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Original Article

Uneven benefits of subthalamic nucleus deep brain stimulation in Parkinson's disease—A 7-year cross-sectional study

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ABSTRACT

Objectives: Subthalamic nucleus deep brain stimulation (STN-DBS) for motor symptoms of Parkinson's disease (PD) is promising. However, the benefits of STN-DBS are uneven for the cardinal motor symptoms, as well as for mentality and activities of daily living as the disease progresses. In this report, we will try to clarify which target symptoms have long-term effects during 7 years of STN-DBS.

Materials and Methods: From February 2002 to February 2011, 120 PD patients who underwent STN-DBS were enrolled in this cross-sectional study. Data analysis was performed at postoperative follow-up periods of 1 year, 2 years, 5 years, and 7 years. The Unified Parkinson's Disease Rating Scale (UPDRS) was evaluated in four combinations of levodopa/DBS, on/off.

Results: With levodopa off/DBS on, the UPDRS Part III score improved significantly within the 7 years of follow-up ($p < 0.001$). Decrements in the degree of improvement in axial symptoms were observed after the 5th year. Despite significant improvement in the UPDRS Part II during the 7 years of follow-up, the score of the Schwab and England Activities of Daily Living Scale declined after the 5th year of DBS. With levodopa off/DBS off, the scores for Part III and all subitems deteriorated in comparison with the preoperative levodopa off score after the 5th year of follow-up. Bradykinesia was significantly worse in the 5th and 7th years ($p < 0.05$ and $p < 0.01$, respectively) and the axial component was significantly worse in the 7th year ($p < 0.05$). Stimulation side effects included hypophonia (20.8%), dysarthria (15%), sialorrhea (14.2%), and decreased memory (14.2%). Other surgically related adverse effects included intracranial hemorrhage (3.3%), pulmonary edema ($N = 3$), deep vein thrombosis ($N = 1$), seizure ($N = 1$), depression ($N = 7$), and mania/hypomania ($N = 11$). Five electrodes were revised and two devices became infected. DBS stimulation parameters remained stable except for a significant reduction in frequency in the 7th year.

Conclusion: Long-term effects of DBS on motor disability are promising. DBS showed uneven beneficial effects, and least improvement in axial symptoms and verbal fluency. The disease progressed despite significant positive effects of DBS on the cardinal motor disability symptoms of PD and quality of life at 7 years.

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1. Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) has widely been accepted as an effective surgical modality to improve all cardinal symptoms of Parkinson's disease (PD) including axial symptomatology [1,2]. In recent years, randomized trials have suggested that STN-DBS is superior to the best medical treatment available for advanced PD in terms of temporal domain and quality

Conflict of interest: none.

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of life (QoL). However, target symptoms that respond best and worst to STN-DBS in the short and long term should be identified to avoid unwarranted expectations from patients, care givers, and physicians prior to surgery [3].

DBS was developed in 1987 and was first applied for the treatment of PD in 1993 [4]. Clinical achievements have outweighed surgical complications even though the underlying mechanisms of action are inconclusive [5]. Nevertheless, the application of DBS has now been extended to psychiatric diseases, epilepsy, and cognitive impairment. DBS may modify clinical presentations and attenuate disabilities, but seems unable to stop disease progression [6].

Although DBS is the optimal surgical alternative for treating PD, the procedure has associated risks and stimulation-related adverse effects. Although these side effects can be transient and minor, they can impact a patient's life significantly. Those side effects may be caused by complicated surgical procedures or hardware problems, can be stimulation induced, or can be the dual effects of DBS and dopaminergic medications. Therefore, most DBS centers emphasize the need for an enthusiastic team that includes experts from different fields of interest.

High-frequency stimulation is the major parameter contributing to the abolition of PD symptoms [7]. A frequency of 130 Hz is generally used as the initial setting, and this seldom changes during chronic stimulation. However, the optimal settings for frequency and associated stimulating parameters in chronic stimulation are debated.

The goals of this study are to clarify target symptoms that have shown a sustained effect, the average stimulation parameters, and procedure-related adverse effects during 7 years of STN-DBS.

