [18], Modified Card Sorting Test [19]);
- Memory (Digit span, [20] Story recall Test [21]);
- Language (Token Test [22], Verbal Fluency Test [23]);
- Reasoning (Raven's Progressive Matrices [24]).

All neuropsychological tests were evaluated with a validation referred to the Italian population. All scores were adjusted for age and schooling, then used to compute tolerance limits. A subject's score is considered normal when it lies within the highest 95% of the population whereas it is pathological if it falls within the lowest 5%. Adjusted scores were then transformed into a 5-point interval scale, from 0 to 4 equivalent scores. Zero corresponds to a score

below the 5% tolerance limit, four means that the individual's score is better than the mean. The main advantage of the equivalent score method is that sector amplitude for equivalent score 1, 2, 3 compared to 0 depends on the tolerance limit at 95%, which in turns depends on the sample size.

Statistical analysis

Descriptive statistics were used to present the patients' group, when appropriate. Data and results are expressed as mean with standard deviation, unless otherwise specified, and represented with boxplot graphics. The standard non-corrected significance level of $p < 0.05$ was used for statistical significance.

All analyses were performed with SPSS Statistics 25, using Wilcoxon matched pair test for comparisons.

Table 1 Demographic and descriptive data

Age at PD onset	45 ± 7 (30–56)
Disease duration at DBS surgery	11 ± 4 (6–20)
Education	10 ± 4 (3–16)
M:F	13:5

All demographics and descriptive data are expressed in years, as mean ± standard deviation. Data in parentheses are the range

Results

Demographics and descriptive statistics

A group of 18 PD patients (13 males and 5 females) was followed up for a mean of 9 years (range 7–10), and 11 of them had also a further follow-up visit (mean 14 years). At the evaluation before DBS surgery, UPDRS III and H&Y staging in OFF state were respectively 40.9 ± 11.2 (21–65) and 3 ± 0.8 (2–5), in ON pharmacological state they were respectively 20.1 ± 9 (7–33) and 2.3 ± 0.3 (2–3). Complete demographic features and descriptive analyses are shown in Table 1. Motor and non-motor features are shown in Table 2.

Results of neuropsychological tests are shown in Table 3.

UPDRS III

In the first condition of the motor examination (med OFF/stim ON) compared to the preoperative OFF state, UPDRS III score decreased by 42%, from 40.9 ± 11.2 to 23.8 ± 7.4 after 1 year ($p = 0.001$). This reduction was respectively of 34% (27 ± 11.8) after 9 years ($p = 0.004$), and of 20% (32.3 ± 16.8) after 14 years ($p = 0.182$).

In the second condition, with both medication and stimulation OFF, compared to the preoperative OFF state, UPDRS III score decreased of 13% after 1 year and of 11% after 9 years, reaching respectively 35.7 ± 9.6 ($p = 0.201$) and 36.6 ± 10.1 ($p = 0.214$). There was, instead, an increase of 12% after 14 years, reaching 45.3 ± 17.6 ($p = 0.722$).

In the third condition (med ON/stim OFF) compared to the preoperative ON state, UPDRS III score decreased of 6%, from 20.1 ± 9 to 18.8 ± 6.4 after 1 year ($p = 0.381$).

