Effect of Bilateral Deep Brain Stimulation of the Subthalamic Nucleus on Freezing of Gait in Parkinson’s Disease

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OBJECTIVE: A prospective cohort study to evaluate the efficacy of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) on freezing of gait (FOG) in patients with advanced Parkinson’s disease. METHODS: Patients (n = 10) with advanced Parkinson’s disease were surgically implanted with microelectrodes to facilitate STN-DBS. Evaluations of FOG, motor function, activities of daily living and neuropsychological function were carried out in on-medication and off-medication states (with and without levodopa treatment), before surgery and at 6 and 12 months postoperatively. RESULTS: STN-DBS was associated with significant improvement in FOG score and neuropsychological function at both 6 and 12 months postoperatively, compared with preoperatively. Significant postoperative improvements were also observed in motor function and activities of daily living. Daily levodopa dosage was significantly lower at both 6 and 12 months postoperatively. CONCLUSIONS: STN-DBS improved FOG in patients with advanced Parkinson’s disease. The significant reduction in levodopa dosage and improvement in neuropsychological function may be the reason for the therapeutic effect seen with STN-DBS.

KEY WORDS: PARKINSON’S DISEASE; SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION; FREEZING OF GAIT; ACTIVITIES OF DAILY LIVING; MOTOR FUNCTION; NEUropsychological FUNCTION; STEREOTACTIC NEUROSURGERY

Introduction
Freezing of gait (FOG) is a disabling episodic gait disturbance that is common among patients with advanced Parkinson’s disease. It typically lasts a few seconds, during which the patient feels as if his or her feet are glued to the ground.1 FOG is frequently associated with falls and injuries, and is a disabling symptom that commonly requires the patient to stay at home or use a wheelchair.2

The pathophysiological basis of Parkinson’s disease is alteration of the neural
circuit involving somatosensory and motor cortical areas. The subthalamic nucleus (STN) plays a crucial role in this neural circuit and its surgical removal may be an alternative to pharmacotherapy. The use of surgery to ablate the STN entered clinical practice in the 1980s, but severe adverse effects have dramatically limited the popularity of this procedure. Electrical deep brain stimulation (DBS) of the STN provides reversible modification of stimulation intensity, frequency and duration to achieve optimal clinical results, and is associated with fewer side-effects. Since the early 1990s, STN-DBS has become a widely accepted therapy for the long-term treatment of Parkinson's disease. Studies evaluating the efficacy of STN-DBS have focused primarily on improvements in classic motor symptoms such as tremor, rigidity and bradykinesia, and less on the amelioration of FOG.

The aim of the current study was to evaluate the efficacy of bilateral STN-DBS for the treatment of FOG in patients with Parkinson's disease. The possible therapeutic mechanisms of STN-DBS were also explored.

Patients and methods

PATIENT POPULATION

Consecutive patients with advanced Parkinson's disease were sequentially enrolled in this 12-month prospective cohort study, which was conducted between June 2008 and January 2012 at the Department of Neurosurgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, China. Inclusion criteria for surgical implantation of microelectrodes to facilitate bilateral STN-DBS were: (i) idiopathic Parkinson's disease; (ii) severe levodopa-related motor complications despite optimal adjustment of antiparkinsonian medication; (iii) no dementia or psychiatric abnormalities; and (iv) no surgical contraindications. All patients were clearly informed of the surgical risks and potential benefits of the intervention and provided written informed consent before study enrolment. The Ethics Committee of the Fourth Military Medical University approved the study protocol (permit number fmmu-10-6688).