2. Materials and methods

2.1. Patients

A total of 120 consecutive PD patients who underwent STN-DBS surgery by the operative team at Tzu Chi General Hospital, Hualien, Taiwan, between February 2002 and February 2011 were enrolled in this study. The diagnosis of PD followed the diagnostic criteria of the United Kingdom PD Society Brain Bank [8]. The inclusion criteria for STN-DBS included the following: (1) good levodopa response on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor; >30%); (2) drug-related complications (e.g., dyskinesia, or "on–off phenomenon") even under optimal anti-parkinsonian medication adjustment; (3) no structural lesions on brain magnetic resonance imaging (MRI); and (4) absence of dementia.

The mean age of these patients at the time of surgery was 59.3 ± 11.1 years. The average duration of disease prior to surgery was 9.8 ± 5.1 years, and the average Hoehn and Yahr staging was 3.3 ± 0.9 in the off medication state. Prior to surgery, all patients showed significant levodopa responsiveness in the UPDRS Part III (41.9 ± 18.3%; Table 1).

All patients participating in this study signed informed consents for STN-DBS surgery and the procedures involved in the study. The study protocol was approved by our institutional review board (IRB 097-32; Tzu Chi General Hospital, Hualien, Taiwan).

2.2. Surgical procedures

A Leksell frame was used for the stereotactic procedure. Images for targeting were obtained from a 1.5/3.0-Tesla MRI unit (General Electric, Milwaukee, WI, USA). The standard settings for preoperative targeting included T1-weighted axial images [repetition time (TR): 26 milliseconds; echo time (TE): 6.9 milliseconds; matrix size: 256 × 192; thickness: 0.7 mm] and T2-weighted axial images (TR: 4800 milliseconds; TE: 95 milliseconds; matrix size: 256 × 192; thickness: 2.0 mm). Each of these sequences was performed in contiguous axial slices. The images were transferred to a neuronavigation workstation (VectorVision; BrainLab, Feldkirchen, Germany, or StealthStation; Medtronic, MN, USA). T1 images were used for identifying and measuring the length of the anterior and posterior commissures. The tentative surgical target coordinates for the tip of the permanent implantable electrode were set at the central border of the STN, which is near the intersection between the line of the anterior border and 2 mm lateral to the red nucleus on T2 images. Quadripolar DBS electrodes (model 3389, Medtronic) were implanted after microelectrode recording (Leadpoint; Medtronic). After 1 week, the electrode cables were connected to an implantable pulse generator (Soletra or Kinetra; Medtronic). The surgical procedures have been described in detail in our previous study [9]. An acute stimulation test was performed 1 week after surgery to select the optimal stimulation contact and parameters for chronic stimulation.

2.3. Clinical evaluations

Mentation, behavior and mood, activities of daily living (ADL), severity of motor symptoms, and levodopa-related complications

Table 1
Clinical and demographic data of PD patients for STN-DBS.

	Preoperatively ($N = 120$)	1 year ($N = 88$)	2 years ($N = 60$)	5 years ($N = 31$)	7 years ($N = 17$)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Sex (F/M)	47/73	33/55	22/38	7/24	4/13
Age at onset	49.5 ± 11.6	49.4 ± 12.1	47.2 ± 12.7	44.9 ± 12.9	43.2 ± 10.8
Age at DBS surgery	59.3 ± 11.1	59.1 ± 11.5	57.5 ± 11.7	54.9 ± 12.4	52.9 ± 11.3
Disease duration at DBS surgery (years)	9.8 ± 5.1	9.7 ± 4.9	10.3 ± 5.5	10.0 ± 5.1	9.7 ± 2.7
Follow-up period (months)		11.2 ± 2.7	25.8 ± 4.0	57.3 ± 7.8	82.2 ± 6.3
MMSE ($N = 104$)	26.2 ± 4.1				
H & Y Stage	3.3 ± 0.9				
SEADL Score (%)	69.7 ± 27.3				
LEDD	779.1 ± 389.5				
L-dopa responsive rate (%) ($N = 119$)					
UPDRS Part I	22.8 ± 28.9				
Part II	42.2 ± 27.0				
Part III	41.9 ± 18.3				
Part IV	−0.2 ± 4.9				
Total	37.7 ± 17.6				

PD = Parkinson's disease; STN-DBS = subthalamic deep brain stimulation.
Data presented as mean ± SD.

