Pallidal Stimulation in Parkinson’s Disease Does Not Induce Apathy

Clément Lozachmeur, M.D.
Sophie Drapier, M.D.
Gabriel Robert, M.D., Ph.D.
Thibaut Dondaine
Bruno Laviolle, M.D., Ph.D.
Paul Sauleau, M.D.
Julie Peron, Ph.D.
Florence Le Jeune, M.D., Ph.D.
David Travers, M.D.
Bruno Millet, M.D., Ph.D.
Marc Vérin, M.D., Ph.D.
Dominique Drapier, M.D., Ph.D.

Background: Whereas apathy is known as a common consequence of subthalamic nucleus deep brain stimulation in Parkinson’s disease, few studies have investigated the psychiatric consequences of internal globus pallidus deep brain stimulation.

Method: Twenty consecutive parkinsonian patients who underwent bilateral pallidal stimulation were assessed 3 months prior to surgery (M−3) and at both 3 (M3) and 6 months (M6) after surgery, using psychiatric, neuropsychological, and motor scales. Apathy, mood state, and anxiety state were scored using the Apathy Evaluation Scale, the Montgomery-Åsberg Depression Rating Scale, and the anxiety scale from the Association for Methodology and Documentation in Psychiatry, respectively.

Results: The mean apathy score remained stable between the preoperative M−3 assessment (37.2±6.2) and both the postoperative M3 (36.9±7.5) and M6 (37.2±5.0) assessments. The mean depression score did not differ between the M−3 assessment and M3 and M6 assessments. There was no difference between the preoperative mean anxiety score and both the postoperative M3 and M6 scores. The mean score for the Mattis Dementia Rating Scale remained stable at each study visit.

Conclusions: The main result of our study is the absence of deterioration in psychiatric and cognitive scores 3 months and 6 months after pallidal stimulation.

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Deep brain stimulation (DBS) is now well established as an adjunct therapy for Parkinson’s disease (PD), especially for patients affected by long-term complications

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From the Dept. of Psychiatry, Centre Hospitalier Guillaume Régnier, Rennes, France (CL, GR, TD, DD); “Behavior and Basal Ganglia” Host Team (Equipe d’Accueil), University of Rennes, Rennes, France (CL, SD,GR, TD, PS, JP, FLJ); DT, BM, MV, DD); Dept. of Neurology, Centre Hospitalier Universitaire Pontchaillou, Rennes, France (SD, TD, JP, MV); Dept. of Psychiatry, Centre Hospitalier Universitaire Pontchaillou, Rennes, France (DT, BM); CHU Rennes, Dept. of Clinical Pharmacology, Centre Hospitalier Universitaire Pontchaillou Rennes, France (BL); INSERM, 0203, Clinical Research Center, Centre Hospitalier Universitaire Pontchaillou, Rennes, France (BL); Dept. of Neurophysiology, Centre Hospitalier Universitaire Pontchaillou, Rennes, France (PS); and Dept. of Nuclear Medicine, Eugene Marquis Center, Rennes, France (FLJ).
Send correspondence to Dr. Lozachmeur; e-mail: c.lozachmeur@chguillaumeregnier.fr

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of levodopa therapy such as motor fluctuations and severe dyskinesias. Indeed, chronic DBS targeting the internal globus pallidus (GPI) and the subthalamic nucleus (STN) has been shown to yield a benefit both in motor function and in functional disability.1–5

Currently, the subthalamic nucleus has become the preferred target because the antiakinetic effect seems to be more robust, which allows a greater reduction of antiparkinsonian drug treatment, and requires less stimulation energy.6–10 However, an increasing number of studies have reported that STN DBS may be associated with neuropsychological, cognitive, and psychiatric dysfunction.11–13

Among these disturbances, apathy, defined as a lack of feeling, emotion, interest, concern, or motivation,14 has been largely described as a very common psychiatric STN DBS side effect.13 The STN is described as being situated in a central position in all five corticobasal ganglial-thalamocortical circuits, which each have specific motor, oculomotor, associative, and limbic functions.15 Neuroanatomical and physiological studies in animals have demonstrated that the STN can be functionally divided into sensorimotor (dorsolateral), limbic (medial), and cognitive (ventromedial) regions.16 Because of the small size of the STN and current diffusion within the structure, STN DBS may act on different functional circuits, either activating or inhibiting different neuronal networks, including emotional and associative circuits. Apathy following STN DBS could be related to the stimulation of the STN associative circuit.

