Subthalamic Stimulation in Parkinson Disease

Behavior and Social Adaptation

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Background: Bilateral subthalamic high-frequency stimulation significantly improves motor functions in patients with advanced forms of Parkinson disease (PD). This favorable effect contrasts with a growing number of reports that the treatment may result in psychiatric complications.

Objective: To analyze the presence of behavioral disorders and social maladjustment in PD patients successfully treated with continuous bilateral subthalamic stimulation.

Design: Prospective study.

Setting: University hospital.

Methods: Twenty PD patients underwent prospective evaluation for behavioral and personality changes, quality of life, and social functioning, 6 and 24 months after surgery to implant bilateral stimulating electrodes within the subthalamic nucleus.

Results: At 6 and 24 months after surgery, parkinsonian motor disability (on-stimulation/off-medication) was improved by 81% and 67%, respectively, and the severity of levodopa-related motor complications was improved by 84% and 70%, respectively. Levodopa-equivalent dosage was decreased by 79% and 66%, respectively; severity of depression was improved by 21% and 33%, respectively; and severity of anxiety was improved by 43% and 64%, respectively. The patients' personality traits were unmodified. Twenty-four months after surgery, the global score for quality of life was improved by 28%, whereas scores for social adjustment remained stable.

Conclusions: Provided that patients with PD are rigorously selected for neurosurgery, subthalamic stimulation (1) improves mood, anxiety, and quality of life; (2) does not result in severe permanent psychiatric disorders or modify patients' personality; and (3) does not ameliorate social adaptation.

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BILATERAL HIGH-FREQUENCY stimulation of the subthalamic nucleus (STN) is recognized as the treatment of choice for advanced levodopa-responsive forms of Parkinson disease (PD). This technique leads to a reduction in the severity of parkinsonian motor disability and levodopa-induced motor complications by 60% to 80%, enables the daily dosage of levodopa to be reduced by 40% to 80%, and has little or no effect on cognitive function. Provided patients are correctly selected, this favorable effect on motor and cognitive functions contrasts with a growing number of reports that the treatment may result in psychiatric complications. Transient mania, depression with increased suicidal risk, pseudobulbar crying, anxiety, and severe behavioral disorders have been reported. However, the retrospective nature of the studies, the limited number of patients undergoing analysis, and the lack of systematic psychiatric assessments make it difficult to draw any general conclusions from these reports. The present study was undertaken to prospectively analyze the effects of bilateral stimulation of the STN on personality, quality of life, the behavioral profile, and social adaptation in a selected sample of 20 levodopa-responsive patients with PD (hereafter referred to as PD patients).

METHODS

We prospectively studied 20 PD patients (13 women and 7 men; mean ± SD age, 54.9 ± 10.3 years) who consecutively underwent surgery between January 1, 2001, and March 31, 2002, for bilateral placement of stimulating electrodes within the STN. Selection criteria for surgery included an advanced form of the disease (Hoehn and Yahr score after ≥12-hour interruption of antiparkinsonian medi-
### Table 1. Effects of Bilateral Stimulation of the STN on Parkinsonian Disability and Psychiatric and Cognitive Status, 6 and 24 Months After Surgery in 20 PD Patients*

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>After Surgery</th>
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<tbody>
<tr>
<td></td>
<td>Off Medication</td>
<td>On Medication</td>
<td>6 Months</td>
</tr>
<tr>
<td>Parkinsonian disability</td>
<td></td>
<td></td>
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<tr>
<td>Parkinsonian motor disability†</td>
<td>42.4 ± 15.4</td>
<td>7.2 ± 4.3 (83)‡</td>
<td>8.0 ± 6.1</td>
</tr>
<tr>
<td>Levodopa-related motor complications§</td>
<td>...</td>
<td>8.0 ± 2.4</td>
<td>1.3 ± 1.1</td>
</tr>
<tr>
<td>Levodopa daily dosage, mg/d</td>
<td>...</td>
<td>1033 ± 464</td>
<td>60 ± 149</td>
</tr>
<tr>
<td>Levodopa-equivalent daily dosage, mg/d$</td>
<td>...</td>
<td>1319 ± 564</td>
<td>281 ± 208</td>
</tr>
<tr>
<td>Cognitive status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattis Dementia Rating Scale score16</td>
<td>...</td>
<td>139.7 ± 5.3</td>
<td>140.6 ± 3.2</td>
</tr>
<tr>
<td>Frontal lobe dysfunction score5</td>
<td>...</td>
<td>45.0 ± 6.3</td>
<td>45.4 ± 4.6</td>
</tr>
<tr>
<td>Psychiatric profile</td>
<td></td>
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<td></td>
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<tr>
<td>Mood disorders (range)¶</td>
<td>...</td>
<td>7.5 ± 4.4 (1-19)</td>
<td>5.9 ± 5.7 (1-27)</td>
</tr>
<tr>
<td>Anxiety (range)#</td>
<td>...</td>
<td>9.1 ± 4.5 (0-20)</td>
<td>5.5 ± 4.1 (0-17)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BAS, Brief Scale for Anxiety; MADRS, Montgomery Asberg Depressive Rating Scale; off medication, after an interruption of antiparkinsonian medication therapy of 12 hours or longer; on medication, currently receiving antiparkinsonian medication; PD, Parkinson disease; STN, subthalmic nucleus; ellipses, not applicable.

