Parkinsonism and Related Disorders 20 (2014) 376–381

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: From the advanced phase towards the late stage of the disease?

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ARTICLE INFO

Article history:
Received 17 September 2013
Received in revised form
7 January 2014
Accepted 13 January 2014

Keywords:
Parkinson's disease
Deep brain stimulation
Subthalamic nucleus

ABSTRACT

Background: Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) is an effective treatment for Parkinson's disease (PD), but only few studies investigated its long-term efficacy. Furthermore, little is known about the role of PD-subtype on STN-DBS long-term outcome.
Objective: To report the results of a long-term follow-up (mean 11 years, range 10–13) on 26 patients bilaterally implanted in two centres.
Methods: Patients were assessed preoperatively and 1, 5 and 11 years after the implant by the Unified Parkinson's Disease Rating Scale (UPDRS) and a battery of neuropsychological tests. Stimulation parameters, drugs dosages, non-motor symptoms and adverse events were also recorded.
Results: At 11 years, stimulation significantly improved the motor symptoms by 35.8%, as compared to the preoperative off-state. Motor complications were well controlled, with a 84.6% improvement of dyskinesias and a 65.8% improvement of motor fluctuations. Despite this, the UPDRS-II-on score worsened by 88.5%, mainly for the worsening of poorly levodopa-responsive symptoms. More than 70% of the patients performed in the normal range in most of the neuropsychological tests, despite the development of dementia in 22.7%. Age at disease onset, axial subscore in off-condition and presence of REM behaviour disorder at baseline were found to be associated with a higher risk of developing disability over time.
Conclusions: Our study confirms the long-term safety and efficacy of STN-DBS in PD. Nevertheless, the functionality of patients worsens over time, mainly for the onset and progression of levodopa-resistant and non-motor symptoms. The role of PD-subtype seems to be relevant in the long-term outcome.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is very effective for the treatment of patients with advanced Parkinson's disease (PD), improving both motor PD symptoms and levodopa-induced motor complications [1]. Some large randomized controlled clinical trials have shown that in the short-term follow-up STN-DBS is superior to best medical treatment alone in controlling motor symptoms and complications and thus improving self-reported quality of life [1–3].

The motor improvement obtained by STN-DBS has been demonstrated up to 5–6 years after surgery [4,5]. Recently, three series have further expanded the time-length of the follow-up, showing that the effect of STN-DBS on motor symptoms persists after 8–10 years of continuous stimulation [6–8]; however, the patients showed a progressive decline in activities of daily living (ADL), consistent with the progression of disease.

One major limitation of these studies is the relatively small number of patients available for very long-term follow-up after STN-DBS, because of the high attrition rate intrinsic to this type of long-lasting observations. In order to overcome this problem, we pooled together two cohorts of PD patients implanted in two Italian DBS centres and followed them for more than 10 years after implantation.

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http://dx.doi.org/10.1016/j.parkreldis.2014.01.012

2. Methods and materials

We studied a series of consecutive patients who underwent bilateral STN implants at the Policlinico Gemelli Hospital (Rome) and at the San Giovanni Battista Hospital (Turin) between January 1998 and January 2001, and who received continuous stimulation for more than 10 years. Sixty-nine PD patients were implanted (Rome: 37 patients; Turin: 32 patients) and 26 of them were included in the study; 43 patients were not included for the following reasons: death, unrelated to DBS ($n = 14$; mean DBS-to-death time: 7.3 years, range 6.1–9.1 years); lost to follow-up because of difficulties to reach our centres or other unknown reasons ($n = 29$) (See Esupp Table 1). The comparison of the demographic and clinical features of the patients from the two centres didn't show any statistically significant difference (See Esupp Table 2), so patients were lumped together for further analyses. All patients had a diagnosis of idiopathic PD and fulfilled inclusion and exclusion criteria proposed by the CAPSIT-PD [9]. The eligible patients signed an informed consent before entering the study.