Because of all these reasons, patients with cognitive impairment or severe psychiatric disease are now excluded from subthalamic surgery. For some of them, GPI appears to be the target of choice.17 Nevertheless, only few studies have investigated the non-motor effects of GPI DBS,18–21 particularly focusing on apathy known as a common consequence of STN DBS.13

To further characterize the psychiatric symptoms that may occur in GPI DBS, we report a prospective study on the incidence of apathy, mood disorders, and anxiety consecutive to GPI DBS in disabled parkinsonian patients.

METHODS

Participants

Twenty consecutive PD patients underwent bilateral GPI DBS between 2005 and 2010. There were 10 men and 10 women with a mean ± standard deviation (SD) age of 60.1 ± 9.1 years, and a mean disease duration of 13.3 ± 5.4 years. All met the criteria of the United Kingdom Parkinson’s Disease Society brain bank for idiopathic PD.22 STN DBS was contraindicated for all patients, due to global cognitive impairment (Mattis Dementia Rating Scale ≤ 130), impaired executive functions, and/or dopa-resistant axial motor signs at baseline, including dysarthria, freezing, and falls.17

All patients were assessed 3 months prior to surgery (M–3) and 3 (M3) and 6 months (M6) after GPI DBS, using psychiatric, neuropsychological, and motor scales.

Standard Protocol Approval, Registration, and Patient Consent

Written informed consent was obtained from each participant and the study met the ethical standards of the responsible committee on human experimentation.

Psychiatric Evaluation

Apathy was scored using the Apathy Evaluation Scale (Clinician version, C-AES).23 This is an 18-item scale with scores ranging from 18 to 72, the highest score reflecting severe apathy. It is recognized as the most psychometrically robust apathy scale across any population and was given “suggested scale” status for PD in a recent review.24 A cut-off score of 42 or above is chosen to define clinical apathy. Mood state was scored using Montgomery–Ásberg Depression Rating Scale (MADRS).25 Anxiety state was scored using the AMDP-AT (Association for Methodology and Documentation in Psychiatry).26 Patients were assessed by trained psychiatrists sensitized to psychiatric disorders in PD.

Neuropsychological Evaluation

The neuropsychological battery included the Mattis Dementia Rating Scale (MDRS)27 for the global cognitive assessment and a battery of tests assessing frontal executive functions, including Nelson’s simplified version of the Wisconsin Card Sorting Test (WCST),28 the Trail Making Test (TMT),29 the Categorical and Literal Fluency (F),30 and the Stroop Test.31

Motor Evaluations

All patients were evaluated according the Core Assessment Program for Intracerebral Transplantation and were scored on the Unified Parkinson’s Disease Rating Scale (UPDRS) II and III,33 the Hoehn and Yahr Score (H&Y),34 and the Schwab and England score (S&E).
Medical Treatment
Total levodopa equivalent dose (LED) was calculated on the bases of the Deuschl et al.’s method. Drug doses and electrical parameters for stimulation were adjusted at follow-up visits during the ensuing months until the best possible clinical conditions were achieved.

Surgical Procedure
Quadrupolar DBS electrodes (3387 Medtronic, Minneapolis, MN) were implanted in the posteroventral part of the two GPis in a single operating session. Antiparkinsonian treatment was stopped the evening before surgery. The patient was awake throughout the procedure and the effect of stimulation on rigidity was assessed by passive movement of the contralateral wrist. The ventral contact was kept above the optic tract, as evidenced by the induction of visual flashes by stimulation. During surgery, the electrodes were connected to an external pulse generator for stimulation testing. Programmable pulse generators (Soletra, Medtronic) were implanted in the subclavicular region 2 days later and connected to the electrodes. The electrode contacts were selected and the electrical parameters (voltage, pulse width, and frequency) adjusted to bring about the greatest improvement in motor symptoms with the fewest side effects. The exact location of the two selected electrode contacts (one on the left and one on the right) was determined using stereotactic coordinates derived from a 3D CT scan performed a few days after surgery.

