RESEARCH ARTICLE

Voltage adjustment improves rigidity and tremor in Parkinson's disease patients receiving deep brain stimulation

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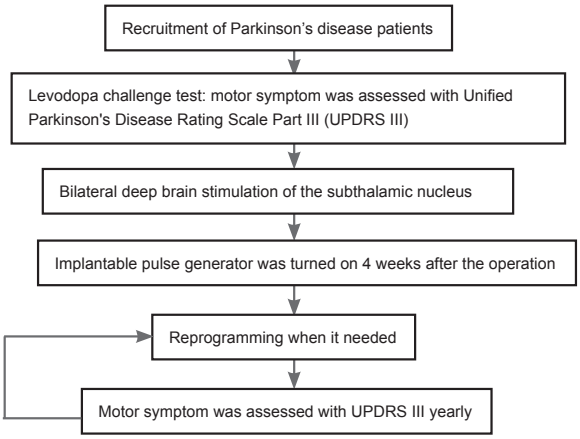
Graphical Abstract

Rigidity followed by tremor and bradykinesia could be best alleviated by adjusting the voltage



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Abstract

Deep brain stimulation of the subthalamic nucleus is recognized as the most effective treatment for moderate and advanced Parkinson's disease. Programming of the stimulation parameters is important for maintaining the efficacy of deep brain stimulation. Voltage is considered to be the most effective programming parameter. The present study is a retrospective analysis of six patients with Parkinson's disease (four men and two women, aged 37–65 years), who underwent bilateral deep brain stimulation of the subthalamic nucleus at the First Affiliated Hospital of Sun Yat-sen University, China, and who subsequently adjusted only the stimulation voltage. We evaluated motor symptom severity using the Unified Parkinson's Disease Rating Scale Part III, symptom progression using the Hoehn and Yahr scale, and the levodopa equivalent daily dose, before surgery and 1 and 2 years after surgery. The 2-year follow-up results show that rigidity and tremor improved, and clinical symptoms were reduced, while pulse width was maintained at 60 μs and frequency at 130 Hz. Voltage adjustment alone is particularly suitable for patients who cannot tolerate multiparameter program adjustment. Levodopa equivalent daily dose was markedly reduced 1 and 2 years after surgery compared with baseline. Our results confirm that rigidity, tremor and bradykinesia can be best alleviated by voltage adjustment. The trial was registered at ClinicalTrials.gov (identifier: NCT01934881).

Key Words: *nerve regeneration; deep brain stimulation; Parkinson's disease; subthalamic nucleus; voltage; pulse width; frequency; tremor; rigidity; bradykinesia; axial symptoms; neural regeneration*

Introduction

Deep brain stimulation (DBS) in the subthalamic nucleus (STN) is regarded as the most effective therapy for moderate and advanced Parkinson's disease (PD) (Pahwa et al., 2003; Moldovan et al., 2015; Preda et al., 2016), particularly for those with refractory motor fluctuations and drug-induced complications (Benabid et al., 2009; Rodriguez-Oroz et al., 2012; Odekerken et al., 2013; Jiang et al., 2015). The efficacy of surgery largely depends on the stimulation target (Wodarg et al., 2012; Scarnati et al., 2016), contacts selected for stimulation (Hilliard et al., 2011), programming of stimulation parameters (Kumar, 2002; Volkmann et al., 2002, 2006; Bronstein et al., 2011) such

as voltage, pulse width, and frequency (Yousif et al., 2012), and medication titration (Kumar, 2002).

China has the largest number of patients with PD worldwide (Dorsey et al., 2007; Jiang et al., 2015), and the number of patients receiving DBS is increasing year by year. But there is still a lack of systematic programming protocols. Moreover, long-term management of stimulation parameters depends on the physician's experience and repeated testing (Moro et al., 2002; Bronstein et al., 2011). In some patients, satisfactory therapeutic effects can be achieved by adjusting voltage parameters; conversely, in others, there is barely any curative effect even after adjustment of multiple parameters, including double negative, bipolar, or interleaving stimulation (Moro et al., 2002; Vercruysse et al., 2014). Considerable time and resources are often required to achieve the optimal strategy.