2.1. Surgical and perioperative procedures

Bilateral STN implants were performed in all patients as previously described [10,11], using two single-channel or one double-channel (Itrel-II, Soletra or Kinetra models, Medtronic, Minneapolis, MN) implantable pulse generators (IPG). Stimulation parameters were then checked to achieve optimal control of motor symptoms and to identify the threshold for side effects.

2.2. Motor assessment

Patients were evaluated preoperatively (baseline) and postoperatively at 1, 5 and 11 years (latest follow-up visit: mean 10.8 years; range 10–13 years).

Preoperative evaluations were performed in the MED-OFF condition (early in the morning, after an overnight withdrawal of all antiparkinsonian drugs) and in the MED-ON condition (levodopa dose 50% higher than the usual morning dose of dopaminergic treatment).

Postoperative assessments were performed in the MED-OFF/STIM-ON (stimulators on, without medication) and in the MED-ON/STIM-ON (stimulators on, after the administration of the same levodopa dose used for the preoperative evaluation).

The motor assessment was performed by means of the section-III of the Unified Parkinson's disease Rating Scale (UPDRS) [12]. In addition to total score (items 18–31), specific subscores were taken into account: bradykinesia (items 19, 23–26, 31), tremor (items 20–21), rigidity (item 22), speech (item 18), gait (item 29), postural stability (item 30) and axial score (items 18, 27–30).

Functional state was assessed by means of UPDRS section-II (ADL; items 5–17); specific subitems were also analysed as individual outcomes: swallowing (item 7), falling unrelated to freezing of gait (FOG) (item 13), FOG (item 14), and sensory complaints related to parkinsonism (item 17).

Motor complications were assessed by means of the total score of the UPDRS section-IV (items 32–42) and by the dyskinesias and fluctuations subscores (items 32–34 and 36–39, respectively).

The levodopa equivalent daily dose (LEDD) was expressed in mg and computed according to standard conversion factors.

2.3. Non motor assessment

Cognitive assessment and a clinical interview aimed at detecting behavioural abnormalities or psychiatric disorders were performed preoperatively and postoperatively at 1, 5 and 11 years.

Patients of both cohorts were administered tasks assessing the overall cognitive status (MMSE), non-verbal abstract reasoning (Raven's Progressive Matrices–RPM' 47), short-term memory (digit span forward; Corsi's block-tapping test forward), executive functions (Modified Wisconsin Card Sorting Test – MWCST) and language (phonological fluency). Moreover, each centre included additional tasks: digital span backward, Corsi's block test backward and Rey's Auditory Verbal Learning Test (RAVLT) in Rome; paired associated learning, attentive matrices and semantic fluency in Turin. The diagnosis of dementia was based on the criteria suggested by Emre et al. [13].

Mood and anxiety were evaluated in Rome by means of Zung's self-rating depression and anxiety scales, in Turin by means of Beck's depression inventory (BDI) and the two sections of the State-Trait Anxiety Inventory (STAI).

We directly asked patients about hypersexuality at baseline, while other impulse control disorders (ICD) were actively researched only in the follow-up, retrospectively looking for their presence in the preoperative. A clear relationship between some ICDs and PD was in fact defined only after year 2000.

Patients were also assessed for the presence of sleep disorders, gastrointestinal symptoms, autonomic dysfunction and sensory symptoms.

2.4. Statistical analyses

To evaluate group outcome on motor, cognitive and behavioural measures the scores were compared by means of Friedman ANOVA; Wilcoxon matched pair test was used for post-hoc comparisons. Between-group comparisons of continuous variables were performed by means of Mann–Whitney *U* test. Categorical data were compared by means of chi^2-test using Fisher correction as needed. A Kaplan–Meier survival analysis was performed in order to compare the clinical progression of patient's autonomy in ADL in relation to UPDRS-III axial subscore in MED-OFF, age at PD onset and presence of REM Behaviour Disorder (RBD), and to report the worsening of ADL and the development of falls in relation to years after STN-DBS, age and disease duration. The survival outcomes were compared by means of the Log-rank test.

The standard non-corrected significance α level of $p < 0.05$ was used to reduce the risk of a type II error. All tests were two-sided and performed using the SPSS-Statistics 20.0 (IBM, USA) software.