Table 2 Pre-operative assessment and 1, 9, 14 years follow-up

		Pre-operative ($n = 18$)	1 year ($n = 18$)	9 years ($n = 18$)	14 years ($n = 11$)
Age		56 ± 7 (42–70)	57 ± 7 (43–71)	65 ± 7 (52–81)	68 ± 8 (57–79)
UPDRS III	OFF/ON	–	23.8 ± 7.4 (12–37)	27.0 ± 11.8 (12–58)	32.3 ± 16.8 (17–69)
	OFF/OFF	40.9 ± 11.2 (21–65)	35.7 ± 9.6 (18–59)	36.6 ± 10.1 (22–60)	45.3 ± 17.6 (22–81)
	ON/OFF	–	18.8 ± 6.4 (8–28)	27.3 ± 10.6 (13–47)	33.5 ± 12.5 (15–56)
	ON/ON	20.1 ± 9 (7–33)	12.8 ± 5 (5–24)	20.6 ± 9.9 (7–42)	26.9 ± 11.7 (10–50)
H&Y	OFF/ON	–	2.4 ± 0.7 (2–3)	2.9 ± 0.8 (1.5–4)	3.1 ± 1.2 (2–5)
	OFF/OFF	3 ± 0.8 (2–5)	2.5 ± 0.7 (2–3)	3.1 ± 0.9 (2–5)	3.7 ± 1.1 (2–5)
	ON/OFF	–	2.3 ± 0.7 (2–3)	2.9 ± 0.8 (2–5)	2.8 ± 0.8 (2–4)
	ON/ON	2.3 ± 0.3 (2–3)	2.3 ± 0.7 (2–3)	2.9 ± 0.9 (1.5–5)	2.8 ± 0.9 (2–4)
Ledd		1163.8 ± 375.3 (520.4–1790)	690.2 ± 426.5 (140.7–1737.5)	879.0 ± 380.2 (75–1700)	743.6 ± 472.7 (550–1795)
Weight		69.6 ± 17.0 (50–123)	78.4 ± 19.2 (61–135)	74.9 ± 15.2 (58–114)	81.2 ± 14.4 (60–103)
PDQ39		60.5 ± 18.2 (29–101)	49.9 ± 17.9 (26–90)	65.2 ± 18.3 (34–100)	70.0 ± 23.4 (28–113)
MMSE		28.2 ± 2.3 (21–30)	27.9 ± 2.1 (23–30)	25.1 ± 4.5 (12–30)	24.6 ± 5.4 (10.7–29)

Data are mean ± standard deviation. Data in parentheses are the range. *UPDRS* Unified Parkinson's Disease Rating Scale. *H&Y* Hoehn and Yahr Staging. *LEDD* Levodopa Equivalent Daily Dose. *PDQ39* Parkinson's Disease Questionnaire. *MMSE* Mini-Mental Scale Examination

Table 3 Neuropsychological tests at pre-operative, 9 and 14 years assessment

	Test	PRE-DBS	9 years	14 years
Attention and executive functions	Att. matr	47 ± 7.6 (30.8–55.3)	41.1 ± 11.7 (22.3–54.8)	40.0 ± 10.1 (26–60)
	TMT A	31.7 ± 15.3 (15–73)	41.9 ± 20 (14–73)	54.2 ± 39.8 (3–138)
	TMT B	91.4 ± 91.2 (0–293)	111.7 ± 82.8 (23–248)	105.6 ± 61.4 (47–210)
	TMT B-A	63.5 ± 77.6 (0–248)	73.6 ± 70.2 (4–178)	77.0 ± 53.8 (10–59)
	Stroop Test	23.8 ± 14.4 (33.3–10,3)	31.5 ± 24 (11–102)	25.4 ± 25.5 (1.3–80)
	Stroop errors	3.2 ± 7.2 (0–16)	9 ± 9 (0–25)	6.9 ± 10.5 (0.5–25.5)
	MCST	5.3 ± 1.3 (2–6)	4.3 ± 2 (1–6)	3.2 ± 1.2 (1–5)
Memory	Digit span	5.6 ± 1.2 (4–9)	5 ± 1 (3–6.4)	5.3 ± 0.8 (4–6.7)
	Story recall test	11.5 ± 3.5 (6.5–18.5)	12.7 ± 3.3 (6.5–18.5)	7.3 ± 4.9 (0.8–14.5)
Language	Token test	32.1 ± 1.9 (29–34.5)	30.2 ± 4.6 (16.3–34.8)	31.2 ± 2.8 (25–34)
	Semantic fluency	44.1 ± 6.4 (34–58)	35.5 ± 12.9 (14–59)	36.1 ± 6.5 (26.2–46.3)
	Phonemic fluency	37.9 ± 10.9 (16–61)	25.6 ± 11.7 (7–50)	23.4 ± 8.1 (11–36)
Reasoning	Raven m	29.0 ± 4.7 (21.5–35)	28.5 ± 5.5 (18.5–34.5)	27.9 ± 6.1 (14.5–34.5)

