Original Article

Long-term Efficacy of Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: A 5-year Follow-up Study in China

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Abstract

Background: Subthalamic nucleus deep brain stimulation (STN DBS) is effective against advanced Parkinson's disease (PD), allowing dramatic improvement of Parkinsonism, in addition to a significant reduction in medication. Here we aimed to investigate the long-term effect of STN DBS in Chinese PD patients, which has not been thoroughly studied in China.

Methods: Ten PD patients were assessed before DBS and followed up 1, 3, and 5 years later using Unified Parkinson's Disease Rating Scale Part III (UPDRS III), Parkinson's Disease Questionnatire-39, Parkinson's Disease Sleep Scale-Chinese Version, Mini-mental State Examination, Montreal Cognitive Assessment, Hamilton Anxiety Scale and Hamilton Depression Scale. Stimulation parameters and drug dosages were recorded at each follow-up. Data were analyzed using the ANOVA for repeated measures.

Results: In the "off" state (off medication), DBS improved UPDRS III scores by 35.87% in 5 years, compared with preoperative baseline ($P < 0.001$). In the "on" state (on medication), motor scores at 5 years were similar to the results of preoperative levodopa challenge test. The quality of life is improved by 58.18% ($P < 0.001$) from baseline to 3 years and gradually declined afterward. Sleep, cognition, and emotion were mostly unchanged. Levodopa equivalent daily dose was reduced from 660.4 ± 210.1 mg at baseline to 310.6 ± 158.4 mg at 5 years (by 52.96%, $P < 0.001$). The average pulse width, frequency and amplitude at 5 years were 75.0 ± 18.21 μs, 138.5 ± 19.34 Hz, and 2.68 ± 0.43 V, respectively.

Conclusions: STN DBS is an effective intervention for PD, although associated with a slightly diminished efficacy after 5 years. Compared with other studies, patients in our study required lower voltage and medication for satisfactory symptom control.

Key words: Deep Brain Stimulation; Follow-Up Studies; Parkinson Disease; Subthalamic Nucleus; Treatment Outcome

Introduction

Currently, subthalamic nucleus deep brain stimulation (STN DBS) is the surgical treatment of choice for advanced Parkinson's disease (PD). STN DBS significantly improves patients' cardinal motor symptoms as well as the quality of life, and reduces their need for medications.[1-3] STN DBS also improves some of the nonmotor features.[4,5] The PD population in China was estimated at 1.99 million in 2005 and is expected to increase to 4.95 million by 2030, accounting for more than 50% of all the PD patients worldwide.[6] However, only a small proportion of Chinese patients receive DBS. Clinical data on the outcome of STN DBS in China is still limited, due to insufficient cases and lack of comprehensive long-term follow-up. Therefore, in

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this article we sought to determine the 1-, 3-, and 5-year results in ten consecutive PD patients who underwent bilateral STN DBS at our center.

Methods

Patients

STN DBS was first introduced into our hospital in 2007. By the end of 2014, it was successfully performed on 54 PD patients. In the present study, we investigated the first 17 patients who received bilateral implants for STN DBS at our hospital between 2007 and 2009. Inclusion criteria included: (1) A diagnosis of idiopathic PD according to the British Parkinson's Disease Society Brain Bank criteria, (2) Age 18–75 years, (3) Disease duration of 5 years or more, (4) Severe levodopa-induced motor complications despite optimal adjustment of anti-Parkinsonian medications, (5) At least 30% improvement in motor symptoms assessed by the Unified Parkinson's Disease Rating Scale Part III (UPDRS III) after a levodopa challenge test, and (6) Normal brain magnetic resonance imaging (MRI). Exclusion criteria included: (1) Presence of cognitive impairment (score <26 on Mini-mental State Examination [MMSE]), (2) Severe psychiatric or behavioral diseases, (3) Conditions such as severe metabolic/cardiac/respiratory/renal/hepatic diseases, (4) Diagnosis of secondary Parkinsonism or multiple system atrophy, or (5) Inability to comply with the study protocol. The study was approved by Medical Ethical Committee of the First Affiliated Hospital, Sun Yat-sen University. A signed informed consent was obtained from each participant prior to their entry into the study.