3. Results

3.1. Motor outcome

The STN-DBS (MED-OFF/STIM-ON condition) significantly improved the motor symptoms as compared to the preoperative MED-OFF by 56.8% at 1 year, 51.9% at 5 years and 35.8% at 11 years (Table 1). Tremor showed the most remarkable improvement (68.6%), followed by rigidity (44.1%), gait (30.4%), and bradykinesia (27.9%); axial symptoms showed only a mild, not significant, amelioration (11.8%), while postural stability was unchanged (0.0%) and speech slightly worsened (−20.0%).

The improvement obtained by stimulation at 1 year persisted after 5 years, although the UPDRS-III score slightly worsened by −11.4%, mainly because of axial symptoms, speech and gait. Otherwise, at 11 years a significant worsening of the total UPDRS-III score was observed if compared to the 1 and 5 years assessments (−48.6% vs. 1 year; −33.3% vs. 5 years).

When compared to the preoperative MED-ON, the combined stimulation-levodopa treatment (MED-ON/STIM-ON) significantly improved the UPDRS-III score only at 1 year (24.2%); no significant differences were observed after 5 years (9.2% amelioration), while a

Table 1
UPDRS scores of the patients ($N = 26$) in the different conditions and at the different follow-up visits.

	MED OFF				MED ON			
	Pre-op[a]	STIM ON			Pre-op[a]	STIM ON		
		1 year[b]	5 years[c]	11 years[d]		1 year[b]	5 years[c]	11 years[d]
UPDRS-III (18–31)	56.7 ± 15.8[b,c,d]	24.5 ± 11.5[a,d]	27.3 ± 13.1[a,d]	36.4 ± 12.5[a,b,c]	20.7 ± 10[b,d]	15.7 ± 9.0[a,c,d]	18.8 ± 11.1[b,d]	29.8 ± 11.7[a,b,c]
Tremor (20–21)	10.5 ± 7.3[b,c,d]	2.8 ± 3.2[a]	1.9 ± 1.8[a,d]	3.3 ± 2.8[a,c]	1.5 ± 1.7[b,c]	0.9 ± 1.1[a,d]	0.7 ± 1.0[a,d]	2.2 ± 1.9[b,c]
Rigidity (22)	11.8 ± 4.0[b,c,d]	6.0 ± 2.9[a]	5.9 ± 4.0[a]	6.6 ± 2.9[a]	5.1 ± 3.4	4.6 ± 3.0	3.7 ± 3.1	5.0 ± 2.5
Bradykinesia (19, 23–26, 31)	23.3 ± 6.7[b,c,d]	11.0 ± 6.8[a,d]	13.1 ± 6.6[a,d]	16.8 ± 7.1[a,b,c]	8.3 ± 5.2[d]	7.0 ± 5.0[c,d]	9.1 ± 6.0[b,d]	14.2 ± 6.6[a,b,c]
Axial symptoms (18, 27–30)	11.0 ± 4.3[b,c]	4.7 ± 2.5[a,c,d]	6.3 ± 3.8[a,b,d]	9.7 ± 4.5[b,c]	4.5 ± 3.8[b,d]	2.3 ± 1.9[a,c,d]	3.8 ± 3.1[b,d]	6.2 ± 4.5[a,b,c]
Speech (18)	2.0 ± 0.6[b,c]	1.2 ± 0.6[a,d]	1.6 ± 0.7[a,d]	2.4 ± 0.8[b,c]	1.3 ± 0.8[b,d]	0.8 ± 0.6[a,c,d]	1.5 ± 0.9[b,d]	2.2 ± 0.9[a,b,c]
Gait (29)	2.3 ± 1.0[b,c,d]	0.7 ± 0.6[a,d]	1.1 ± 1.1[a,d]	1.6 ± 1.2[a,b,c]	0.9 ± 1.1[b]	0.4 ± 0.5[a,c,d]	0.9 ± 0.9[b]	1.3 ± 1.3[b]
Postural stability (30)	1.9 ± 1.1[b,c]	1.1 ± 0.9[a,d]	1.3 ± 1.0[a,d]	1.9 ± 1.1[b,c]	1.3 ± 1.0[b,d]	0.9 ± 0.8[a,d]	1.1 ± 1.1[d]	1.8 ± 1.0[a,b,c]
UPDRS-II (5–17)	–	–	–	–	10.4 ± 9.1[b,d]	6.3 ± 3.8[a,c,d]	9.7 ± 7.6[b,d]	19.6 ± 7.9[a,b,c]
Swallowing (7)	–	–	–	–	0.3 ± 0.6[d]	0.3 ± 0.8[d]	0.7 ± 0.8[d]	1.5 ± 1.0[a,b,c]
Falls (13)	–	–	–	–	0.8 ± 1.3[b]	0.2 ± 0.4[a,d]	0.5 ± 1.0[d]	1.2 ± 1.2[b,c]
Freezing (14)	–	–	–	–	0.7 ± 1.0[b]	0.3 ± 0.5[a,c,d]	0.7 ± 0.9[b,d]	1.5 ± 1.3[b,c]
Sensory complaints (17)	–	–	–	–	0.5 ± 0.8	0.3 ± 0.6	0.4 ± 0.8	0.3 ± 0.6
UPDRS-IV (32–42)	–	–	–	–	10.4 ± 2.9[b,c,d]	1.4 ± 1.7[a,d]	2.2 ± 3.0[a]	3.3 ± 3.2[a,b]
Dyskinesias (32–34)	–	–	–	–	5.2 ± 2.2[b,c,d]	0.6 ± 1.2[a]	1.0 ± 1.5[a]	0.8 ± 1.4[a]
Fluctuations (36–39)	–	–	–	–	3.8 ± 1.1[b,c,d]	0.2 ± 0.7[a,d]	0.8 ± 1.5[a]	1.3 ± 1.7[a,b]