The aim of the present retrospective study was to explore which symptom could be best improved by voltage adjustment, and thus identify the most appropriate strategy for STN DBS programming. Moreover, we wish to share our experience to help guide those new programming centers in China.

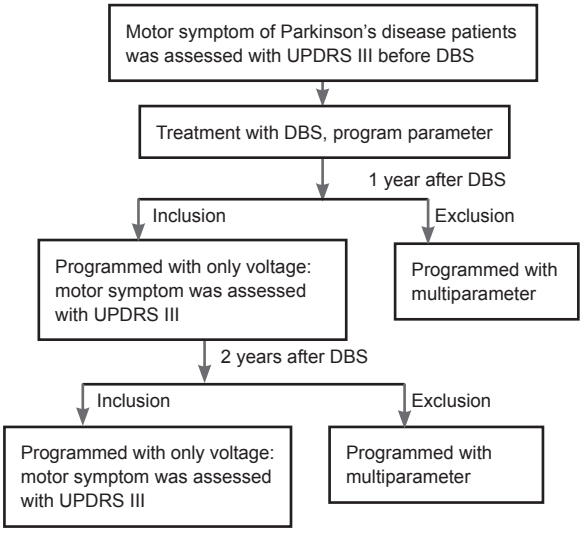

Figure 1 Clinical flow chart.
DBS: Deep brain stimulation; UPDRS III: Unified Parkinson's Disease Rating Scale Part III.

Subjects and Methods

Subjects

From 2007 to 2012, 33 patients with PD received bilateral STN DBS in the First Affiliated Hospital, Sun Yat-sen University, China. Of these, six (four men and two women) received implantable pulse generators in which only voltage changes were programmed during the 2-year follow-up. Inclusion criteria were as follows (Jiang et al., 2015): (1) idiopathic PD, meeting the criteria of the UK Parkinson's Disease Society Brain Bank (Hughes et al., 1992); (2) aged 18–75 years; (3) disease duration ≥ 5 years; (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) (Fahn and Elton, 1989) after a levodopa challenge test (Defer et al., 1999); (6) normal brain magnetic resonance imaging results. Exclusion criteria were as follows: (1) presence of cognitive impairment (Mini-Mental State Examination score < 26) (Folstein et al., 1975); (2) severe psychiatric or behavioral disorders; (3) other clinical conditions, such as severe metabolic, cardiac, respiratory, renal or 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 the Medical Ethical Committee of the First Affiliated Hospital, Sun Yat-sen University, China (approval No. [2008]20). Signed informed consent was obtained from each patient prior to their participation in the study. The participant flow chart is shown in **Figure 1**.

Bilateral STN DBS

In all patients, quadripolar stimulation electrodes (Model 3389S, Medtronic Inc., MN, USA) were implanted bilaterally in the STN and connected to an implantable pulse generator (Kinetra, Medtronic Inc.) in the right subclavicular area. All patients were assessed before surgery, and 1 and 2 years postoperatively, in off-medication and on-medication states (without and with medication, respectively), using the UPDRS III. Tremor, rigidity, bradykinesia, and axial symptoms were assessed.

DBS programming was generally performed at three main stages: (1) patients returned to the clinic for initial programming 1 month after implantation; (2) further programming 2–4 weeks after initial programming; and (3) slight adjustment during the stabilization stage (Volkmann et al., 2006).