Study protocol

PD patients indicated for STN DBS were selected by neurologists in the clinic. A week before surgery, they were admitted to the Neurology Department for preoperative evaluation, including: (1) Motor function in both "off" and "on" states, assessed by the UPDRS III, (2) Quality of life, assessed by Parkinson's Disease Questionnaire-39 (PDQ-39), (3) Sleep, assessed by Parkinson's Disease Sleep Scale Chinese Version (PDSS-CV), (4) Emotion, assessed by Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD), (5) Cognition, assessed by MMSE and Montreal Cognitive Assessment (MoCA), and (6) Brain MRI. Eligible patients were transferred to neurosurgery department for implantation of DBS device. The implantable pulse generator (IPG) was turned on a month after surgery and patients returned to the clinic at 1, 3, and 5 years for follow-up. In addition, dosages of anti-Parkinsonian drugs, side effects, and stimulation parameters were recorded at each follow-up.

The "off" state was defined as the patients' motor function after withdrawal of anti-Parkinsonian medications for at least 12 h; the "on" state referred to the condition treated with medications fully.[7] Preoperatively, the patients' "on" state was evaluated by a levodopa challenge test using 150% of the usual morning dose. Postoperatively, they were evaluated with their IPGs on, using the usual morning dose instead of the challenge dose to avoid severe dyskinesia. Medications were converted into an equivalent dose of immediate-release levodopa (Madopar, Roche, Basel, Switzerland), according to the following formula: 100 mg immediate-release levodopa = 133 mg controlled-release levodopa = 1 mg pramipexole = 100 mg piribedil = 10 mg selegiline; each dose of levodopa was 25% more effective with entacapone.[8]

Surgery

One day before surgery, all patients underwent a brain MRI scan. On the day of surgery, a brain computed tomography (CT) scan with a Leksell G frame (Elekta AB, Stockholm, Sweden) mounted on the skull was performed before surgery. The CT image was then fused to the MRI scan using Stereotactic Planning Software (iPlan, Brainlab, Feldkirchen, Germany) for target determination and trajectory planning. Implantation of electrodes was performed under local anesthesia, under stereotactic guidance and microelectrode recording (MER) technique. The quadripolar leads (Model 3389, Medtronic, Minneapolis, MN, USA) were inserted into target position if satisfactory signals from MER were obtained. Intraoperative test stimulation was performed to monitor improvements of Parkinsonian signs and stimulation-induced side effects. After ensuring accurate electrode placement, the leads were secured at the burr-hole site with an anchoring device (Stimloc, Medtronic, Minneapolis, MN, USA). A similar procedure was repeated on the opposite side. Finally, an IPG (Kinetra, Medtronic, Minneapolis, MN, USA) was implanted subcutaneously in the right sub-clavicular area and connected to extended leads under general anesthesia.

Programming

A month after surgery, patients returned in the "off" state for initial programming. The IPG was turned on and all the contacts were tested according to a standard protocol.[9] With the IPG as anode, the tested contact as cathode, pulse width of 60 μs and frequency of 130 Hz, the amplitude was gradually increased to 5–6 V in increments of 0.5–1.0 V or until intolerable side effects manifested. Tremor and rigidity of the tested limbs were scored and all the adverse effects, if any, were recorded each time the amplitude was increased. The electrode contact with the lowest threshold for inducing a benefit and the highest threshold for side effects was finally selected for chronic stimulation. After the IPG was switched on, patients came back in 2 weeks for further programing. If they were satisfied, the setting was maintained with some room for self-adjustment of voltage (±0.4 V). Patients who were unsatisfied returned as needed, but at least 2 weeks after the prior session. In the subsequent programming sessions, stimulating parameters and medications were progressively adjusted for maximum improvement. Usually we avoid programing and medication adjustment within the 3 months before follow-up.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and analyzed using independent-samples

t-test or the ANOVA for repeated measures. Least significant difference *t*-test was used for *post-hoc* multiple comparison of data at baseline, 1, 3, and 5 years. Fisher's exact test was adopted for categorical variables. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyzes were performed with SPSS software, version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 17 patients initially included, three had a history of unilateral pallidotomy; three died from diseases unrelated to DBS, three were lost to follow-up because they lived too far away from our center, and one was unable to cooperate during the evaluation because of hearing loss. Finally, 10 patients completed the 1-, 3-, and 5-year follow-up studies. Their baseline characteristics are detailed in Table 1.