Statistical Analysis
Statistical analysis was performed using Statistica 8.0 (StatSoft, Tulsa, OK). Data are presented as means± standard deviation (SD). The scores of the different scales rated before surgery, 3 months and 6 months afterward were compared using nonparametric repeated-measures analysis of variance (Friedman test) because these variables were non-normally distributed. If of significant difference, pairwise comparisons were performed between the different times of evaluation using the Wilcoxon rank sum test. For all analyses, a p value of <0.05 was considered significant. All reported p values are two-sided.

RESULTS

Psychiatric and Neuropsychological Results (Tables 1 and 2)
There was no significant difference between preoperative assessment and both postoperative M3 and M6 assessments for apathy, depression, anxiety, and neuropsychological evaluations.

Motor Results (Table 3)
There was an improvement in the scores for the main motor manifestations of the disease between the preoperative off-dopa and postoperative off-dopa/on-stim conditions. The effect was significant for the UPDRS III between the preoperative and both the postoperative M3 and M6 scores in the off-dopa condition. There was a significant improvement in S&E scores in the off-dopa condition between the preoperative score and the postoperative M6 score. Although not significant, there was the same tendency for H&Y score in the off-dopa.

Medical Treatment (Table 2)
The L-dopa equivalent dose remained unchanged at every evaluation.

DISCUSSION

Few studies have been performed with the objective to evaluate the non-motor effects of GPi DBS in PD. Okun et al. in the COMPARE study, a prospective blinded randomized trial comparing the cognitive and mood effects of unilateral STN DBS versus unilateral GPi DBS in patients with PD, did not find any significant mood differences between STN and GPi DBS groups on the Visual Analog Mood Scale from pre-DBS to post-DBS performance at 7 months. Nevertheless, more patients in the STN group had experienced postsurgical mood and cognitive adverse events (e.g., anxiety, confusion, irritability, aggressiveness, obsessive compulsive or manic symptoms, decreased confidence/motivation) than in the GPi group. Anderson et al, in a randomized, blinded
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TABLE 2. Neuropsychological Characteristics of Patients, 3 Months Before Surgery and 3 and 6 Months After Surgery in GPi-Stimulated Patients

<table>
<thead>
<tr>
<th>Rating Scales</th>
<th>Baseline (M–3) Mean±SD</th>
<th>DBS (M+3) Mean±SD</th>
<th>DBS (M+6) Mean±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRS (/144)</td>
<td>133.1±7.2</td>
<td>132.9±8.6</td>
<td>133.2±9.5</td>
<td>0.69</td>
</tr>
<tr>
<td>TMT (B-A)</td>
<td>109.9±46.1</td>
<td>122.7±99.4</td>
<td>128.1±92.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Stroop test</td>
<td>−2.4±8.9</td>
<td>−0.9±9.7</td>
<td>−2.3±8.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Literal Fluency</td>
<td>22.1±11.5</td>
<td>19.5±8.0</td>
<td>21.2±9.8</td>
<td>0.22</td>
</tr>
<tr>
<td>WCST errors</td>
<td>9.0±7.1</td>
<td>9.3±9.0</td>
<td>8.3±6.5</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Neuropsychological data are presented as raw scores.

DBS: deep brain stimulation; GPi: internal globus pallidus; MDRS: Mattis Dementia Rating Scale; TMT (B-A): difference between the time scores of part B and part A of the Trail Making Test (seconds); WCST: Wisconsin Card Sorting Test.

*p values calculated by Friedman test.

comparison of the safety and efficacy of STN and GPi DBS in patients with advanced PD also reported more cognitive and behavioral changes after STN than GPi implantation, though they did not use any validated psychiatric scale. In the same line but not in PD, Hälbig et al.18 did not find any change in neuropsychiatric measures of 15 patients with dystonia after GPi DBS. Recently, Kirsch-Darrow et al.21 assessed apathy prior to DBS and 6 months post-DBS (STN and GPi). They showed an increase of apathy after surgery but did not find any relationship between apathy and DBS site.