Four weeks after surgery, the patients returned for initial programming in the off-medication state. The implantable pulse generator was turned on, and eight contacts were tested in accordance with a standard protocol (Volkmann et al., 2002; Volkmann et al., 2006) to identify the therapeutic window and the side-effect threshold. Usually, the implantable pulse generator was used as the anode and one contact as the cathode. The amplitude was gradually increased from 0 V to 5 V in increments of 0.5–1.0 V, unless unbearable adverse effects occurred, while the pulse width and frequency were maintained at 60 μs and 130 Hz, respectively (Picillo et al., 2016). During the process, adverse effects and improvements in motor symptoms were observed and recorded (Deuschl et al., 2006). Generally, rigidity was the most useful sign for confirming the benefit of stimulation because it occurred several seconds after voltage adjustment. After all contacts were tested, the best contact in each side was chosen as the cathode, and the pulse width and frequency were set at 60 μs and 130 Hz, respectively. The amplitude was set at around 1.5 V, and the final adjustment was made according to the motor symptoms. Two weeks after the implantable pulse generator was turned on, patients came back for reprogramming (small to moderate increase in voltage). A little authority was given to patients, so they could adjust this parameter at home, according to their symptoms. When frequency was set at 130 Hz and pulse width at 60 μs, the therapeutic voltage did not usually exceed 3.5 V.

Assessment

UPDRS III was conducted before surgery, and 1 and 2 years postoperatively. Stimulation settings, including voltage, pulse width, and frequency, were recorded at 1 month, 1 year and 2 years after surgery. During the 2 years of follow-up, the voltage was adjusted at every clinical visit, but the pulse width and fre-

quency remained unchanged. Levodopa equivalent daily dose and Hoehn and Yahr stage (Fahn and Elton, 1989) were also noted in detail. Hoehn and Yahr stages were as follows. Stage 1: unilateral involvement only; stage 1.5: unilateral and axial involvement; stage 2: bilateral involvement without impairment of balance; stage 2.5: mild bilateral disease with recovery on pull test; stage 3: mild to moderate bilateral disease, some postural instability, physically independent; stage 4: severe disability, still able to walk or stand unassisted; stage 5: wheelchair bound or bedridden unless aided.

Statistical analysis

Continuous variables are presented as the mean ± SD and were analyzed using paired *t*-tests. Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients

After we excluded those who received pulse width and frequency adjustments, or double cathode or bipolar stimulation, six of 33 patients remained. Changes in voltage alone were programmed in these patients for 2 years postoperatively. Their baseline characteristics are shown in **Table 1**.

Motor symptoms of patients with PD treated by DBS

Total UPDRS III score, tremor, rigidity, bradykinesia and axial symptoms in the off-medication and on-medication states are shown in **Table 2**. Rigidity, tremor and bradykinesia improved well. In the off-medication (on-stimulation) state, total UPDRS III scores and rigidity sub-scores improved from baseline by 57.1% at 1 year and 65.4% at 2 years ($P < 0.01$). Bradykinesia