Table 2
In the state of levodopa Off DBS On, UPDRS sections I, II, III and IV at different follow-up periods.

UPDRS	Preoperatively ($N = 120$)	1 year DBS ($N = 88$)	2 years DBS ($N = 60$)	5 years DBS ($N = 31$)	7 years DBS ($N = 17$)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Part I	4.6 ± 2.8	2.9 ± 1.9***	2.9 ± 2.1***	3.3 ± 1.9*	3.8 ± 2.0
Part II	21.0 ± 9.3	12.8 ± 7.8***	12.8 ± 7.8***	14.3 ± 7.4***	14.6 ± 7.9**
Part III	45.6 ± 14.7	27.1 ± 11.1***	26.7 ± 11.6***	28.7 ± 10.1***	28.8 ± 13.6***
Brady	19.0 ± 6.0	13.2 ± 5.0***	12.8 ± 4.9***	14.5 ± 4.7***	14.3 ± 6.6**
Tremor	5.8 ± 5.2	1.4 ± 2.2***	1.6 ± 2.8***	1.0 ± 1.5***	0.9 ± 1.3***
Rigidity	9.7 ± 4.1	4.8 ± 3.2***	4.4 ± 3.3***	5.1 ± 3.3***	4.7 ± 4.6***
Posture & gait	4.1 ± 1.8	2.7 ± 1.5***	2.7 ± 1.7***	3.1 ± 1.4**	3.2 ± 1.6*
Axial	9.3 ± 4.0	6.7 ± 3.4***	6.8 ± 3.7***	7.0 ± 3.0**	7.5 ± 3.6
Part IV	5.5 ± 3.8	1.7 ± 1.9***	1.8 ± 2.2***	1.9 ± 2.4***	1.8 ± 1.9***
Total	76.7 ± 25.6	44.6 ± 19.8***	44.2 ± 20.9***	48.2 ± 17.7***	49.0 ± 22.5***
H & Y stage	3.3 ± 0.9	2.7 ± 0.8***	2.7 ± 0.7***	2.8 ± 0.7***	2.9 ± 0.9
SEADL score (%)	69.7 ± 27.3	86.7 ± 19.2***	87.2 ± 17.1***	80.3 ± 22.4*	78.2 ± 24.0
LEDD	779.1 ± 389.5	425.1 ± 258.4***	425.3 ± 226.6***	567.1 ± 359.3**	514.2 ± 402.8**
LEDD reduction (%)		39.0 ± 35.9	36.5 ± 37.4	10.0 ± 70.8	16.8 ± 68.6
MMSE ($N = 104$)	26.2 ± 4.1	26.0 ± 4.9	25.0 ± 6.3	23.9 ± 7.5	24.2 ± 7.6

Med = anti-parkinsonian medication; DBS = deep brain stimulation; UPDRS = Unified Parkinson's Disease Rating Scale.
Data presented as mean ± SD, data in parentheses of LEDD represent reduction percentage compared with pre-operation.
*$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.

(UPDRS Parts I, II, III, and IV) were evaluated 1 month prior to surgery and 1 year, 2 years, 5 years, and 7 years after surgery. The "medication off" status in the motor examination was evaluated at least 12 hours after withdrawal of dopaminergic medication, as defined by the Core Assessment Program for Surgical Interventional Therapy in PD [10]. The magnitude of the levodopa response in "medication on" state was assessed after administration of a dose of levodopa/benserazide (Roche Products; Roche, Basel, Switzerland) equivalent to or 1.5 times the usual morning dose. Bradykinesia scores included items 23, 24, 25, 26, and 31 of the UPDRDS Part III. Evaluation of the axial scores included subitems 18 (speech), 27 (rising from a chair), 28 (posture), 29 (gait), and 30 (posture instability) of the UPDRS. All patients were evaluated post-operatively in four conditions: (1) stimulation "off" and medication "off"—after DBS was switched off for at least 4 hours and the patient had no dopaminergic treatment for 12 hours; (2) stimulation "on" and medication "off"—after stimulation was switched on for at least 2 hours; (3) stimulation "off" and medication "on"; and (4) stimulation "on" and medication "on".