Our results are in line with most of these previous studies, showing that there is no depression or anxiety after GPi DBS. Furthermore, we confirm the results of our previous study,17 indicating that GPi DBS in advanced Parkinsonian patients with contraindications for STN DBS is effective in reducing cardinal and axial motor symptoms in the off-dopa condition and also preserves cognitive functions, even for patients at high risk (i.e., displaying cognitive decline at baseline). When focusing on apathy assessment, we showed that GPi DBS may be safe for parkinsonian patients, which constitutes a main difference with our previous report concerning apathy post-STN DBS,13 using exactly the same design in the same center. Our results support the idea that there is a clear relationship between apathy and DBS site. Several hypotheses can be made to explain this difference.

We did not find any levodopa reduction before and after surgery, which could explain that there was no postoperative apathy score increase. There are mixed findings regarding whether apathy after DBS is related to reductions in levodopa dosage. Therefore, several studies did not find any relationship between apathy and reduction in levodopa, despite substantial reductions in LED.21, 37-41 In the light of these results, we can assume that the absence of apathy after GPi DBS is not linked with the stability of LED after surgery.

The territories of basal ganglia have been anatomically divided into sensorimotor, associative, and limbic regions.42 Because the GPi (~478 mm³) is a bigger nucleus than the STN (~158 mm³),42,43 we can assume that either the lesion itself or stimulation effect of STN would be more

TABLE 3. Motor Scores and Levodopa-Equivalent Daily Dose Before and After Surgery in Gpi-Stimulated Patients

<table>
<thead>
<tr>
<th>Rating Scales</th>
<th>Off-Dopa</th>
<th>On-Dopa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (M–3) Mean±SD</td>
<td>DBS (M+3) Mean±SD</td>
</tr>
<tr>
<td>UPDRS II (/52)</td>
<td>22.4±8.1</td>
<td>17.1±7.9⁶</td>
</tr>
<tr>
<td>UPDRS III (/180)</td>
<td>40.7±15.9</td>
<td>25.2±13.5⁶</td>
</tr>
<tr>
<td>Schwab and England (/100%)</td>
<td>48.0±20.8</td>
<td>59.3±28.1</td>
</tr>
<tr>
<td>Hoehn and Yahr (/5)</td>
<td>3.4±0.9</td>
<td>2.7±1.0</td>
</tr>
<tr>
<td>LED</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

GPi: internal globus pallidus; LED: L-dopa equivalent dose (mg/24 h); UPDRS: United PD Rating Scale.

*p values calculated two-tailed Wilcoxon test.

⁵M+3 versus M+6, p=0.005.
⁶M–3 versus M+6, p=0.003.
⁷M+3 versus M+6, p=0.003.
⁸M+3 versus M+6, p=0.005.
⁹M–3 versus M+3, p=0.0005.
¹⁰M–3 versus M+6, p=0.004.
¹¹M–3 versus M+6, p=0.006.
¹²p=0.94 (Friedman test).
likely to affect non-motor pathways potentially involved in apathy than would the GPi. Thus, changes in mood, cognitions, and motivation after STN DBS could be the result of the current spread to non-motor portions of the nuclei.19,42,43

At last, cortical-subcortical neuronal pathways involved in GPi DBS may be different from STN DBS. Concerning STN DBS, correlations have been observed between variation in apathy scores and changes in glucose metabolism, using fluorodeoxyglucose-positron emission tomography (FDG-TEP). These correlations were positive in the right frontal middle gyrus [Brodmann area (BA) 10] and right inferior frontal gyrus (BA 46 and BA 47), and negative in the right posterior cingulated gyrus (BA 31) and left medial frontal lobe (BA 9).44 These results confirmed the role of the subthalamic nucleus in associative and limbic circuitry in humans and suggest that it is a key basal ganglia structure in motivation circuitry. The stability of apathy scores after GPi DBS support the hypothesis that GPi has a lesser influence on the limbic circuit. Further studies using FDG-PET are needed to confirm this hypothesis.

As a conclusion, while evidence is provided for the safety of the pallidal target regarding neuropsychiatric functions, we believe that GPi should be considered as the target of choice for advanced PD patients who are refractory to adjustments in medication and cannot benefit from STN surgery because of axial motor or cognitive contraindications.

The authors report no financial relationships with commercial interests.

References

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