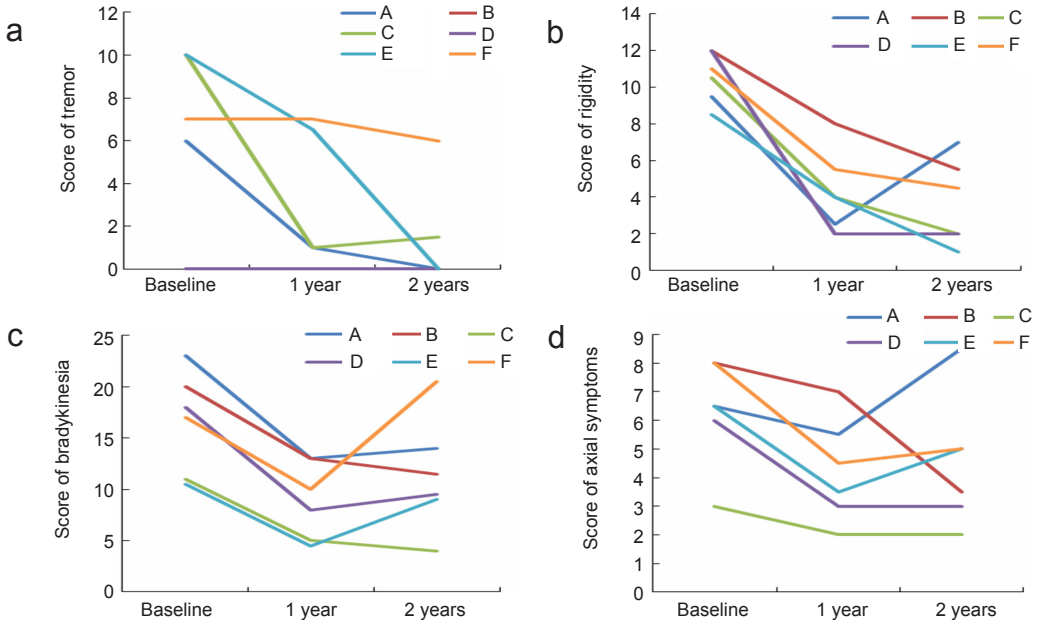

Figure 2 UPDRS III of six patients at 1 and 2 years after surgery in the off-medication state.
(a) Tremor score; (b) rigidity score; (c) bradykinesia score; (d) axial symptoms score. A–F: The six study patients. Higher scores indicate greater symptom severity. UPDRS III: Unified Parkinson's Disease Rating Scale Part III.

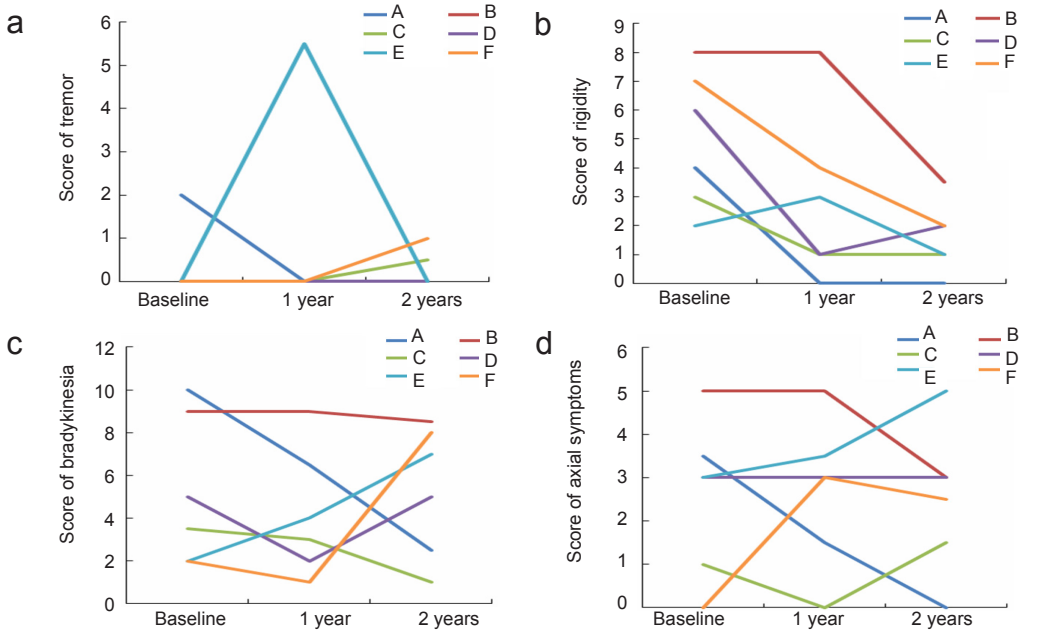

Figure 3 UPDRS III of six patients at 1 and 2 years after surgery in the on-medication state
(a) Tremor score; (b) rigidity score; (c) bradykinesia score; (d) axial symptoms score. A–F: the six study patients. Higher scores indicate greater symptom severity. UPDRS III: Unified Parkinson's Disease Rating Scale Part III.

score improved from baseline by 48.5% at 1 year ($P < 0.01$) and 34.7% at 2 years ($P < 0.05$). Moreover, tremor scores improved by 76.4% between baseline and 2 years ($P < 0.05$), and axial scores improved by 31.7% between baseline and 1 year ($P < 0.01$). In the on-medication state, rigidity was further improved at 2 years compared with baseline ($P < 0.01$).