The total amount of antiparkinsonian medication was expressed as the levodopa equivalent daily dosage (LEDD), which is the sum of the following: the dose of regular levodopa–benserazide (or levodopa–carbidopa), 0.75 times the dose of controlled-release levodopa–benserazide (or levodopa–carbidopa), 10 times the dose of bromocriptine, and 25 times the dose of ropinirole. In patients taking entacapone, the dose was multiplied by a factor of 1.25 [11].

Cognition and memory were evaluated with the UPDRS Part I and minimental state examination. The extent of dependency in daily living was examined with the UPDRS Part II and Schwab and England Activities of Daily Living Scale (SEADL).

2.4. Statistical analysis

Descriptive statistics (mean and standard deviation) were used for continuous variables, whereas categorical variables were described as percentages. The main UPDRS section scores (Parts I, II, III, and IV) and LEDD, which were considered continuous variables and collected at different times (baseline and 1 year, 2 years, 5

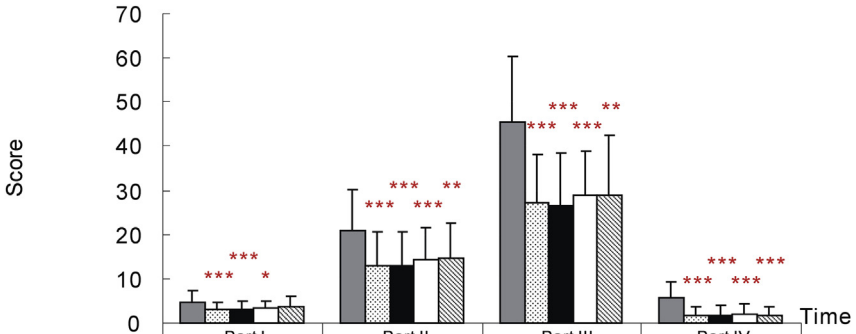

Fig. 1. Scores on the UPDRS Parts I, II, III, and IV during follow-up with levodopa off/DBS on. DBS = deep brain stimulation; UPDRS = Unified Parkinson's Disease Rating Scale. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 3
In the state of levodopa Off DBS Off, UPDRS sections I, II, III and IV at different follow-up periods.

UPDRS	Preoperatively ($N = 120$)	1 year DBS ($N = 84$)	2 years DBS ($N = 55$)	5 years DBS ($N = 31$)	7 years DBS ($N = 17$)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Part I	4.6 ± 2.8	4.2 ± 2.3	3.7 ± 2.3	4.9 ± 2.1	5.5 ± 1.8
Part II	21.0 ± 9.3	21.5 ± 10.2	21.6 ± 9.3	26.9 ± 9.7**	29.5 ± 10.4***
Part III	45.6 ± 14.7	45.6 ± 15.2	45.2 ± 15.1	50.4 ± 14.2	52.9 ± 14.8
Brady	19.0 ± 6.0	19.2 ± 6.2	19.4 ± 6.1	21.5 ± 5.7*	23.3 ± 6.4**
Tremor	5.8 ± 5.2	6.0 ± 4.9	5.9 ± 5.2	6.7 ± 5.6	4.9 ± 4.0
Rigidity	9.7 ± 4.1	9.2 ± 3.8	9.2 ± 3.9	9.9 ± 3.8	10.8 ± 4.5
Posture & gait	4.1 ± 1.8	4.0 ± 1.9	3.8 ± 1.8	4.5 ± 1.6	4.8 ± 2.1
Axial	9.3 ± 4.0	9.3 ± 4.3	9.0 ± 3.7	10.3 ± 4.0	11.9 ± 5.0*
Part IV	5.5 ± 3.8	4.7 ± 3.1	4.7 ± 3.3	4.7 ± 2.3	4.2 ± 2.4
Total	76.7 ± 25.6	75.9 ± 26.8	75.2 ± 26.0	86.8 ± 25.2	92.1 ± 25.9*
H & Y stage	3.3 ± 0.9	3.2 ± 0.9	3.1 ± 0.8	3.6 ± 0.9	3.8 ± 1.0 *
SEADL score (%)	69.7 ± 27.3	70.9 ± 25.4	72.2 ± 21.8	53.2 ± 27.7**	47.6 ± 29.9**
MMSE ($N = 104$)	26.2 ± 4.1	26.2 ± 4.8	25.8 ± 4.8	23.7 ± 7.6	23.9 ± 7.5