Motor outcome

With regard to the "off" state, the total UPDRS III scores at 1, 3 and 5 years were significantly improved by 48.69%, 38.14%, and 35.87%, respectively, compared with the baseline [Table 2], representing therapeutic efficacy of STN DBS alone at different time points. Statistical difference was observed between the scores at 1 and 5 years ($P = 0.014$), but differences between 1 and 3 years ($P = 0.111$) and between 3 and 5 years ($P = 0.742$) were insignificant, indicating a slight loss of effectiveness over time. Of the motor symptoms, maximum improvement was observed in rigidity (49.77% at 1 year, 66.36% at 3 years, 63.13% at 5 years), followed by tremor (48.46% at 1 year, 35.38% at 3 years, 54.62% at 5 years) and bradykinesia (50.30% at 1 year, 30.84% at 3 years, 29.04% at 5 years). Axial symptoms improved by 42.06% during the first year, but worsened progressively and returned to the baseline score at 5 years. Speech, rated by Item 18 of UPDRS III, responded to STN DBS the same way as axial symptoms and got even worse than baseline after 5 years. No significant difference between pre- and post-operative total UPDRS III scores was seen in the "on" state. However, rigidity was improved by 65.59% at 3 and 5 years compared with the baseline score, suggesting a synergistic effect of medication and stimulation.

Table 1: Preoperative characteristics of the 17 patients (mean ± SD)

Characteristics	Completed the study	Dropped out of the study	*P*
Number	10	7	Not applicable
Gender (male/female)*	6/4	3/4	0.637
Age at surgery (years)	59.4 ± 9.3	64.2 ± 6.8	0.296
Disease duration at surgery (years)	9.3 ± 2.9	10.7 ± 2.9	0.376
Previous pallidotomy*	2	1	1.000
"off" state Hoehn-Yahr stage	2.9 ± 0.3	3.4 ± 0.5	0.016
"on" state Hoehn-Yahr stage	2.4 ± 0.5	2.3 ± 0.7	0.735
Improvement of challenge test (%)	64.0 ± 12.8	63.3 ± 12.4	0.754

*These variables were analyzed by Fisher's exact test; others without star mark were analyzed using independent-samples *t*-test. SD: Standard deviation.

Quality of life

Compared with baseline, the PDQ-39 summary index score improved by 58.18% at 3 years [Table 3], with no significant difference in scores at 1 and 5 years, indicating an improvement from baseline to 3 years and a subsequent decline. Dimension scores of mobility, emotional well-being, and stigma were significantly reduced from baseline to 3 years, by 55.56%, 77.66%, and 79.63%, respectively. Emotional well-being also improved in the first year. Scores of other dimensions at 1, 3, and 5 years were not significantly altered from the baseline.

Neuropsychological and sleep evaluation

No significant changes in cognition, emotion or sleep were observed from baseline to 5 years, as measured by MMSE, MoCA, HAMA, HAMD, and PDSS-CV, except an improvement in MoCA score at 3 years [Table 4].

Table 2: UPDRS III scores at baseline, 1, 3 and 5 years in "off" and "on" states (mean ± SD)

UPDRS III subscales	Item number	Range of scores	State	Baseline ($n = 10$)	1 year ($n = 10$)	3 years ($n = 10$)	5 years ($n = 10$)	*P*		
								1 year vs. baseline	3 years vs. baseline	5 years vs. baseline
Total	18–31	0–108	Off	44.1 ± 9.8	22.6 ± 8.4	27.3 ± 8.2	28.3 ± 7.6	<0.001	<0.001	<0.001
			On	15.6 ± 6.2	13.8 ± 5.8	13.5 ± 7.4	18.5 ± 5.5	0.554	0.474	0.387
Tremor	20–21	0–28	Off	6.5 ± 4.7	3.4 ± 3.7	4.2 ± 2.8	3.0 ± 3.3	0.007	0.053	0.010
			On	1.0 ± 1.5	1.5 ± 2.3	1.0 ± 1.3	1.3 ± 2.1	0.638	1.000	0.841
Rigidity	22	0–20	Off	10.9 ± 3.5	5.5 ± 2.8	3.7 ± 3.1	4.0 ± 3.9	<0.001	<0.001	<0.001
			On	4.7 ± 2.7	4.1 ± 2.4	1.6 ± 1.2	1.6 ± 1.4	0.627	0.007	0.006
Akinesia	23–26, 31	0–36	Off	16.7 ± 7.1	8.3 ± 3.8	11.6 ± 3.3	11.9 ± 4.4	<0.001	0.011	0.013
			On	5.6 ± 3.6	4.3 ± 3.1	5.7 ± 4.5	8.2 ± 3.7	0.313	0.978	0.164
Axial symptoms	27–30	0–16	Off	6.3 ± 1.4	3.7 ± 2.0	4.8 ± 1.4	5.7 ± 2.6	0.003	0.028	0.594
			On	2.6 ± 2.1	2.7 ± 1.4	2.7 ± 1.0	4.2 ± 2.1	0.899	0.939	0.165