Att. matr Attentional matrices. *TMT* Trail Making Test. *MCST* Modified Card Sorting Test. *Raven m* Raven's Progressive matrices
Results are expressed as mean ± standard deviation. with minimum and maximum values in parentheses

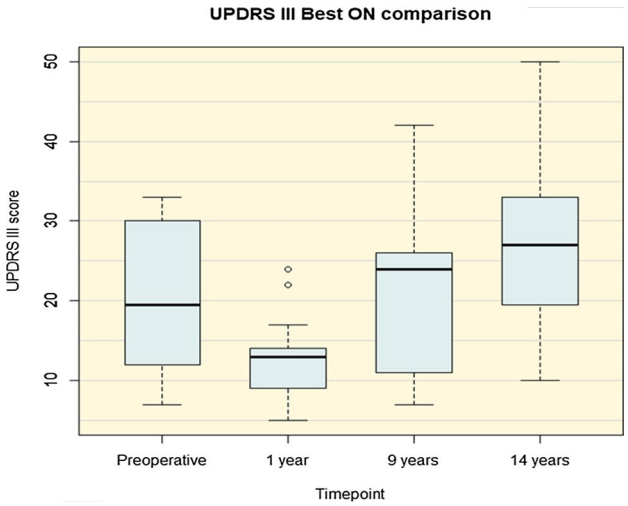

Fig. 1 Boxplot of UPDRS III scores in med-on/stim-on

There was, conversely, an increase respectively of 36% (27.3 ± 10.6) after 9 years ($p = 0.039$), and of 59% (33.5 ± 12.5) after 14 years ($p = 0.005$).

In the fourth and last condition, with both medication and stimulation ON, compared to the preoperative ON state, UPDRS III score decreased of 36%, reaching 12.8 ± 5 after 1 year ($p = 0.005$). On the contrary, there was no change (20.6 ± 9.9) after 9 years ($p = 0.85$), and there was an increase of 28% (26.9 ± 11.7) after 14 years ($p = 0.154$) (Fig. 1).

Moreover, after 14 years UPDRS III score showed a difference of 20% between "med ON/stim OFF" (33.5 ± 12.5) and "med ON/stim ON" (26.9 ± 11.7) conditions ($p = 0.003$).

Sub-items and Hoehn and Yahr staging

Motor sub-items have been evaluated in "med OFF/stim OFF" and "med ON/stim ON" conditions, compared respectively to preoperative OFF and ON states. All results are shown in Table 4.

LEDD, Weight and QoL

Compared to the preDBS condition LEDD decreased, from 1163.8 ± 375.3, of 40% after 1 year, reaching 690.2 ± 426.5 ($p = 0.003$); of 20% after 9 years, reaching 879 ± 380.2 ($p = 0.028$); of 40% after 14 years, reaching 743.6 ± 472.7 ($p = 0.016$).

These patients increased their weight (expressed in kg) of 10% after 1 year ($p = 0.001$), as well as after 9 and 14 years (Fig. 2).

PDQ-39 increased of 20% after 1 year ($p = 0.003$), then to increase of 10% after both 9 ($p = 0.859$) and 14 years ($p = 0.314$).

Cognitive and neuropsychological performance

Table 5 shows changes in cognitive tests, in relation to pre-DBS results (Table 6).

Figure 3 shows MMSE trend, where preoperative MMSE was 28.2 ± 2.