Values are mean ± standard deviation. The letters (a), (b), (c), (d) indicate a significant difference between two specific conditions ($p < 0.05$, Friedman test and post-hoc Wilcoxon matched pair test) Abbreviations: MED OFF: without medication; MED ON: with medication; STIM OFF: without stimulation; STIM ON: with stimulation. UPDRS: Unified Parkinson's Disease Rating Scale.

worsening was found at 11 years (−44.0%); at this last visit, the main worsening was observed for speech and bradykinesia subscores (−69.2% and −71.1%, respectively), while only rigidity maintained a response similar to the baseline (Table 1).

Compared to baseline, the UPDRS-II ON score showed a 88.5% worsening at 11 years, while it was significantly improved by 39.4% at 1 year and globally unchanged at 5 years (6.7% amelioration) (Table 1). FOG was significantly improved only at 1 year (57.1%); at 5 years it was unchanged, while its score worsened at the latest follow-up (−114.3%). Falls unrelated to FOG were improved at 1 and 5 years (75.0% and 37.5%), while they worsened at latest visit (−50.0%).

At 11 years speech was severely affected (item 5 score >2) in 8/26 patients, falls occurred in 17/26 patients and FOG in 18/26 patients. Sensory symptoms did not change over time, whereas swallowing significantly worsened at the latest follow-up.

Motor complications were greatly improved by STN-DBS as compared to baseline; at 11 years, the UPDRS-IV score showed a 68.3% improvement (Table 1). Dyskinesias were steadily controlled up to the latest follow-up with an 84.6% improvement, whereas a progressive, not significant, worsening of fluctuations was found as compared with the 5 years assessment. Nevertheless, at 11 years the improvement of fluctuations was still remarkable (65.8%).

3.2. Non-motor outcome

At 11 years the cognitive and behavioural data were available only for 22 patients (Table 2). As compared to baseline, there was a remarkable decline of performance on the phonological verbal fluency task, and a statistically significant but slight decline in performances on other tasks assessing short-term memory (Corsi's block test forward), episodic memory (immediate and delayed recall of RAVLT), executive functions (WCST) and attention (Attentive Matrices). Moreover, 5 out of 22 patients (22.7%) developed dementia.