The above variables met the assumption of sphericity ($P>0.1$) and the ANOVA for repeated measures showed significant time effects ($P<0.05$), indicating changes during the follow-up period. *Post-hoc* multiple comparison was performed with LSD *t*-test. A reduction in scores indicates an improvement in function. UPDRS: Unified Parkinson's Disease Rating Scale; LSD: Least significant difference; SD: Standard deviation.

Medications and stimulation parameters

Medications were calculated as the total levodopa equivalent daily doses (LEDDs) according to the conversion formula indicated previously. Compared with preoperative LEDD (660.4 ± 210.1 mg), postoperative LEDDs decreased by 45.30% ($P = 0.004$), 58.83% ($P < 0.001$), and 52.96% ($P < 0.001$), respectively, in 1 year (361.3 ± 250.9 mg), 3 years (271.9 ± 162.3 mg), and 5 years (310.6 ± 158.4 mg). No statistical differences occurred between postoperative LEDDs at different time points ($P > 0.05$). One patient had stopped taking anti-Parkinsonian drugs since the first year after surgery while the others received a combination of levodopa and dopamine agonists. Monopolar configurations with one contact were used in all ten patients at 5 years. Amplitude but not pulse width or frequency significantly increased from 1 to 5 years [Table 5]. Four patients had their first replacement of IPG after a mean period of 5.6 ± 0.5 years (with battery voltage of 2.49 ± 0.17 V at replacement), while the others still used the initial IPG (with battery voltage of 2.65 ± 0.03 V at 5 years follow-up).

Adverse events

In all the 17 patients, adverse events (AEs) occurred during the study period as follows:

Events related to surgery: A "microlesion effect" was observed shortly after DBS surgery in all of the patients, lasting for 1–2 weeks. A case of subcutaneous seroma and a case of transient hallucination occurred, and both resolved completely. No serious surgery-related AEs (e.g., hemorrhage, infection, or delirium) occurred, and

Table 3: PDQ-39 index scores and dimension scores at baseline, 1, 3 and 5 years (mean ± SD)

Dimensions of PDQ-39	Item number	Baseline (n = 10)	1 year (n = 10)	3 years (n = 10)	5 years (n = 10)	P		
						1 year vs. baseline	3 years vs. baseline	5 years vs. baseline
PDQ-39 SI*,†	1–39	32.4 ± 14.1	19.8 ± 8.5	13.5 ± 10.5	26.1 ± 9.7	0.032	<0.001	0.120
Mobility*,†	1–10	47.3 ± 20.8	31.8 ± 20.5	21.0 ± 17.2	37.5 ± 27.1	0.030	0.003	0.165
ADL*,†	11–16	37.9 ± 19.7	20.4 ± 12.5	15.4 ± 21.0	22.9 ± 16.3	0.055	0.032	0.064
Emotion*,†	17–22	39.2 ± 23.8	14.6 ± 9.7	8.8 ± 11.9	21.7 ± 13.6	0.004	0.001	0.040
Stigma*,†	23–26	33.8 ± 29.0	20.6 ± 18.2	6.9 ± 15.7	15.0 ± 17.2	0.237	0.011	0.037
Social support	27–29	16.7 ± 31.4	5.0 ± 8.1	0.8 ± 2.6	6.7 ± 12.3	0.322	0.152	0.413
Cognition*	30–33	27.5 ± 14.5	26.9 ± 12.2	18.8 ± 17.2	35.6 ± 22.8	0.885	0.246	0.140
Communication†	34–36	26.7 ± 21.4	15.0 ± 13.5	12.5 ± 14.8	38.3 ± 19.7	0.163	0.045	0.268
Bodily discomfort*	37–39	30.0 ± 25.5	24.2 ± 16.9	24.2 ± 20.6	30.8 ± 20.1	0.477	0.398	0.926

