Acute Deep-Brain Stimulation of the Internal and External Globus Pallidus in Primary Dystonia

Functional Mapping of the Pallidum

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Background: Dystonia is a syndrome characterized by prolonged muscle contractions that cause sustained twisting movements and abnormal posturing of body parts. Patients with the severe and generalized forms can benefit from bilateral high-frequency pallidal stimulation.

Objective: To investigate the functional map of the globus pallidus (GP) in patients with primary generalized dystonia.

Design: Prospective multicenter, double-blind, video-controlled study in patients treated at a university hospital.

Setting: University secondary care centers.

Patients: Twenty-two patients with primary generalized dystonia.

Interventions: Acute internal and external pallidal deep-brain stimulation or pallidal deep-brain stimulation.

Main Outcome Measures: The clinical effects of acute bilateral high-frequency ventral vs acute dorsal pallidal stimulation were assessed with the Movement subscale of the Burke-Fahn-Marsden Dystonia Rating Scale. Intrapallidal localization of the contacts of the quadripolar electrodes was performed using a 3-dimensional atlas–magnetic resonance imaging coregistration method by investigators blinded to the clinical outcome.

Results: Bilateral acute ventral stimulation of the GP significantly improved the Burke-Fahn-Marsden Dystonia Rating Scale score by 42% and resulted in stimulation of contacts located in the internal GP or medullary lamina in 18 of 21 patients. Bilateral acute dorsal pallidal stimulation, primarily localized within the external GP, had variable effects across patients, with half demonstrating slight or no improvement or even aggravation of dystonia compared with baseline.

Conclusions: Ventral pallidal stimulation, primarily of the internal GP or medullary lamina or both, is the optimal method for the treatment of dystonia. The varying effects across patients of bilateral acute dorsal pallidal stimulation, primarily of the external GP, suggest that unknown factors associated with dystonia could have a role in and contribute to the effects of the electrical stimulation.

Arch Neurol. 2007;64(9):1281-1286

Dystonia is a syndrome characterized by prolonged muscle contractions that cause sustained twisting movements and abnormal posturing of body parts. Patients with severe and generalized forms of dystonia benefit from pallidotomy and bilateral high-frequency pallidal stimulation. The beneficial effects of lesioning or high-frequency stimulation of the globus pallidus (GP) have long represented a paradox because, according to the model of basal ganglia function, the abnormal involuntary movements are predicted to be aggravated by pallidotomy. In the present study, we used the reversibility of electrical stimulation and the anatomical characteristic of the GP to investigate the paradox of pallidal surgery by analyzing the effects of high-frequency stimulation applied in different areas of the GP in 22 patients with primary generalized dystonia. When the posteroverentral part of the GP is targeted for surgery using quadripolar electrodes, the most ventral contacts are likely to be localized within the internal globus pallidus (GPI) and the dorsal contacts within the external globus pallidus (GPE) or its ventral border. This enabled us to explore the effects of ventral vs dorsal electrical stimulation of the GP.
After Surgery

Table 1. Effects of Bilateral Ventral vs Dorsal High-Frequency Stimulation on Dystonia Motor Disability in 22 Patients With Primary Generalized Dystonia

<table>
<thead>
<tr>
<th>BFM Movement Subscale Criteria (Range)</th>
<th>Before Surgery Baseline Score</th>
<th>Ventral Stimulation Score</th>
<th>Dorsal Stimulation Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial (neck and trunk) (0-24)</td>
<td>12.7 ± 8.0</td>
<td>6.3 ± 6.4 b</td>
<td>8.4 ± 6.4 b</td>
</tr>
<tr>
<td>Right limbs (lower and upper) (0-32)</td>
<td>14.1 ± 8.3</td>
<td>9.3 ± 6.5 b</td>
<td>11.8 ± 8.4</td>
</tr>
<tr>
<td>Left limbs (lower and upper) (0-32)</td>
<td>14.7 ± 9.3</td>
<td>8.7 ± 7.3 c</td>
<td>11.7 ± 9.2</td>
</tr>
<tr>
<td>Face (eyes and mouth) (0-16)</td>
<td>2.2 ± 2.5</td>
<td>0.75 ± 1.1 b</td>
<td>1.7 ± 2.6</td>
</tr>
<tr>
<td>Speech and swallowing (0-16)</td>
<td>2.7 ± 3.8</td>
<td>1.7 ± 3.0</td>
<td>1.7 ± 2.8</td>
</tr>
<tr>
<td>Total score (0-110)</td>
<td>46.3 ± 21.1</td>
<td>26.7 ± 14.9 c</td>
<td>33.6 ± 18.2 b</td>
</tr>
</tbody>
</table>

Abbreviation: BFM, Burke-Fahn-Marsden (range, 0-120, with higher scores indicating greater impairment).

a Data are given as mean ± SD.

b P < .05.
c P < .01.