Analysing the raw postoperative scores of cognitive variables 11 years after STN-DBS more than 70% of the patients performed in the normal range on global cognitive functions, abstract reasoning, memory and phonological verbal fluency. Conversely, the percentage of patients who performed in the normal range was lower on variables assessing executive functions and on a task of semantic verbal fluency (Table 2).

No significant changes on depression were observed. Anxiety significantly improved at 11 years in respect to baseline only in the Rome cohort, while a slight, not significant, worsening was found in the Turin cohort.

At baseline, 3 patients had visual hallucinations and all but one have recovered at latest visit, while other 4 patients have manifested such symptom in the meanwhile; no patient had hypersexuality at baseline, whereas it was reported at 11 years by 3 patients. One patient experienced pathological gambling in the follow-up; since we did not directly ask about the presence of this specific ICD at baseline, it was impossible to directly relate it to DBS. One patient had symptoms of levodopa addiction, with complete remission after surgery; none had pathological shopping or punding. No patient in our cohorts committed suicide or manifested suicidal intentions.

RBD was reported by 8 patients at baseline and at 1 year, by 12 patients at 5 years and by 18 patients at 11 years; symptoms of restless leg syndrome were reported at baseline by one patient, who no longer complained any symptom after surgery; no patient reported such symptoms at 5 years, whereas 5 patients reported them at 11 years. Severe constipation was reported by 4 patients at baseline; two of them improved at latest follow-up whereas additional 5 patients had developed it in the meanwhile. Of the 9 patients complaining of urinary symptoms at baseline, two patients improved at 11 years whereas other 8 patients had developed them over the follow-up; at the latest visit, urinary incontinence occurred in 12 patients. No patient reported symptoms of orthostatic hypotension at baseline and 5 had developed it in the meanwhile.

3.3. Baseline features associated with functional decline

The role of age at PD onset, axial symptoms subscore in MED-OFF and occurrence of RBD on the long term functional decline (UPDRS-II-ON worsening) was evaluated by means of a Kaplan–Meier survival analysis, dividing patients in two subcategories for each variable (younger age vs. older age at PD onset – median value 42.5 y; lower vs. higher axial symptoms subscore in MED-OFF – median value 8; presence or absence of RBD) and comparing their clinical progression over time. As shown in Esupp Fig. 1, a slower decline of functionality was observed in patients with younger age

Table 2
Results obtained on cognitive and behavioural variables at baseline, 1, 5 and 11 years ($N = 22$).