Med = anti-parkinsonian medication; DBS = deep brain stimulation; UPDRS = Unified Parkinson's Disease Rating Scale.
Data presented as mean ± SD, data in parentheses of LEDD represent reduction percentage compared with pre-operation.
*$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$.

years, and 7 years) after STN-DBS, were compared by means of generalized estimating equations. *Post hoc* comparison with the Bonferroni method was adopted when comparing the results of short- and long-term follow-ups. All p values were two tailed and a $p < 0.05$ was considered significant. Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Effectiveness of STN-DBS (levodopa off/DBS on compared with preoperative levodopa off) (Table 2, Fig. 1)

3.1.1. UPDRS Part I: mentality

Significant improvement was noted within the first 2 years after surgery ($p < 0.001$). No significant improvement was observed in the 7th year after surgery (Table 2, Fig. 1).

3.1.2. UPDRS Part II: ADL and SEADL

Significant improvement on the UPDRS Part II was observed within 7 years after STN-DBS ($p < 0.001$ at the 1st year, 2nd year, and 5th year; $p < 0.01$ at the 7th year). However, effects of DBS on SEADL declined after the 5th year ($p < 0.05$) and were diminished in the 7th year postoperatively (statistically nonsignificant).

3.1.3. UPDRS Part III: motor function

With levodopa off/DBS on, the UPDRS Part III score improved significantly within 7 years of follow-up ($p < 0.001$). Decrements in the degree of improvement were observed on Part III axial symptoms after the 5th year.

3.1.4. UPDRS Part IV: levodopa treatment complications

Significant improvement was noted within 7 years after STN-DBS surgery.

3.2. LEDD reduction

Significant reduction was noted in the LEDD within 7 years after STN-DBS surgery ($p < 0.001$ in the first 2 years, and $p < 0.01$ at the 5th year and 7th year; Table 2).

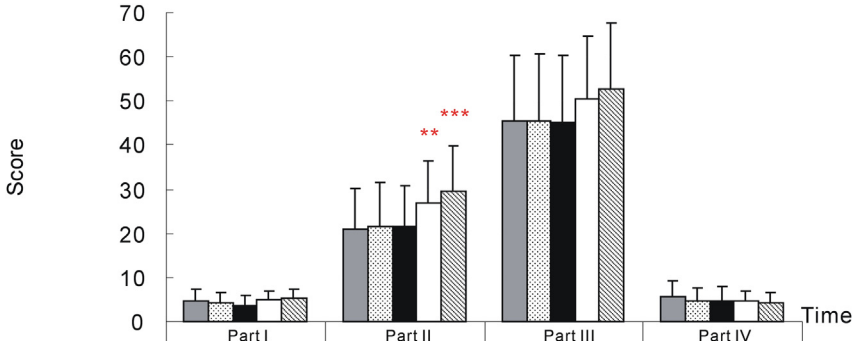

Fig. 2. Scores on the UPDRS Parts I, II, III, and IV during different follow-up periods with levodopa off/DBS off. DBS = deep brain stimulation; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 4
Adverse effects after STN-DBS.

Postoperative morbidity ($N = 120$)	N	%
Mortality	0	0.0
Adverse effects related to stimulation		
Hypophonia	25	20.8
Dyskinesias	23	19.2
Dysarthria	18	15.0
Sialorrhea	17	14.2
Decreased memory	16	13.3
Eyelid apraxia	7	5.8
Increased libido	5	4.2
Dystonia	5	4.2
Paresthesias	4	3.3
General neurological and surgical complications		
Weight gain	33	27.5
Perioperative confusion	14	11.7
Mania/hypomania	11	9.2
Depression	7	5.8
Pulmonary edema	3	2.5
Seizures	1	0.8
Deep vein thrombosis	1	0.8
Hemorrhage	4	3.3
Asymptomatic	2	1.7
Symptomatic, total recovery	1	0.8
Symptomatic, partial recovery	1	0.8
Hardware-related complications		
Lead problems	5	4.2
Leads that needed to be repositioned (Unilateral)	4	3.3
Leads that needed to be repositioned (Bilateral)	1	0.8
Infections of the hardware	2	1.7
Battery failure	2	1.7
IPG migration	1	0.8
Wire revision	6	5.0

STN-DBS = subthalamic deep brain stimulation, data presented as number (percentage).