*Unless otherwise indicated, data are expressed as mean ± SD. Single numbers in parentheses represent the percentage of improvement compared with the off-medication preoperative Unified Parkinson’s Disease Rating Scale (UPDRS) part III score and the preoperative on-medication score for the other variables.

†Measured by the UPDRS part III score.14
‡P<.001.
§Measured by the UPDRS part IV score.14
||P<.005.
¶Measured by the MADRS score.21
#Measured by the Brief Scale for Anxiety score.24

### Psychiatric profile
- Quality of life was evaluated using a validated French version of the Temperament and Character Inventory–Revised, a 260-item, self-administered, true-false questionnaire to assess the dimensions of personality (novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness, and self-transcendence).

### Neurocognitive assessment
- The Mattis Dementia Rating Scale for global cognitive assessment, a 105-item, self-administered, true-false questionnaire, permits an estimation of “efficiency,” “interpersonal behavior,” and “disagreement-conflict.” An additional section explores the global adjustment score according to the opinion of the interviewer (M.G.).

We compared scores at baseline and 24 months after surgery using a paired Wilcoxon rank sum test. We chose this non-parametric test because of the small sample size and the non-normally distributed data. P<.05 was considered statistically significant. Data obtained at 6 months are included in Tables 1, 2, 3, and 4. Statistical analyses were performed using SAS statistical software, version 8.1 (SAS Institute Inc, Cary, NC).
RESULTS

Twenty-four months after neurosurgery, the severity of parkinsonian motor disability (on-stimulation/off-medication condition) was decreased by 67%, the severity of levodopa-related motor complications was decreased by 70%, and the levodopa-equivalent daily dosage was decreased by 66% compared with the preoperative state (Table 1). The cognitive status (Mattis Dementia Rating Scale and frontal lobe dysfunction scale scores) was not significantly modified. Compared with the preoperative state, bilateral STN stimulation significantly improved the Montgomery Asberg Depressive Rating Scale score by 33% and the Brief Scale for Anxiety score by 64%, 24 months after neurosurgery (Table 1).

Nine of 20 patients had experienced depressive episodes during the course of the disease before surgery (Table 2). During the 6 months after surgery, a depressive episode was observed in 4 patients, 2 of whom had no history of depression. The first, a 54-year-old man with an 8-year history of PD (levodopa-equivalent dosage, 1800 mg/d), developed sad mood, loss of initiative, and dissatisfaction, despite a 95% improvement of his parkinsonian motor disability. Depression resolved within 3 weeks after levodopa therapy (300 mg/d) was reintroduced. The second patient, a 59-year-old woman, developed a severe depressive state after the death of her caregiver and was still depressed 24 months after stimulation.

Two patients had a history of hypomania, one of whom experienced a transient episode of hypomania at the time of the surgery. In 2 other patients with no history of mood disorders, a transient hypomaniac state was observed, 6 months after surgery in one case (which resolved with reduction of the daily dosage of dopamine agonists) and 24 months after surgery in the other (which resolved spontaneously).

Agoraphobia, which was present in 4 patients before surgery, had disappeared 6 months after surgery in 2 cases. Agoraphobia recurred 24 months after surgery in the other 2 patients: one had a mild freezing of gait incompletely controlled by surgery and the other had a mild persistent tremor. Social phobia, observed in 3 patients 1 month before surgery, had disappeared 6 months after surgery and had reappeared 24 months after surgery in the 3 patients, including the 2 who had an intermittent recurrence of mild tremor or freezing of gait. Generalized anxiety, obsessive-compulsive, panic, and posttraumatic stress disorders were dramatically improved 6 months after surgery, and this favorable effect was maintained or amplified 24 months after surgery (Table 2).

Patients’ quality of life (Parkinson’s Disease Questionnaire) was significantly improved by 28% at 24 months after neurosurgery (Table 2). Four domains of the Parkinson’s Disease Questionnaire score (mobility, activities of daily living, stigma, and bodily discomfort) were significantly improved, whereas 4 other domains (emotional well-being, social support, cognition, and communication) were not. The Social Adjustment Scale global score and subscores (work, social life and leisure activities, family life, marital relations, and interaction with children) were not modified by STN stimulation 24 months after neurosurgery (Table 4). There was no change...
in the scores for personality traits as evaluated by the Temperament and Character Inventory–Revised 24 months after STN stimulation compared with the preoperative state (Figure).