		Pre-op[a]	1 years[b]	5 years[c]	11 years[d]	% of patients scoring in the normal range at 11 years
Overall cognitive assessment	UPDRS-I	3.8 ± 2.3[b,c]	1.7 ± 1.4[a,c,d]	0.7 ± 1.1[a,b,d]	3.7 ± 2.1[b,c]	–
	MMSE	27.8 ± 2.4	29.1 ± 1.1	27.0 ± 1.8	26.6 ± 3.2	81.8
Abstract reasoning	RPM' 47	28.2 ± 4.6	28.2 ± 4.1	26.6 ± 4.3	25.1 ± 6.0	76.2
Short term and long term memory	Digit span: forward	5.1 ± 1.1	5.6 ± 0.7	5.3 ± 1.0	5.1 ± 0.9	86.4
	Corsi's block test: forward	4.9 ± 0.9[d]	4.8 ± 0.9[d]	4.3 ± 1.2	4.1 ± 1.3[a,b]	72.7
	Digit span: backward (Rome)	3.9 ± 0.8	4.3 ± 1.5	3.8 ± 1.9	3.4 ± 0.8	90.9
	Corsi's block test: backward (Rome)	4.5 ± 0.9	4.3 ± 1.1	3.8 ± 1.2	4.1 ± 0.8	90.9
	RAVLT: immediate recall (Rome)	38.8 ± 13.6[d]	42.2 ± 16.5[d]	35.2 ± 13.8[d]	31.4 ± 13.1[a,b,c]	81.8
	RAVLT: delayed recall (Rome)	9.0 ± 3.8[d]	9.0 ± 5.3[d]	7.6 ± 4.0[d]	5.6 ± 3.7[a,b,c]	81.8
	Paired associated learning (Turin)	12.8 ± 2.8	11.2 ± 2.8	11.1 ± 3.6	11.0 ± 3.5	72.7
Executive functions and attention	WCST: number of categories	5.0 ± 1.7[b,d]	5.5 ± 1.2[a,d]	4.5 ± 1.5[b,d]	3.4 ± 2.2[a,b,c]	50.0
	WCST: perseverative errors	5.5 ± 8.3[b,c]	1.6 ± 3.6[a,d]	3.1 ± 3.3[a,d]	6.1 ± 4.9[b,c]	45.0
	WCST: total errors	7.9 ± 8.8[b]	5.7 ± 7.4[a,c,d]	12.4 ± 8.0[b]	13.1 ± 10.4[b]	–
	Trail Making B (Turin)	228.1 ± 124.5	165.3 ± 59.2[d]	263.3 ± 181.1[d]	385.6 ± 236.7[b,c]	33.3
	Attentive matrices (Turin)	45.3 ± 6.5[c,d]	47.9 ± 5.7[c,d]	29.0 ± 5.0[a,b]	25.3 ± 13.3[a,b]	72.7
Language	Phonological fluency	35.0 ± 11.7[c,d]	31.8 ± 14.8[d]	25.4 ± 12.1[a,d]	21.0 ± 10.4[a,b,c]	77.3
	Semantic fluency (Turin)	19.4 ± 5.3	17.4 ± 5.2	16.5 ± 6.5	15.9 ± 5.0	63.6
Depression	Zung depression scale (Rome)	38.6 ± 4.3	31.0 ± 8.9	NA	40.3 ± 8.2	–
	Beck depression inventory (Turin)	17.8 ± 11.5	14.3 ± 8.2	20.3 ± 13.0	16.7 ± 7.2	–
Anxiety	Zung anxiety scale (Rome)	43.4 ± 6.5[b,d]	27.3 ± 6.7[a]	NA	34.4 ± 8.8[a]	–
	STAI-x1 (Turin)	47.7 ± 8.2	45.3 ± 5.9	47.1 ± 8.0	52.1 ± 8.8	–
	STAI-x2 (Turin)	47.1 ± 9.7	47.1 ± 6.8	48.1 ± 8.1	49.5 ± 5.9	–

Values are mean ± standard deviation. The letters (a), (b), (c), (d) indicate a significant difference between two specific conditions ($p < 0.05$, Friedman test and post-hoc Wilcoxon matched pair test). Abbreviations: UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: mini-mental state examination; NA: not assessed; RAVLT: Rey's auditory verbal learning test; RPM' 47: Raven's progressive matrices'47; STAI: State-Trait Anxiety Inventory; WCST: Wisconsin card sorting test.

at PD onset, lower axial subscore at baseline and absence of RBD at baseline.

Moreover, we reported the worsening of ADL and the development of falls in relation to years after DBS, patients age and disease duration: as shown in Esupp Fig. 2, the ADL significant worsening was estimated at an average age of 70 years-old, after 11 years of STN-DBS and 24 years of PD. Similar findings were observed for falls (Esupp Fig. 3), with an onset estimated at 73 years old, after 12 years of STN-DBS and more than 30 years of PD.

3.4. Medication dosage and stimulation parameters

The mean preoperative LEDD was significantly reduced by 57.3% at 1 year, by 41.5% at 5 years and by 32.2% at 11 years (See Esupp Table 3). At 11 years 1 patient did not take any dopaminergic medication, 1 patient took only DA, 13 patient only levodopa, and the remaining 11 a combined treatment. No patient was on apomorphine or enteric levodopa.

Esupp Table 3 also details stimulation parameters and duration of IPG life across the follow-up period.

3.5. Safety

The AE are listed in Table 3. Hypophonia and dysarthria were the most frequent persistent AE. Some patients displayed dystonic features, manageable by parameters adjustment only in a few cases. Device-related AE were recorded in a minority of patients: four patients suffered a minor skin dehiscence along the cable length in the neck region due to bacterial infection, resolved by antibiotic treatment; lead migration was reported in three other patients.