Table 4 Changes of motor items in relation to pre-DBS

		1 year	9 years	14 years
UPDRS III	Med-off/Stim-on	−42% ($p=0.001$)	−34% ($p=0.004$)	−20% (ns)
	Med-off/Stim-off	−13% (ns)	−11% (ns)	+12% (ns)
	Med-on/Stim-off	−6% (ns)	+36% ($p=0.039$)	+59% ($p=0.005$)
	Med-on/Stim-on	−36% ($p=0.005$)	+3% (ns)	+28% (ns)
Tremor	Med-off/Stim-off	–	−44% (ns)	−34% (ns)
	Med-on/Stim-on	–	−43% (ns)	−59% ($p=0.03$)
Rigidity	Med-off/Stim-off	–	−33% ($p=0.005$)	−17% (ns)
	Med-on/Stim-on	–	−64% ($p=0.001$)	−63% ($p=0.007$)
Bradykinesia	Med-off/Stim-off	–	+4 (ns)	+15% (ns)
	Med-on/Stim-on	–	+26% (ns)	+71% (ns)
Axial	Med-off/Stim-off	–	−7% (ns)	+9% (ns)
	Med-on/Stim-on	–	+46% ($p=0.03$)	+30% (ns)
H&Y	Med-off/Stim-off	−16% ($p=0.012$)	+3% (ns)	+23% (ns)
	Med-on/Stim-on	−1% (ns)	+23% ($p=0.031$)	+20% (ns)

ns non-significant. *UPDRS* Unified Parkinson's Disease Rating Scale. *H&Y* Hoehn and Yahr Staging
Values are expressed as percentage (in parentheses, *p* values when statistically significant)

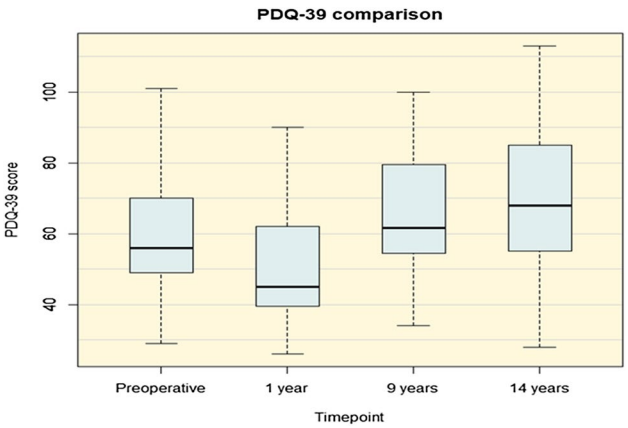

Fig. 2 Boxplot of PDQ-39 scores

Mood

BDI-II has been evaluated 1 and 14 years after surgery, with an increase of 30% from 11.8 ± 6.5 to 15 ± 6.8 ($p = 0.018$).

Discussion

In our study, advanced PD patients with STN-DBS have been assessed longitudinally up to 14 years from a motor and non-motor perspective. Results showed that DBS alone (stim ON/med OFF) significantly improved the UPDRSIII score in the short term (after one year from implantation) and in mid-term (9 years follow-up) but that the benefit subsided in the long term (14 years follow-up). This finding is in line with the previous literature where DBS, when switched on, improved motor symptoms, at 1 year and 5 years compared to baseline and during longer follow-up time points. Nevertheless, benefits decreased with longer follow-up [25].

Conversely, the same long-term improvement was not seen in the other three conditions of the motor examination. In the "double" OFF state, without medication and stimulation, UPDRS III showed a little improvement at 1 and 9 years after DBS surgery, but then returned to pre-DBS scores after 14 years.

In other studies, patients with STN-DBS were assessed in an OFF period and after the stimulation was stopped for a short period. Surprisingly, this approach identified no significant difference in UPDRS III scores at 5–10 years when compared with OFF-period scores at baseline. Worsening relative to baseline was expected, but given that the data were collected only a short time after stimulation was stopped, this observation more likely stated that the full effects of stimulation had not completely 'washed out' rather than a neuroprotective effect of stimulation [26, 27].

In the third condition of motor examination, assessed 1 h after the administration of the levodopa dose 50% higher than the usual morning dose of dopaminergic treatment, UPDRS III significantly worsened at 9 years and especially at 14 years. Compared to the "double OFF" state, in the med-ON condition the stimulator had already been OFF for about 2 h. This could have led to a more accurate and realistic stimulation OFF state, compared to the previous one (med OFF/stim OFF) that could be biased by a short OFF time.