SURGICAL PROCEDURE

The surgical procedure was performed as described previously. The STN was located by contrast ventriculography and magnetic resonance imaging (MRI). A sagittal angle of 85° and a coronal angle of 80° were used to obtain an extraventricular and extracapsular trajectory for the surgical approach. The STN was located 4 mm below the anterior commissure–posterior commissure (AC–PC) plane, 11 – 12 mm lateral to the midline of the third ventricle, at the midpoint of the AC–PC line. Electrophysiological recording and stimulation were used for further refining of the target location, and quadripolar electrodes (DBS Lead Model 3389; Medtronic, Minneapolis, MN, USA) were implanted bilaterally during a single operation. The electrode locations were verified postoperatively by long acquisition, high-resolution T2-weighted MRI acquired in both the axial and coronal planes under strict stereotactic conditions. A few days after implantation of the electrodes, a programmable pulse generator (Itrel® II; Medtronic) was implanted subcutaneously on each side of the head while the patients were under general anaesthesia. Stimulation settings were progressively adjusted until the optimal parameters (90 µs pulse width, 185 Hz, 1.5 – 2.4 V) were achieved. These stimulation parameters were consistently maintained throughout the 12-month study period.
CLINICAL EVALUATION
Patients were evaluated before surgery and at 6 and 12 months postoperatively during electrical stimulation of the STN. Assessments were performed when patients had taken no dopaminergic medication for 10 – 12 h (off-medication) and during periods of maximal clinical benefit (on-medication; 1 h after a dose of levodopa 50% higher than the usual morning dose, 24 h after off-medication testing).

Patients were assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS) motor (UPDRS III; score 0 – 108) and activities of daily living (UPDRS II; score 0 – 52) systems. Evaluation of FOG used a 16-point questionnaire, with scores ranging from 0 to 4 for each symptom (0, absence of symptoms; 4, the most severe symptoms; overall score was the mean of the 16 individual scores). Global cognitive assessment of neuropsychological function was performed with the Mattis Dementia Rating Scale (score 0 – 144) in both the off- and on-medication states.

STATISTICAL ANALYSES
Data were presented as mean ± SD. Statistical analyses were carried out using one-way analysis of variance followed by Bonferroni post-hoc analysis. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS® statistical package, version 18.0 (SPSS Inc., Chicago, IL, USA) for Windows®.

Results
The study enrolled 10 patients (six males, four females; age 61.7 ± 3.9 years, range 55 – 69 years) with advanced Parkinson’s disease (disease duration 12.0 ± 2.3 years, range 8 – 15 years; levodopa therapy duration 10.5 ± 1.9 years, range 8 – 14 years). None of the patients died or was lost to follow-up.

Off-medication FOG scores were significantly lower at 6 and 12 months postoperatively (1.2 ± 0.3 and 1.5 ± 0.2, respectively) compared with baseline (3.4 ± 0.5; P < 0.05 for both comparisons; Fig. 1). There was a similar decrease in on-medication FOG scores at 6 and 12 months postoperatively (0.8 ± 0.2 and 0.6 ± 0.25, respectively) compared with baseline (2.1 ± 0.6; P < 0.05 for both comparisons; Fig. 1). There was no significant difference between 6- and 12-month postoperative values in either the on-medication or off-medication states.

Mean daily levodopa dosage was significantly lower at 6 and 12 months postoperatively compared with baseline (P < 0.01 for both comparisons; Table 1), with no significant difference between the 6- and 12-month postoperative dosages.

Neuropsychological function (Mattis Dementia Rating Scale) was significantly improved compared with baseline at 6 and 12 months postoperatively in both the off- and on-medication states (P < 0.05 for all comparisons; Table 1). UPDRS III and UPDRS II scores were significantly decreased in both the off- and on-medication states compared with baseline (P < 0.05 for all comparisons; Table 1). There were no significant differences between the 6- and 12-month Mattis Dementia Rating Scale, UPDRS III or UPDRS II scores in either the on-medication or off-medication states.

Discussion
Freezing of gait occurs in 50 – 60% of patients with Parkinson’s disease and is often
FIGURE 1: Effect of bilateral subthalamic nucleus deep brain stimulation on freezing of gait (FOG) in patients with advanced Parkinson’s disease (n = 10). FOG was evaluated both off-medication (no dopaminergic medication for 10 – 12 h) and on-medication (1 h after a dose of levodopa 50% higher than the usual morning dose, 24 h after off-medication testing) before surgical implantation of microelectrodes (baseline) and at 6 and 12 months postoperatively. Data presented as mean ± SD. *P < 0.05 versus baseline; one-way analysis of variance followed by Bonferroni post-hoc analysis.