3.3. Disease progression (levodopa off/DBS off compared with preoperative levodopa off) (Table 3, Fig. 2)

3.3.1. UPDRS Part I: mentality

Deterioration was noted after the 5th year of STN-DBS, although it was not statistically significant (Table 3, Fig. 2).

3.3.2. UPDRS Part II: ADL and SEADL

Scores on both UPDRS Part II and SEADL deteriorated significantly after the 5th year of STN-DBS ($p < 0.01$ and $p < 0.001$ at the 5th year and 7th year, respectively).

3.3.3. UPDRS Part III: motor function

Scores for Part III and all subitems deteriorated compared with the preoperative levodopa off score after the 5th year. Bradykinesia was significantly worse at the 5-year and 7-year follow-ups ($p < 0.05$ and $p < 0.01$, respectively) and the axial component was significantly worse at the 7-year follow-up ($p < 0.05$).

3.3.4. UPDRS Part IV: levodopa treatment complications

Persistent improvement was noted within 7 years of STN-DBS, although it was not statistically significant.

3.4. Adverse effects after STN-DBS (Table 4)

High incidences of stimulation side effects, such as hypophonia (20.8%), dysarthria (15%), sialorrhea (14.2%), and decreased memory (13.3%) were observed (Table 4). However, most of these were transient, and could be improved by changing stimulation parameters and medications. The most serious adverse effect was intracranial hemorrhage ($N = 4$, 3.3%), but only one patient had a sequela. Patients who experienced postoperative pulmonary edema ($N = 3$), deep vein thrombosis ($N = 1$), and seizure ($N = 1$) all recovered well. Postoperative depression ($N = 7$), mania/hypomania ($N = 11$), and perioperative confusion ($N = 14$) were transient. Five patients with suboptimally placed electrodes had revisions. Implants were needed to be removed in one of the two patients with infection. Two patients with standard stimulation parameters experienced early termination of the implantable pulse generator battery. No deaths were reported during this study.

3.5. DBS stimulation parameters during 7 years of follow-up (Table 5)

Stable voltage and pulse width were maintained through 7 years of follow-up (Table 5). A signification reduction in the stimulation frequency was noted at the 7th year compared with the 1st year postoperatively (139.4 ± 16.6 Hz and 120.6 ± 22.4 Hz, at the 1st year and 7th year, respectively; $p < 0.05$).

4. Discussion

STN-DBS had significant beneficial effects on all cardinal motor symptoms of PD as well as on ADL in this 7-year study. However, the significant effects on axial symptoms faded after the 5th year. This may also have resulted from the high incidence of hypophonia, dysarthria, and sialorrhea during this study period. These findings suggest disease progression, in which axial symptoms are more complicated and may involve associative circuits [12]. This is especially true with levodopa off/DBS off, and compared with preoperative off; all cardinal symptoms of motor components deteriorated after the 5th year. Furthermore, bradykinesia and axial symptoms were significantly poorer at the 5th year and 7th year than preoperatively. These findings also suggest that STN-DBS does not provide a neuroprotective effect against PD, and the results are consistent with the natural progression of PD [4]. Zibetti et al [7] and Merola et al [13] demonstrated a sustained DBS effect on cardinal motor symptoms over 9 years; however, this might have been due to an inadequate period with the battery turned off prior to assessment. Our protocol defined a DBS off time of 4 hours prior to UPDRS assessment, and we could not duplicate their results.

Table 5
Stimulation parameters during different follow-up periods.

	1 year		2 years		5 years		7 years	
	Ch1 ($N = 55$)	Ch2 ($N = 53$)	Ch1 ($N = 48$)	Ch2 ($N = 49$)	Ch1 ($N = 29$)	Ch2 ($N = 30$)	Ch1 ($N = 16$)	Ch2 ($N = 16$)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Voltage	3.2 ± 0.6	3.1 ± 0.7	3.4 ± 0.6	3.4 ± 0.6	3.5 ± 0.4	3.6 ± 0.4	3.7 ± 0.5	3.4 ± 0.6
Pulse width	62.2 ± 7.9	61.1 ± 5.8	62.5 ± 8.4	63.7 ± 9.9	63.1 ± 9.3	64.0 ± 10.4	65.6 ± 12.1	63.8 ± 10.2
Frequency	139.4 ± 16.6	139.0 ± 16.4	147.4 ± 20.1	147.7 ± 20.0	130.7 ± 23.1	131.2 ± 22.9	120.6 ± 22.4*	120.6 ± 22.4*

Data presented as mean ± SD, Ch: channel; *$p < 0.05$, comparison with 1 year.