The fourth and last condition was the "best" ON condition, assessed 1 h after switching on the stimulator. In this ON-ON state, there was a significative improvement at

Table 5 Changes of cognitive items in relation to pre-DBS

		9 years	14 years
Global cognition	MMSE	−11% ($p=0.002$)	−13% ($p=0.017$)
Attention and Executive functions	Att. matr	−13% ($p=0.028$)	−15% ($p=0.046$)
	TMT A	+32% (ns)	+71% ($p=0.046$)
	TMT B	+22% (ns)	+16% (ns)
	TMT B-A	+16% (ns)	+21% (ns)
	Stroop Test	+32% (ns)	+7% (ns)
	MCST	−18% ($p=0.027$)	−39% ($p=0.011$)
Memory	Digit span	−11% (ns)	−4% (ns)
	Story recall test	+11% (ns)	−36% (ns)
Language	Token test	−6% (ns)	−3% (ns)
	Semantic fluency	−19% (ns)	−18% (ns)
	Phonemic fluency	−32% ($p=0.001$)	−38% ($p=0.018$)
Reasoning	Raven m	−2% (ns)	−4% (ns)

Values are expressed as percentage (in parentheses, *p* values when statistically significant)

ns non-significant. *Att matr* Attentional matrices. *TMT* Trail Making Test. *MCST* Modified Card Sorting Test. *Raven m* Raven's Progressive matrices

Table 6 Equivalent points of MCST, Story recall test, Semantic fluency and Phonemic fluency at pre-operative assessment, 9 and 14 years follow-up

	Pre-operative	9 years	14 years
MCST	3 (5.3 ± 1.3)	2 (4.3 ± 2)	1 (3.2 ± 1.2)
Story recall test	2 (11.5 ± 3.5)	3 (12.7 ± 3.3)	0 (7.3 ± 4.9)
Semantic fluency	4 (44.1 ± 6.4)	3 (35.5 ± 12.9)	3 (36.1 ± 6.5)
Phonemic fluency	4 (37.9 ± 10.9)	2 (25.6 ± 11.7)	2 (23.4 ± 8.1)

Values are mean equivalent points, referred to normative values of the Italian population for each test (in parentheses, mean ± standard deviation)

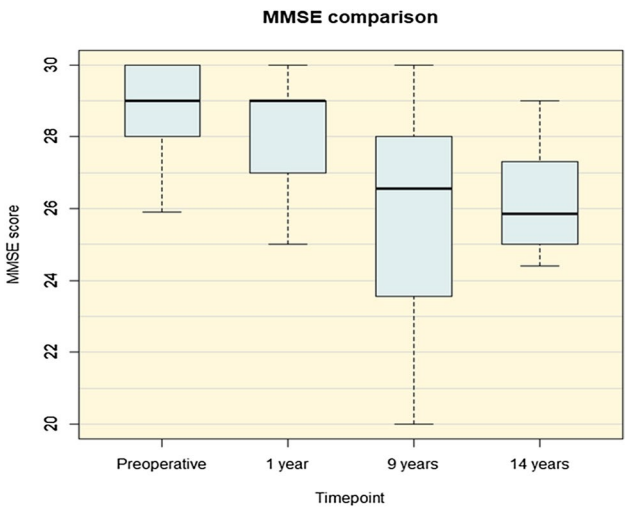

Fig. 3 Boxplot of MMSE at pre-DBS, 1 year, 9 and 14 years)

1 year, but not at 9 years after surgery. UPDRS III showed, instead, a worsening after 14 years.

In literature, UPDRS III ON-period scores generally worsened compared to baseline by the 5-year time point, despite some improvements seen at 1 year. This observation probably reflected the fact that STN-DBS is a symptomatic treatment of OFF periods and does not improve symptoms during the ON period, which reflects the sensitivity of symptoms to levodopa at this stage of the disease [25].