*The assumption of sphericity was met, $P>0.1$; Geisser-Greenhouse correction was applied to variables that failed the sphericity test when computing the P values for time effect; †The ANOVA for repeated measures showed significant time effects, $P<0.05$. PDQ-39 SI: PDQ-39 summary index score; SD: Standard deviation; ADL: Activities of daily living; PDQ-39 SI and scores of eight dimensions range from 0 to 100, with lower scores indicating better quality of life; Dimension score: Sum of scores of each item in the dimension divided by the maximum possible score of all the items in the dimension, multiplied by 100. PDQ-39 SI: Sum of dimension total scores divided by 8; PDQ-39: Parkinson's Disease Questionnaire-39.

Table 4: Sleep, cognition and emotion at baseline, 1, 3 and 5 years (mean ± SD)

Items	Range of scores	Baseline (n = 10)	1 year (n = 10)	3 years (n = 10)	5 years (n = 10)	P		
						1 year vs. baseline	3 years vs. baseline	5 years vs. baseline
PDSS-CV	0–150	103.4 ± 23.0	114.4 ± 17.1	112.7 ± 22.8	113.4 ± 15.6	0.234	0.460	0.323
MMSE*	0–30	28.9 ± 0.9	28.8 ± 0.6	29.2 ± 0.8	28.2 ± 1.5	0.726	0.434	0.173
MoCA*,†	0–30	24.3 ± 3.1	24.6 ± 1.3	26.9 ± 1.7	24.1 ± 3.1	0.842	0.014	0.772
HAMD	0–76	7.9 ± 7.4	5.7 ± 3.7	7.0 ± 4.4	6.7 ± 4.6	0.540	0.829	0.754
HAMA	0–56	6.1 ± 3.7	4.4 ± 2.1	4.1 ± 2.2	3.6 ± 3.5	0.321	0.243	0.308

*The assumption of sphericity was met, $P>0.1$; †The ANOVA for repeated measures showed significant time effects, $P<0.05$. PDSS-CV: Parkinson's Disease Sleep Scale-Chinese Version; MMSE: Mini-mental State Examination; MoCA: Montreal Cognitive Assessment; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; SD: Standard deviation. Higher scores indicate better results in PDSS-CV, MMSE, and MoCA, but the worse outcome for HAMA and HAMD.

Table 5: Stimulation parameters at 1, 3 and 5 years (mean ± SD)

Parameters	1 year (n = 10)	3 years (n = 10)	5 years (n = 10)	P		
				1 year vs. 3 years	1 year vs. 5 years	3 years vs. 5 years
Amplitude (V)*,†	2.16 ± 0.34	2.41 ± 0.46	2.68 ± 0.43	0.001	<0.001	0.010
Pulse width (μs)	70.5 ± 14.68	72.0 ± 15.09	75.0 ± 18.21	0.330	0.267	0.428
Frequency (Hz)	142.0 ± 15.76	145.0 ± 14.69	138.5 ± 19.34	0.163	0.332	0.127

*The assumption of sphericity was met, $P>0.1$; †The ANOVA for repeated measures showed significant time effects, $P<0.05$. SD: Standard deviation.

no repositioning was needed because of electrode migration or fracture. No AEs were related to DBS device.

Events related to stimulation or disease: One patient developed apraxia of eyelid opening; four had speech disturbance; and two experienced troublesome dyskinesia. After optimization of parameters and medications, symptoms were partly relieved and tolerable. With longer follow-up, gait deterioration and falls were common. Worsening gait in 11 patients and falls in nine patients were the most frequent AEs and the most common reasons for reprogramming. Although some temporary relief (usually lasting for several days to weeks) was achieved by changing the stimulation settings, the effect was sometimes offset by worsening of other symptoms. One patient developed occasional on-off phenomenon; one developed end-of-dose chest distress, which was considered to be a nonmotor symptom of PD after exclusion of cardiac and respiratory diseases; three gained more than 5 kg of weight.