TABLE 1:
Baseline and 6- and 12-month postoperative levodopa dosage, neuropsychological function (Mattis Dementia Rating Scale14), Unified Parkinson’s Disease Rating Scale (UPDRS) III (motor)12 and UPDRS II (activities of daily living)12 scores in patients with advanced Parkinson’s disease treated with bilateral subthalamic nucleus deep brain stimulation (n = 10)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baselinea</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa, mg/day</td>
<td>1051 ± 196.1</td>
<td>272 ± 55.9**</td>
<td>257 ± 36.2**</td>
</tr>
<tr>
<td>Mattis Dementia Rating Scale score</td>
<td></td>
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<tr>
<td>Off-medication</td>
<td>85.5 ± 6.1</td>
<td>122.8 ± 9.9*</td>
<td>128.4 ± 13.2*</td>
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<tr>
<td>On-medication</td>
<td>80.3 ± 4.9</td>
<td>132.6 ± 8.6*</td>
<td>119.3 ± 9.9*</td>
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<td>UPDRS III (motor) score</td>
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<td></td>
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<tr>
<td>Off-medication</td>
<td>65.9 ± 4.0</td>
<td>27.2 ± 5.9*</td>
<td>26.4 ± 6.0*</td>
</tr>
<tr>
<td>On-medication</td>
<td>34.7 ± 3.9</td>
<td>13.1 ± 2.5*</td>
<td>16.5 ± 2.9*</td>
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<tr>
<td>UPDRS II (activities of daily living) score</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Off-medication</td>
<td>30.4 ± 5.1</td>
<td>14.7 ± 3.0*</td>
<td>15.1 ± 2.7*</td>
</tr>
<tr>
<td>On-medication</td>
<td>14.3 ± 4.1</td>
<td>6.7 ± 1.8*</td>
<td>6.2 ± 1.6*</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD.

*aBefore surgical implantation of microelectrodes.

Off-medication defined as no dopaminergic medication for 10 – 12 h.

On-medication defined as 1 h after a dose of levodopa 50% higher than the usual morning dose, 24 h after off-medication testing.

*P < 0.05, **P < 0.01 compared with baseline; one-way analysis of variance followed by Bonferroni post-hoc analysis.
resistant to medication. The primary characteristic of FOG is a transient and sudden inability to begin walking, with the patient feeling as though their feet are glued to the ground. FOG is frequently associated with falls and injuries. In a 12-month prospective study, 2160 falls were observed among 113 patients with Parkinson’s disease. The majority of these falls occurred as a result of FOG and 25% caused injury, highlighting the debilitating nature and clinical importance of FOG. FOG is a major factor contributing to deterioration in the quality of life of patients with Parkinson’s disease. The pathophysiological mechanism underlying FOG remains largely unknown, however, the findings of the present study indicate that STN-DBS was an effective therapy for FOG in patients with advanced Parkinson’s disease. Compared with baseline, STN-DBS was associated with significant improvement in FOG score and UPDRS III and UPDRS II scores at 6 and 12 months after surgery, both on and off-medication.

Although the mechanism underlying FOG remains unclear, it has been suggested that high cumulative amounts of levodopa may lead to FOG. STN-DBS was associated with significant reduction in levodopa dosage compared with baseline in the present study. This reduced levodopa requirement may, therefore, be an important mechanism by which STN-DBS exerts its therapeutic effect on FOG.

Although FOG has been traditionally been viewed as a dopaminergic motor symptom of Parkinson’s disease, evidence suggests that mental and cognitive functions may also play an important role. Nonmotor factors may predispose towards or provoke FOG symptoms. External auditory and visual cues, such as metronome stimulation, can improve FOG, further suggesting that FOG is strongly influenced by mental and cognitive function. There were significant improvements in neuropsychological function at 6 and 12 months after surgery in the current study, which may have alleviated the severity of FOG. In our opinion, improvement in neuropsychological function may also be an important mechanism underlying the therapeutic effect of STN-DBS on FOG.

In conclusion, these current findings demonstrate the efficacy of STN-DBS for the treatment of FOG in patients with advanced Parkinson’s disease. The significant reduction in levodopa dosage and improvement in neuropsychological function may be the reason for the therapeutic effect seen with STN-DBS.

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Conflicts of interest
The authors had no conflicts of interest to declare in relation to this article.

References
subthalamic nucleus deep brain stimulation in Parkinson’s disease

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