Comparing "med ON/stim OFF" and "med ON/stim ON" states at 14 years, there was a significant improvement in UPDRS III. This means that STN-DBS was still helpful in the "best" ON phase, also many years after the implantation, and gave an advantage over the medication alone.

Regarding the sub-item analysis, tremor and especially rigidity showed the best response during long-term follow-up. Tremor was reduced in OFF/OFF and ON/ON states, at 9 and 14 years after DBS implantation. This reduction was statistically significant only with both medication and stimulation ON at 14 years. Rigidity had a significant improvement in both conditions at 9 and 14 years. Bradykinesia generally worsened in both states at both follow-up points. STN-DBS showed no improvement on axial symptoms, with a significant worsening, even in the ON/ON state, at 9 years. Similarly, H&Y significantly improved in the "double" OFF condition at 1 year, then it began to worsen in both OFF/OFF and ON/ON states. This result confirms the lack of DBS effect on axial issues and a poor effect on bradykinesia.

In several studies, motor subscores demonstrated that substantial DBS-induced improvements in rigidity and tremor during OFF periods were maintained at 5 years and beyond, whereas beneficial effects of DBS on bradykinesia

and axial signs seen at 1 year have started to decline by 5 years [28]. By contrast, in the ON periods, akinesia and axial signs have generally worsened in comparison with baseline by 5 years. One study indicated that at a mean of 10 years after DBS surgery, DBS improved UPDRS III scores, particularly for tremor, rigidity and limb bradykinesia [4].

In another study, substantial improvements over baseline scores for tremor and rigidity were seen at 5 years. At the same time point, improvements in bradykinesia were lower, and gait and balance scores were approaching baseline severity [29]. In a meta-regression analysis on the effects of STN-DBS on axial signs, 'postural instability/gait disturbance' (PIGD) in the OFF period would have worsened to the preoperative state after 9 years, whereas PIGD in the ON period would have reached preoperative severity after only 2 years [30]. These findings confirm that STN-DBS provides symptomatic treatment for the OFF periods and that, at the same time, the disease continues to progress.

LEDD significantly decreased up to 14 years after DBS surgery, so, also at the last follow-up visit, the need for antiparkinsonian medication was still consistently reduced compared with preoperative levels. In other studies, chronic bilateral STN stimulation allowed LEDD to be stopped or greatly reduced [31], with a consequent decline in levodopa-induced dyskinesias.

On the contrary, there was a significant weight gain 1 year after surgery, then this increase persisted but it was no more significant. Weight gain is a well-known adverse event of STN-DBS in PD [32]. Concerning the quality of life, PDQ-39 showed an initial and significant improvement, but it worsened again at nine and 14 years. This could be explained by the concurrent progression of PD. A recent study observed that after a strong and statistically significant improvement in overall quality of life (decrease in PDQ-39 score) 1 year after surgery, patients tend to regress almost completely in the long term [33]. The observed decline in overall quality of life from year 1 to year 5 might be explained by the development of non-levodopa-responsiveness associated with long-term natural course of PD [34].

Global cognitive functioning significantly worsened after 9 years of DBS and this worsening remained stable at 14 years. However, MMSE resulted clinically pathologic (< 24) only in one patient out of 10 at 14 years. This could be explained by the normal aging, given the baseline age of these patients, combined with the disease progression. This finding agrees with previous meta-analysis studies that showed little impact of STN-DBS on global cognition, showing the most significant cognitive deficits in semantic and phonemic fluency [35], with a postoperative decline of verbal fluency and lesser impact on other cognitive tasks [36].

Regarding the specific neuropsychological tests, Attentional Matrices, MCST and Phonemic fluency had a statistically significant worsening at 9 years, which continued also at 14 years. In the Attentional matrices, the number of matrices barred by patients diminished, because patients became slower in their selection skills. This result, as well as the significantly longer time taken in the TMT A at 14 years, could be linked to the aging, since these tests are influenced by motor functioning and age. Indeed, our TMT results are within the normative values of Italian healthy subjects. The TMT B-A highlights attention issues; it showed a slowdown, but not significant.