Continuous monopolar electrical stimulation (20 patients, 40 electrodes; mean±SD of 2.75±0.4 V was applied through 1 [n=35] or 2 [n=5] contacts with a mean±SD frequency of 144±27 Hz and a pulse width of 60 microseconds [n=37] or 90 microseconds [n=3]). Transient treatment-related adverse effects included a leg venous thrombosis that resolved after 3 months of treatment with anticoagulants (n=1), infection of the stimulator area that resolved after antibiotic treatment and temporary removal of the stimulator (n=1), and stimulation-induced hypophonia ameliorated by adjunction of dopaminergic treatment (n=2). Permanent adverse effects included eyelid-opening apraxia (n=2); persistence of disabling dyskinesias related to dopaminergic treatment, subthalamic stimulation, or both (n=2); and significant weight gain (>10 kg; n=2).

The long-term favorable effect of STN stimulation on mood (Table 2) is consistent with 2 previous results, showing that mild to moderate depression could benefit from long-term STN stimulation. None of the patients with postoperative depression have had suicide attempts as occurred in 25% of patients in another study. Although the possibility of a premorbid psychiatric condition cannot be excluded in the latter study, the high postoperative proportion of suicide attempts is unexpected. Because suicide attempts are known to be associated with impulsivity, it may be hypothesized that inappropriate or exaggerated behaviors could occur as a result of impaired emotional responses to external or cognitive stressors when stimulation directly affects limbic neuronal circuits related to the STN.

The robust improvement of anxiety traits observed 24 months after surgery (Table 2) is in agreement with a previous report but contrasts with the results of another study in which general anxiety was aggravated postoperatively. The retrospective nature of the latter study, along with the particular psychopathology of the population studied, may account for this discrepancy. Several factors may have contributed to the favorable effect of STN stimulation on anxiety, a result that has also been reported after pallidal stimulation. The improvement of anxiety may be ascribed to the amelioration of motor symptoms, owing to the close temporal relationship between anxiety and motor fluctuations and the beneficial effects of levodopa therapy on anxiety. Another possibility is that anxiety, known to coexist with depression in PD, improved as a result of the amelioration of mood disorders (Table 2). Finally, it cannot be excluded that...
the improvement of anxiety resulted from the direct modulation of anxiety-related neuronal systems.\textsuperscript{35}

We failed to detect postoperative personality changes in our patients (Figure) and thus conclude that STN stimulation does not contribute per se to permanent psychiatric disorders, provided that patients are carefully selected (ie, in the absence of depression or a history of severe personality disorders) and the postoperative medical management is adequately performed.\textsuperscript{30} In line with the results of a previous study,\textsuperscript{12} however, patients with substance abuse were excluded. The fact that a recent report suggested that patients with dopamine replacement therapy dependence may benefit from stimulation\textsuperscript{36} suggests that further studies are needed to clarify this issue.

Despite the marked postoperative improvement in motor disability, the patients’ quality of life was only moderately ameliorated. The 28% amelioration of the Parkinson’s Disease Questionnaire summary index mainly resulted from the improvement of items related to parkinsonian motor disability, whereas items unrelated to mobility were not improved (Table 3), a finding that is consistent with another report.\textsuperscript{37} Moreover, the personal, familial, professional, and social adaptation of patients was unexpectedly unchanged 24 months after neurosurgery compared with the preoperative state (Table 4). The reasons for the absence of amelioration of patients’ social adjustment are unclear. Factors such as cognitive impairment, psychiatric disorders, or personality changes triggered postoperatively are not contributive (Table 2 and Figure). Although patients were in a state of well-being (Table 4), the occurrence of apathy in some patients cannot be excluded, as previously suggested.\textsuperscript{29,30} Nevertheless, it is our impression that other possible causes should also be taken into consideration, such as the preoperative psychological and sociological status of the patients.

CONCLUSIONS

Provided that patients with PD are carefully selected, in particular without a history of severe personality disorders, (1) we confirm the remarkable efficacy of bilateral STN stimulation on parkinsonian motor disability, without modifications of the general cognitive status of patients; (2) we show that STN stimulation does not induce permanent or severe psychiatric adverse effects or modification of patients’ personality, and that it helps to ameliorate mood disorders and anxiety; and (3) we show that neurosurgery is accompanied by an improvement in quality of life that does not significantly change patients’ personal and socioprofessional adaptation. The latter result, which will need to be confirmed in a larger series of patients, points to the necessity of careful preoperative analysis of the motor, intellectual, and psychiatric profile of patients and their personal, familial, and socioprofessional status to help them to anticipate their psychological and social situation after surgery.

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REFERENCES