4. Discussion

STN-DBS efficacy on PD motor symptoms is well documented in the short- and medium- term, up to 5–6 years [4,5], while a few papers with a small number of examined patients addressed the long-term efficacy of this procedure [6–8].

In our study STN-DBS alone significantly improved PD motor symptoms up to 11 years after surgery. Tremor and rigidity showed the best response to stimulation, while the effect on axial symptoms was lost at the latest follow-up. Postural stability and speech displayed the worst response: postural stability was unchanged, while speech score was below the baseline off-condition. Gait improvement due to stimulation remained significant at the latest assessment, even though a progressive loss of efficacy over the time was noticed.

The combined stimulation-levodopa treatment determined a further improvement as compared to stimulation alone at each follow-up visit. However, comparing the MED-ON/STIM-ON scores

Table 3
Side effects observed in the 26 patients who completed the study.

Side effect		N. of patients (%)
Transient	Headache	4 (15.4)
	Seizure	1 (3.8)
	Urinary urgency	1 (3.8)
	Akathisia	1 (3.8)
Persistent	Hypophonia	14 (53.8)
	Dysarthria	13 (50.0)
	Depressive symptoms	6 (23.1)
	Weight gain	6 (23.1)
	Eyelid opening apraxia	5 (19.2)
	Apathy	5 (19.2)
	Increased sexuality	4 (15.4)
	Oral district dystonia	4 (15.4)
	Dysphagia	3 (11.5)
	Blepharospasm	2 (7.7)
	Limb dystonia	2 (7.7)
Surgical	Brain hemorrhage	0 (0.0)
	Ext. carotid rupture	1 (3.8)
Device related	Skin dehiscence or infection	4 (15.4)
	Lead migration	3 (11.5)
	Unexplained switching-off	1 (3.8)
Stimulation induced	Oral district spasm	10 (38.5)
	Hypophonia	8 (30.8)
	Limb dystonia	2 (7.7)
	Blepharospasm	2 (7.7)

with the preoperative MED-ON, a significant improvement was observed only at 1 year; at 11 years, all symptoms except rigidity significantly worsened. A reduced magnitude of the response to levodopa was noticed also for symptoms usually considered drug-responsive, and this could have different explanations: during the follow-up patients were taking a levodopa amount smaller than in the preoperative, and this could affect the response to levodopa challenge [14]; chronic STN-DBS could affect the magnitude of levodopa response, probably due to long-term plastic changes of the dopaminergic system [15]; the quality of levodopa responsiveness deteriorates over time.

Motor fluctuations and dyskinesias greatly improved with DBS, and this effect was preserved in the long-term. Dyskinesias subitems showed a sustained improvement greater than 80%, while motor fluctuations – almost disappeared at 1 year – slightly worsened at the latest follow-up.

The UPDRS-II-ON score significantly improved 1 year after surgery, but this improvement was lost after 5 years and at 11 years the score was significantly worsened. Our findings agree with what observed in other studies [6–8], and could be chiefly explained by the progression of the disease over time [16]. While the cardinal PD symptoms keep on improving with stimulation, there is a progressive emerging of poorly levodopa-responsive symptoms, mainly axial symptoms, speech problems and postural instability. At 11 years, 30.7% of patients had severe speech difficulties, falls occurred in 65.4% and FOG in 69.2%. Also non-motor symptoms became relevant (46% urinary incontinence, 19.2% symptomatic postural hypotension), further increasing patient's disability.

The neuropsychological assessment confirmed a worsening of phonological verbal fluency after STN-DBS, as already described in the short-term [17].

Executive functions, attention and memory worsened during the follow-up, but it was mainly due to the development of dementia in 22.7% of subjects; indeed, over 70% of patients remained into the range of normality in the neuropsychological tests after 11 years. Only the executive functions worsened in a relevant percentage, as expected in advanced PD patients [18].