Events unrelated to surgery or stimulation: One patient had prolonged low-grade fever of unknown origin; one had vertebral compression fracture; two were bed-ridden and died of pneumonia; one had a stroke and became paralyzed; one died of rectal cancer. Altogether three deaths were caused by severe AEs unrelated to surgery or stimulation. Notably, one patient who died of pneumonia underwent a 3.0-Tesla MRI scan 1 year after surgery despite prior warning by the neurologists, resulting in cognitive impairment, gait disturbance, and oculomotor defect.

Discussion

In this first comprehensive long-term follow-up study on STN DBS in China, we report the 5-year outcome of ten consecutive PD patients who underwent continuous bilateral STN DBS.

In the "off" state, motor symptoms were significantly improved by 35.87% at 5 years following STN DBS compared with baseline. However, there was a decline in the therapeutic efficacy compared with the improvement of 48.69% at 1 year. Rigidity, tremor, and bradykinesia were effectively controlled by STN DBS during the study period, while axial symptoms showed a diminishing response over time. Despite a slight loss of stimulation efficacy, "on" state motor scores at 1, 3 and 5 years did not vary significantly, indicating that the combination of medication and stimulation produced an effect similar to that of an overdose of levodopa and allowed a stable control of Parkinsonism. But with longer follow-up, gradual worsening of "on" state motor function is expected, as levodopa-resistant symptoms will develop and compromise the initial benefits.

Improvements by STN DBS alone at 1, 3 and 5 years are relatively low in our center compared with those reported by other countries.[10-12] The lower stimulation voltage in our patients may account for the difference. Decline in the efficacy of DBS may result from depleted battery and development of stimulation-resistant symptoms. According to other 5 years studies and a few studies over 8 years, the benefit of DBS for tremor, rigidity, and bradykinesia persisted, but not for axial symptoms,[10-15] consistent with our study. Clinical and pathological studies suggest that PD is a multisystem disorder. In addition to the dopaminergic system, PD also involves the noradrenergic, glutamatergic, cholinergic, and serotoninergic pathways.[16,17] Initial symptoms are amenable to dopaminergic therapy. As the disease progresses, nondopaminergic symptoms, such as axial symptoms and nonmotor symptoms develop, and dopaminergic therapy become less effective.[18] As we know, only levodopa-sensitive symptoms show a good response to STN DBS, so it's not surprising that improvement in levodopa-resistant axial symptoms is limited and temporary.

Patients' quality of life is improved by 58.18% by the third year after surgery mostly in terms of improved mobility and emotional well-being. The improvement gradually declined, probably due to disease progression and lower battery. Patients' cognition, sleep, and emotional ability remained almost unchanged. Our patients had relatively high preoperative MMSE and MoCA scores, and, therefore, carried a lower risk of postoperative cognitive deterioration. But given the simplicity of the scales used for cognitive assessment, it is possible that some subtle cognitive impairment is left undetected. A trend toward better sleep and emotional scores following STN DBS suggests that a larger sample size with adequate statistical power may be able to produce a positive result.

As STN DBS relieved most of the motor symptoms, patients no longer needed levodopa at preoperative doses. With the gradual increase of stimulation voltage, anti-Parkinsonian medications were carefully tapered. About a 50% reduction in medication was maintained throughout the 5 years follow-up period. The extent of medication reduction in our patients was similar to that reported by Krack *et al*.,[10] but our LEDDs were smaller compared with the previous study. Similar differences were observed compared with other 5 years studies.[19-21] The unique approach in China contributes to lower LEDDs. In China, using the smallest possible dose of medication for satisfactory symptom control is highly recommended, while complete relief of symptoms is avoided.[22] The goal is to reduce motor complications and allow adjustment for medication in the future. Therefore, neurologists in China tend to delay medical treatment until the patients no longer endure the disease, and then prescribe a small dose enough to maintain their activities of daily living. According to a nationwide survey in China, the median LEDD was 450 mg for PD patients with a median disease duration of 50 months.[23] However, whether the actual need for medications is different between Chinese patients and those in other countries remains unknown. The lower voltage in our patients is explained as follows: (1) Some patients have a low threshold for side effects and therefore cannot bear a higher voltage; (2) The smaller body size might play a role in determining the lower effective

voltages in Chinese patients; and (3) A relatively low voltage exerts a therapeutic effect as long as the electrodes are placed in the STN precisely.