In the off-medication state, four patients (A, C, E, and F) showed significant improvement in tremor at 1 and 2 years postoperatively. The remaining two (B and D) did not develop tremor, even by the 2-year follow-up.

Rigidity was greatly ameliorated at 1 year; four patients (B, C, E, and F) showed further improvement at 2 years, but patient A showed slightly worse rigidity at 2 years than at 1 year, and patient D showed no change between 1 and 2 years.

All patients showed marked improvement in bradykinesia at 1 year; but at 2 years, four (A, D, E, and F) showed worse symptoms than at 1 year.

Axial symptoms were slightly alleviated by long-term DBS at year 1, but reverted to the previous level at year 2 (**Figure 2**).

In the on-medication state, tremor was absent in five patients (B, C, D, E, and F) before surgery. At 1 year postoperatively, patient E started off with tremor, but it was controlled with long-term DBS and medication at 2 years. Tremor worsened in two of the five patients (C and F) 2 years after operation. Four patients (A, C, D, and F) showed improvement in rigidity at 1 and 2 years. Patient B showed no improvement in rigidity until 2 years. Rigidity in patient E was slightly aggravated at 1 year, but was alleviated at 2 years. In terms of bradykinesia, three patients (A, B, and C) showed improvement at 1 and 2 years. Patients D and F had less symptomatic improvement at 2 years. Manifestations in patient E were exacerbated at the 2-year follow-up. Axial symptoms showed no notable improvement. The condition of patients A and B was slightly better under chronic stimulation. The condition of patient D remained stable. The condition of the other three patients (C, E, and F) worsened slightly (**Figure 3**).

Generally, tremor and rigidity showed the greatest improvement bilaterally at 1 year, with further improvement at 2 years. Bradykinesia was less severe at 1 year than at 2 years. Improvement in axial symptoms was inferior to that in other symptoms.

Table 1 Patient characteristics

Item	Data
Gender (male/female)	4/2
Age of disease onset (year)	50.7±11.2(37–65)
Age at operation (year)	60.0±11.4(42–72)
Disease duration at operation (year)	9.3±3.0(5–13)

Continuous data are presented as the mean ± SD (range).

Stimulation parameters

Voltage parameters for all patients at 1 month, 1 year and 2 years postoperatively are listed in **Table 3**. The voltage increased with time. In the limb of onset, voltage increased in four patients, remained unchanged in one, and decreased slightly in another. The mean voltage at 1 month was 1.76 ± 0.29 V in the limb of onset and 1.47 ± 0.24 V in the contralateral limb. At 1 year, the voltage was 2.27 ± 0.20 V in the limb of onset and 1.88 ± 0.34 V in the contralateral limb. The mean value increased to 2.33 ± 0.22 V in the limb of onset and 2.03 ± 0.43

Table 2 UPDRS III and sub-scores at baseline, 1 year and 2 years in off-medication and on-medication states

	On state			Off state		
	Baseline	1 year	2 years	Baseline	1 year	2 years
UPDRS III	16.0±7.9	13.7±7.5	12.9±6.2	48.3±4.8	24.8±7.9**	25.8±12.1**
Tremor	0.3±0.8	0.9±2.2	0.3±0.4	5.5±4.5	2.6±3.3	1.3±2.4*
Rigidity	5.5±2.2	3.8±3.1	2.1±1.7**	13.3±1.5	5.7±2.7**	4.6±2.7**
Bradykinesia	5.9±3.8	4.8±3.7	5.8±3.3	19.6±5.3	10.1±4.4**	12.8±6.3*
Axial symptoms	2.6±1.8	2.7±1.7	2.5±1.7	6.3±1.8	4.3±1.8**	4.5±2.3

Continuous data are presented as the mean ± SD. *$P < 0.05$, **$P < 0.01$, *vs.* baseline (paired *t*-test). Higher scores indicate greater symptom severity. UPDRS III: Unified Parkinson's Disease Rating Scale Part III. Meaning of UPDRS III and sub-scores are shown in Additional file.