In the MCST, patients statistically worsened in their cognitive flexibility, with a lower ability in processing and keeping stimuli. This could be read as a possible deterioration in executive functions, the same deterioration that affects phonemic fluency more than the language itself. The clinical worsening of the MCST was, instead, borderline, because our patients reached an average score just above the equivalent score of 0 [37]. Similarly, the statistical worsening in the Phonemic verbal fluency did not reflect a clinically significant impairment. Although the decline in verbal fluency observed after implantation of STN-DBS seems to begin immediately after surgery, poor performance on verbal fluency tasks is often seen in PD patients who are not treated by neurosurgery and in those treated by pallidotomy [36].

On the other hand, there was a clinically significant worsening, based on the equivalent scores, in Story recall Test and MCST at 14 years, as well as a significant increase in Stroop Test errors already at 9 years. The Story recall and MCST reached respectively an equivalent score of 0 (four patients out of 9) and 1 (three patients out of 9, whereas other two patients reached 0) at 14 years [23]. In the Stroop Test, errors made by our patients were just above the normal threshold at the pre-DBS assessment and became clinically pathologic already after 9 years; the Stroop time score remained, instead, within the normal range [38].

This means that patients, on average, became pathologic over the years since DBS implantation in specific efforts of memory, language and executive functions. A previous review of the literature reported similar results: verbal fluency progressively decreased after STN-DBS; executive function was unchanged in the intermediate postoperative stage (1–2 years), while in the early (< 6 months) and later stages (> 5 years) it tended to decline. However, the reduction in verbal fluency did not seem to decrease the overall quality of life, because STN-DBS improved the motor symptoms, which might offset the negative emotional impact of cognitive decline [39].

There was a significative tendency, regarding patients who arrived at the 14 years follow-up, towards a mild depressive mood. In another study, STN-DBS transiently enhanced mood and psychosocial functioning at one year.

In the 3-year follow-up this positive effect disappeared and returned to baseline. Moreover, the same study suggested that in PD patients with no to mild psychosocial and psychiatric disturbances, outcome was not affected by preoperative symptom severity [40].

Summarizing our results, the STN stimulation alleviates motor problems and the general disability, thus prolonging the period in which the overall quality of life is still acceptable. It enables a better control of the disease, both with medication and reducing the pharmacologic need itself. However, PD patients get progressively worse, mainly for the onset and progression of non-motor and axial symptoms resistant to treatment. These slowly increase over time and the functional state of patients declines. Despite some side effects like weight gain, STN-DBS demonstrates a long-lasting improvement also of LEDD. On the other hand, this therapy does not seem to significantly impact cognition, which still follows the natural course of PD. Moreover we did not find significant evidence regarding neuropsychiatric correlates.

The main strength of this study lies in the long-term assessment of these patients, based on a motor and a complete neuropsychological evaluation, taking into account also mood deflexion and quality of life.

Our study has however, some limitations, mostly due to the difficulty of recruiting patients with PD, treated with DBS and with long (> 7 years) follow-up: as a result our cohort was composed of a relatively small sample of PD patients and we have lost 7 of them at the 14 years follow-up, thus reducing the statistical power of the analyses. Moreover, according to the monocentric and non-controlled design of our study, a wider variability in PD patients' cohort and the comparison with a control group with equal age and disease duration are warranted to refine the description of long-term STN-DBS effects.

We can conclude, based on the experience of our center, that STN-DBS remains, over the years, an effective treatment for complicated PD and that the benefits related to this treatment are still important also in the very long-term follow-up. In general, STN-DBS seems to be relatively safe from a cognitive point of view in carefully selected patients (dementia is an absolute contraindication for DBS surgery).

However, further studies on long-term mechanisms of DBS are required, considering larger samples and the potential neuroprotective effect of this treatment.

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Compliance with ethical standards

Conflicts of interest Nothing to report.

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