METHODS

The study was part of the prospective multicenter French Stimulation du Pallidum Interne dans la Dystonie Study evaluating the efficacy and safety of palilal deep-brain stimulation in 22 patients with primary generalized dystonia. Quadrupolar electrodes (model 3389; Medtronic Inc, Minneapolis, Minnesota) were implanted bilaterally in the posteroventral area of the GPi, identified either by stereotactic brain magnetic resonance imaging (MRI) or by MRI with ventriculography and intraoperative electrophysiologic guidance. The positions of the quadrupolar electrodes were checked postoperatively in all patients but 1 at MRI performed before connection of the leads to a neurostimulator (Kinetra; Medtronic Inc) placed in the subclavicular area. Localization of the electrodes and each of their 4 contacts was performed by 2 investigators (I.Y. and E.B.), who were blinded to the clinical outcome, by using a 3-dimensional atlas–MRI coregistration method, a procedure that consists of fusion of an anatomical atlas with the MRI for each patient.²

Twenty-two patients (11 males and 11 females; median age at surgery, 30 years [age range, 14-54 years]; having a clinical diagnosis of primary generalized dystonia (median age at onset, 8 years [age range, 5-38 years]; duration of disease, 18 years [range, 4-37 years]) were prospectively studied. All patients underwent clinical evaluation, but the dorsal and ventral contacts were localized in only 21 patients. The patients were evaluated preoperatively (baseline) and 1 month after surgery in 2 different conditions: bilateral ventral and dorsal pallidal stimulation. The ventral contact was defined as the most ventral contact (contacts 0 or 1 of the 4 contacts) that did not elicit visual adverse effects (by current diffusion to the optic tract), and the dorsal contact was systematically defined as contact 3. For each hemisphere, electrical parameters used for ventral or dorsal contacts were selected as follows: pulse width, 60 to 90 µs; frequency, 130 Hz; and highest amplitude to obtain the best benefit–adverse effects ratio. The patients served as their own controls and were blinded to the stimulation conditions. They were evaluated on different days with randomization to the stimulation condition (ventral or dorsal contact stimulation). The effects of stimulation on movement were videotaped using a standardized protocol after at least 48 hours of stimulation and were blindly assessed on the videotapes by an independent investigator (M.V.) using the Movement subscale of the Burke-Fahn-Marsden Dystonia Rating Scale (BFM).³ The study was approved by the ethical committee of the Salpêtrière University Hospital, Paris, France, and all of the patients gave written informed consent.

Scores at baseline and 1 month after surgery were compared using a paired Wilcoxon rank sum test. This nonparametric test was chosen because of the small sample size and the abnormally distributed data. Comparison of the effects of ventral vs dorsal stimulation was made using a weighted κ coefficient. P < .05 was considered statistically significant. Statistical analyses were performed using the SAS 9.1 statistical package (SAS Institute Inc, Cary, North Carolina).

RESULTS

EFFECTS OF VENTRAL VS DORSAL STIMULATION

Effects of ventral vs dorsal stimulation are given in Table 1 and shown in Figure 1. Bilateral high-frequency ventral palilal stimulation significantly improved by 42% the total BFM Movement subscore compared with preoperative status (Table 1). The BFM subscores for the neck and trunk (axial), right and left limbs, and face improved by 50%, 34%, 61%, and 65%, respectively, whereas scores for speech and swallowing did not change. Overall, with stimulation of the ventral contacts, 15 of 22 patients experienced significant improvement (>50% in 11 patients and 25%-50% in 4; Figure 1A), 6 demonstrated improvement of less than 20% (Figure 1A), and dystonia slightly worsened in 1 patient.