Table 3 Voltage parameters (V) in each patient at 1 month, 1 year and 2 years after STN DBS surgery

			1 month		1 year		2 years	
Patient	Gender	Age (year) at operation	Onset limb	Contralateral limb	Onset limb	Contralateral limb	Onset limb	Contralateral limb
A	Female	54	1.5	1	2	1.65	1.95	2.1
B	Male	42	2.25	1.8	2.4	1.9	2.5	1.9
C	Male	61	1.5	1.5	2.2	2.15	2.45	2.4
D	Male	72	1.8	1.5	2.6	2.25	2.6	2.35
E	Male	72	1.5	1.5	2.3	1.25	2.15	1.15
F	Female	59	2	1.5	2.1	2.1	2.3	2.25
Mean ± SD	–	60.0±11.4	1.76±0.29	1.47±0.24	2.27±0.20#	1.88±0.34	2.33±0.22#	2.03±0.43

#$P < 0.05$, *vs.* 1 month (paired *t*-test).

V in the contralateral limb at 2 years. There were statistically significant differences in voltage between 1 month and 1 year, and between 1 month and 2 years, in the limb of onset ($P < 0.05$). The increases in voltage over time may be due to disease progression and reductions in medication.

Medication and Hoehn & Yahr stage

The mean levodopa equivalent daily dose at baseline, 1 year, and 2 years was 671.58 ± 203.85 mg, 402.38 ± 188.89 mg, and 391.27 ± 120.78 mg, respectively. The levodopa equivalent daily dose reduced markedly at 1 and 2 years. The Hoehn and Yahr stage in the off-medication state was 2.83 ± 0.26 at baseline, 2.42 ± 0.38 at 1 year and 2.58 ± 0.74 at 2 years. In the on-medication state, the Hoehn & Yahr stage was 2.33 ± 0.41 at baseline, 2.00 ± 0.00 at 1 year and 2.00 ± 0.55 at 2 years.

Discussion

Improvement in motor symptoms after parameter programming

In the present study, we evaluated 1-year and 2-year follow-up data from patients who received STN DBS and subsequent voltage adjustments only, and analyzed the relationship between voltage and motor symptom improvement. Our study showed that voltage adjustment could improve parkinsonism, specifically rigidity, tremor and bradykinesia. The findings were consistent with those of a previous study (Moro et al., 2002).

In the off-medication state, tremor was less severe 1 year after DBS surgery than before surgery, and was further improved at 2 years after surgery. Similarly, rigidity in limbs was alleviated bilaterally, with a greater improvement at 2 years. Tremor and rigidity showed greater improvement in the limb of onset than in the contralateral limb. Improvement in bradykinesia was better at 1 year than at 2 years postoperatively, and in the limb of onset than in the contralateral limb at 2 years, although the reverse was true at 1 year. Although axial symptoms were improved at 1 and 2 years, improvement was not as good as in other symptoms. Together, the results indicate that voltage adjustments best improved tremor, rigidity, and bradykinesia. Motor symptoms were alleviated better in the limb of onset than in the contralateral limb. The improvement in axial symptoms revealed the benefit of voltage programming, suggesting that adjusting amplitude in DBS does not markedly influence axial symptoms. This finding was identical to that reported previously (Rodriguez-Oroz et al., 2005; Fasano et al., 2010).

In the on-medication state, we observed a slight loss of stimulation efficacy from voltage programming. This suggested that the combination of medication and stimulation produced an effect similar to that of an overdose of levodopa and allowed stable treatment of parkinsonism. We predict that as levodopa-resistant symptoms develop and reduce the initial benefit, there will be a gradual worsening of on-medication state motor function.