The relatively low percentage of patients with dementia at 11 years does not coincide with the estimation of cognitive impairment in PD from other studies. In the Sydney Multicentre Study, where a cohort of de novo PD patients was studied over a 20 years period, the researchers observed a 48% of demented patients after 15 years, while at 20 years this percentage increased to 80% [19,20]. One possible explanation for this difference could be the earlier age at PD onset of our population (mean 42.5 y) and the absence of cognitive deficits as inclusion criteria for surgery. Moreover, it is likely to suppose that the presence of cognitive impairment could account for a number of dropouts, and this could represent a bias of the study.

Hallucinations initially improved, probably because of the LEDD reduction. At the latest follow-up 19.2% of patients had hallucinations, but almost all of these patients were demented. At 11 years 13.0% of patients showed hypersexuality, not present at baseline. Interestingly, this was observed despite the significant reduction of dopaminergic therapies, whose role in the ICD development is well documented [21]. The possibility of induction of new onset ICD by STN-DBS has been already reported [22], even if other studies demonstrated an improvement of pre-existing ICD after DBS [23]. The central position of the STN within the basal ganglia thalamocortical associative and limbic circuits could explain its role in promoting the onset of ICD in some patients [24]; STN-DBS can indeed interfere with the response inhibition pattern, leading to an increase of impulsivity [25]. This finding further supports the necessity of a psychiatric surveillance of the patients after STN-DBS.

Several studies indicated that the clinical course and progression of PD are very variable, suggesting the presence of different PD subtypes with a different evolution [26,27]. Young age at PD onset has been associated with a slow-progressive disease, with few non-levodopa-responsive symptoms but a higher incidence of motor fluctuations and dyskinesias [28], while a clinical phenotype characterized by the presence of postural instability and gait difficulty (PIGD) seems to be linked to a rapidly-progressive PD course [29]. Moreover, young-onset PD patients treated by STN-DBS seem to show a lower incidence of stimulation/medication resistant symptoms as compared to patients with a later PD-onset [30]. A better outcome of STN-DBS has been also described for PD patients without RBD [31]. Actually, the presence of RBD probably reflects the widespread of neurodegeneration in the brainstem, and it seems to be associated with the worsening of axial symptoms over time [32].

We studied the possible role of age at PD onset, UPDRS-III axial subscore in MED-OFF and presence of RBD at baseline as risk factors for the development of disability. As a measure of disease progression and disability we considered the worsening of UPDRS-II-ON score. A high UPDRS-III axial subscore at baseline, a late-onset PD and the presence of RBD at baseline were all associated with a higher risk of developing disability under STN-DBS. A high axial subscore and the presence of RBD are likely to indicate a 'PIGD-like' PD subtype, with an unfavourable progression [29], and this should be taken into account during the selection of DBS candidates. On the other hand, early-onset PD patients showed a lower risk of developing disability over time, confirming what previously observed [30].

The low AE rate we observed confirmed STN-DBS as a safe and well-tolerated procedure.

One limitation of this study, shared by the others long-term follow-up studies, is the high number of drop-outs (62.3%) that could overestimate the DBS effectiveness and underestimate the rate of side effects. Unfortunately, complete clinical data on the dropped-out patients were not available; some subjects did not perform the scheduled clinical evaluations because living far away from the referring Centres. However, it is also possible that patients with more severe disease complications may have not been included in the analyses, suggesting a possible selection bias that should be considered in the interpretation of our data.

In conclusion, our study confirmed the safety and the long-term efficacy of STN-DBS. Despite this, PD patients progressively worsened, mainly for the onset and progression of levodopa-resistant and non-motor symptoms and the functional state of patients significantly declined.

The relatively high number of patients evaluated, in comparison with the other long-term follow-up studies, represents one of the strengths of the present paper.

Moreover, this is the first study that addressed the possible role of some clinical features of patients as predictors of the long-term clinical outcome of STN-DBS. Age at PD onset, OFF axial subscore and presence of RBD at baseline were found to be associated with a higher risk of developing disability over time, suggesting that PD subtype probably plays a pivotal role in determining the disability progression also in STN-DBS treated PD patients.

Acknowledgement

Funding: This work was supported by the Italian Ministry of University and Research (Relevant National Interest Project number 2001062543 to AA).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.01.012.

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