Although some studies have suggested that STN stimulation might be superior to globus pallidus internal (GPi) segment stimulation for most cardinal symptoms of PD [14], GPi-DBS may have a superior effect on axial symptoms, such as speech, posture instability, and gait [9,11]. In a randomized blinded study, Burchiel et al [15] and Anderson et al [16] showed that L-dopa axial symptoms were clinically improved in GPi segment but not STN stimulation in patients with advanced PD. A large, multicenter cohort study on advanced PD patients conducted by Rodriguez-Oroz et al [17] showed that although both STN and pallidal stimulation had long-term effects on motor symptoms, axial symptoms became worse in the STN stimulation group. The pedunculopontine nucleus is believed to be involved in the modulation of locomotor activity and may be another target for DBS that provides a synergistic effect on devastating and treatment-resistant posture instability [18–21].

In this study, cognitive function was stable over 7 years and this somewhat contrasts with previous long-term results [13]. This might be due to a short disease duration at the time of surgery and a short follow-up period. A high incidence of transient mania/hypomania and dyskinesia soon after the surgery might be due to the current diffusion effect within STN and an add-on effect of stimulation with pre-existing dopaminergic therapy [22]. Postoperative dual management of DBS settings and medications may be crucial to a satisfactory outcome [23].

During the evolution of PD, axial symptoms remain a critical problem. Among axial symptoms, verbal fluency may be affected negatively by STN-DBS. Changes in motor symptoms show a strong dependency on the frequency of stimulation [24]. De Gaspari et al [25] and Wojtecki et al [26] showed that, unlike high-frequency stimulation, low-frequency (10 Hz) stimulation has a positive modulation effect on verbal fluency. Because of the high incidence of hypophonia/dysarthria noted in this study, the stimulation frequency in these patients was subsequently reduced during the 7-year follow-up period. We did observe better speech in these patients, which echoed Wojtecki's results. Stefani et al [27] demonstrated that the success of PPN-DBS in PD gait performance is also related to low-frequency (25 Hz) stimulation. Although the stimulation targets are different, this may give us a clue to harness speech disability in addition to parameter adjustment.

Although DBS is efficacious for the management of various movement disorders, its mechanism of action remains unknown and is worthy of study [28]. Previous studies suggest that effective DBS over-rides oscillatory pathological activity and replaces it with more regularized neuronal firing patterns [29]. The most likely mechanism of DBS is stimulation-induced modulation of pathological network activity [30]. Several human and animal studies also support the disease-modifying effects of STN-DBS on dopaminergic-related symptoms in the early-stage PD [9,13,31]. The progression of nondopaminergic responsive symptoms such as speech, gait, and mood in the long term suggests that STN-DBS modifies neuronal circuits and their individual neuronal types to different degrees.

This is a cross-sectional study with a representative subset of 120 patients with PD who underwent STN-DBS and was followed up for a specific period. Although some data were missing in this retrospective study that may have contributed to bias, we found consistent results compared with other published studies [23]. Unlike a longitudinal study, this study cannot show the true natural course of this subset of patients within a 7-year study period. We also could not find a relationship between axial motor symptom deterioration and the high incidence of hypophonia/dysarthria/sialorrhea, and deterioration of ADL with time in the present study.

In conclusion, the long-term effects of DBS on motor disability are promising. DBS showed uneven beneficial effectiveness, and least improvement in axial symptoms and verbal fluency. The disease progressed slowly despite significant positive effects of DBS on the cardinal motor disability symptoms of PD and on QoL. ADL and QoL improved remarkably after STN-DBS surgery, but these benefits faded after 5 years. When axial symptoms are the major presentations, clinicians should bear in mind the shortcomings of DBS in order to meet patient expectations.

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