Programming parameters

In our study, six out of 33 patients with PD who underwent STN DBS showed sustained benefit from voltage-adjusted programming alone. This might be because the symptoms in these patients were relatively mild compared with those of patients needing multiparameter programming. Thus, adjusting only the stimulation amplitude can achieve satisfactory clinical benefits. Moreover, some patients cannot tolerate the side effects caused by increasing pulse width or frequency, which include dizziness, blurred vision, worsening of speech and gait, and stimulation-induced dyskinesia (Fasano et al., 2015; Nonnekes et al., 2015; Ramdhani et al., 2015; Vallabhajosula et al., 2015; Baizabal-Carvallo and Alonso-Juarez, 2016). Voltage adjustment might be the best choice in such cases.

Therefore, for patients with mild to moderate tremor- or rigidity-dominant parkinsonism, we suggest voltage adjustment with fixed frequency and pulse width as the first strategy. This can relieve symptoms as well as extending battery life. Frequency or pulse width adjustment, or other changes in configuration, can then be considered in those who fail to obtain benefit from changing the voltage alone.

Anti-parkinsonism drugs and Hoehn & Yahr stage

Voltage programming can enable drug doses to be reduced while retaining satisfactory clinical effects. We observed that as the stimulation amplitude gradually increased, the dose of anti-parkinsonism drugs reduced. This decrease in medication dose will also reduce drug-induced side effects. This finding was consistent with the reports from other centers (Rodriguez-Oroz et al., 2005; Gan et al., 2007; Lilleeng et al., 2015).

The Hoehn and Yahr stage showed a decreasing trend at 1 and 2 years after surgery, compared with the baseline. This indicated that voltage parameter programming might not only improve motor symptom severity, but also slow the progression of disease (Rodriguez-Oroz et al., 2005; Gan et al., 2007; Lilleeng et al., 2015).

Together, the present results and existing knowledge of programming indicate that selecting appropriate patients is vital to ensuring the effects of parameter programming postoperatively. For those with rigidity, bradykinesia, or tremor as the main symptom, priority selection with voltage adjustment is possible. Further rigorous studies should be conducted to validate the present findings.

In conclusion, voltage adjustments can improve movement in patients with PD, as demonstrated in UPDRS III assessments at baseline and at 1 and 2 years after surgery. Rigidity, tremor and bradykinesia were the symptoms that showed the best alleviation after voltage adjustment, and effects were more pronounced in the limb of onset than in the contralateral limb.

The study had some limitations. First, the sample size was small. Second, for ethical reasons, this was a retrospective study without randomization. A prospective study with a larger sample size and longer follow-up time, together with a detailed comparison of the effect of each parameter, might shed more light on the best parameter setting in bilateral STN stimulation for PD.

Author contributions: *LC conceived and designed the study. SHX, YML, YC, WBX, LLJ, QYG, JLL, JY, YFZ, LW, and WRC performed the experiments. GJ analyzed data. PZ reviewed the paper. LC and SHX reviewed and edited the paper. All authors approved the final version of the paper.*
Conflicts of interest: *The abstract as written communication was presented at the 18th Zhongshan International Neurology Summit Conference at November 28, 2015.*
Research ethics: *The study protocol was approved by the Medical Ethical Committee of the First Affiliated Hospital, Sun Yat-sen University, China (approval No. [2008]20). The study was conducted in accordance with the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (identifier: NCT01934881).*
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Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the form, patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*
Data sharing statement: *Datasets analyzed during the current study are available from the corresponding author on reasonable request.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewers: *L Cocito, Università Degli Studi Di Genova, Italy; Lilla Bonanno, IRCCS Centro Neurolesi "Bonino-Pulejo", Italy.*
Additional file: *Meaning of UPDRS III and subscores.*

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