In conclusion, the 5 years outcome of our study is generally consistent with the results of other long-term studies, suggesting that STN DBS is safe and effective even 5 years after implantation, with sustained control of rigidity, tremor and bradykinesia in the off-medication state. DBS is also associated with a favorable effect on patients' quality of life, but long-term improvement is limited by disease progression and battery life. Postoperative changes in cognition, sleep, and emotion were insignificant.

The study limitations are as follows: First, the small sample size inevitably leads to decreased statistical power; second, the 41% (7/17) loss to follow-up probably leads to bias and compromises the validity of our study; and finally, due to the patients' unwillingness to turn off the IPG and their intolerance of the condition without medication and stimulation, data of the "on" and "off" states with the IPG off are not available. A comprehensive, rigorous, and well-designed study is needed to investigate further the efficacy and safety of STN DBS in PD.

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Conflicts of interest

There are no conflicts of interest.

References

1. Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, *et al.* Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): A randomised, open-label trial. Lancet Neurol 2010;9:581-91.
2. Weaver FM, Follett KA, Stern M, Luo P, Harris CL, Hur K, *et al.* Randomized trial of deep brain stimulation for Parkinson disease: Thirty-six-month outcomes. Neurology 2012;79:55-65.
3. Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, *et al.* Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610-22.
4. Deuschl G, Paschen S, Witt K. Clinical outcome of deep brain stimulation for Parkinson's disease. Handb Clin Neurol 2013;116:107-28.
5. Castrioto A, Lhommée E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol 2014;13:287-305.
6. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, *et al.* Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007;68:384-6.
7. Defer GL, Widner H, Marié RM, Rémy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 1999;14:572-84.
8. 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 2010;25:2649-53.
9. Volkmann J, Moro E, Pahwa R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. Mov Disord 2006;21 Suppl 14:S284-9.
10. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, *et al.* Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925-34.
11. Gervais-Bernard H, Xie-Brustolin J, Mertens P, Polo G, Klinger H, Adamec D, *et al.* Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: Five year follow-up. J Neurol 2009;256:225-33.
12. Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, *et al.* Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. Brain 2010;133:2664-76.
13. Zibetti M, Merola A, Rizzi L, Ricchi V, Angrisano S, Azzaro C, *et al.* Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. Mov Disord 2011;26:2327-34.
14. Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: A blinded evaluation. Arch Neurol 2011;68:1550-6.
15. Lilleeng B, Gjerstad M, Baardsen R, Dalen I, Larsen JP. Motor symptoms after deep brain stimulation of the subthalamic nucleus. Acta Neurol Scand 2015;131:298-304.
16. Devos D, Defebvre L, Bordet R. Dopaminergic and non-dopaminergic pharmacological hypotheses for gait disorders in Parkinson's disease. Fundam Clin Pharmacol 2010;24:407-21.
17. Halliday G, Lees A, Stern M. Milestones in Parkinson's disease – Clinical and pathologic features. Mov Disord 2011;26:1015-21.
18. Jenner P. Treatment of the later stages of Parkinson's disease – Pharmacological approaches now and in the future. Transl Neurodegener 2015;4:3.
19. Schüpbach WM, Chastan N, Welter ML, Houeto JL, Mesnage V, Bonnet AM, *et al.* Stimulation of the subthalamic nucleus in Parkinson's disease: A 5 year follow up. J Neurol Neurosurg Psychiatry 2005;76:1640-4.
20. Wider C, Pollo C, Bloch J, Burkhard PR, Vingerhoets FJ. Long-term outcome of 50 consecutive Parkinson's disease patients treated with subthalamic deep brain stimulation. Parkinsonism Relat Disord 2008;14:114-9.
21. Romito LM, Contarino MF, Vanacore N, Bentivoglio AR, Scerrati M, Albanese A. Replacement of dopaminergic medication with subthalamic nucleus stimulation in Parkinson's disease: Long-term observation. Mov Disord 2009;24:557-63.
22. Tian YY, Tang CJ, Wu J, Zhou JS. Parkinson's disease in China. Neurol Sci 2011;32:23-30.
23. Zhang ZX, Chen H, Chen SD, Shao M, Sun SG, Qu QM, *et al.* Chinese culture permeation in the treatment of Parkinson disease: A cross-sectional study in four regions of China. BMC Res Notes 2014;7:65.