Bilateral high-frequency dorsal palilal stimulation significantly improved the total BFM movement subscore by 23% (Table 1). The axial subscore improved by 34% compared with preoperative status, but the subscores for the right (P = .06) and left (P = .06) limbs, speech and swallowing, and face did not improve (Table 1). Overall, with bilateral high-frequency dorsal palilal stimulation, symptoms in 4 patients improved more than 50%; in 6, by 25% to 50%; and in 12, by less than 20% (Figure 1A). In 3 patients, symptoms worsened (data not shown). Of these 3 patients, 1 required interruption of the stimulation condition after 7 hours of dorsal test stimulation because of painful dystonic posture that was worse than in the preoperative state. Because the stimulation conditions were emergently returned to therapeutic values on the ventral contacts, the dystonia severity score could not be evaluated during the dorsal stimulation condition.
EFFECT OF VENTRAL VS DORSAL STIMULATION: INTRAGROUP COMPARISON

The effects of dorsal vs ventral contact stimulation were compared within specific subgroups of patients. These subgroups were delineated according to the amplitude of improvement in response to the therapeutic ventral stimulation as follows: good (>50%), moderate (50%-25%), or poor (slight or none, <25%), and the results were expressed for each subgroup separately (Figure 1B).

Among the 11 patients in whom bilateral high-frequency ventral stimulation resulted in marked improvement (ie, good responders, >50% improvement), only 3 patients demonstrated similar or better (patient 1) improvement after bilateral high-frequency dorsal pallidal stimulation; in the others, the improvement was less significant (moderate [50%-25%] or poor) (Figure 1B). In the subgroup of 4 patients in whom bilateral high-frequency ventral pallidal stimulation resulted in moderate improvement (50%-25%), only 1 patient demonstrated similar improvement after bilateral high-frequency dorsal pallidal stimulation; in the others, the condition was aggravated (Figure 1B). In the subgroup of 7 patients in whom bilateral high-frequency ventral stimulation resulted in less than 25% improvement (poor responders), only 1 patient (patient 12) demonstrated some improvement after bilateral high-frequency dorsal pallidal stimulation; in 3 patients each, symptoms were unchanged or worsened (Figure 1B).

Overall, this intragroup comparison of the effect of ventral vs dorsal bilateral high-frequency pallidal stimulation indicated that, despite variable effect across patients, dorsal pallidal stimulation was significantly less effective (P<.006) or could even aggravate BFM scores. The patients in whom dystonia worsened or only slightly improved (0%-25%) had, preoperatively, severe tonic posturing. No patients developed stimulation-induced movement disorders.

Stimulation parameters were monopolar (case being positive) for both ventral and dorsal test stimulation. The electrical parameters for the ventral contacts were similar for the right (3.7±0.5 V, 130 Hz, 72±20 µs) and left hemispheres (3.7±0.7 V, 130 Hz, 85.6±18 µs). They were in the same range for the pallidal dorsal stimulation delivered through the right (4.1±0.8 V, 130 Hz, 70.9±28.6 µs) and left leads (4.0±0.9 V, 130 Hz, 88.6±85 µs).

EFFECT OF INTRAPALLIDAL LOCALIZATION

Effects of high-frequency ventral vs dorsal pallidal stimulation according to the locations of the stimulating contacts were analyzed in the 21 patients with available postoperative MRIs and are given in Table 2. One example of localization of the contacts is shown in Figure 2. The contacts in the patients in whom bilateral high-frequency ventral pallidal stimulation provided improvement of greater than 50% or of 50% to 25% were localized in GPe-GPi (n=7), GPe-internal medullary lamina (Lam), or Lam-GPe (n=4) for the right and left hemispheres, respectively (Table 2). In the same patients, bilateral high-frequency stimulation delivered through the dorsal contacts, located in the GPe-GPe (n=2), GPe-Lam, or Lam-GPe (n=5), provided either less or no benefit compared with that obtained with ventral pallidal stimulation. In 2 additional patients (patients 1 and 22), the ventral contacts were located within the GPi-GPi and the dorsal contacts were located in Lam-Lam. In these patients, bilateral high-frequency ventral pallidal stimulation resulted in greater improvement in 1 patient (patient 22) and slightly less improvement in the other (patient 1) compared with bilateral dorsal test stimulation (Table 2). On the whole, except in 1 patient (patient 2), those who obtained the most beneficial effect (>50% and 50%-25%) had at least 1 contact in either the ventral GPi or the ventral area of the Lam.

In 3 patients, the ventral and dorsal contacts were within the same structure (ie, GPi in patients 7 and patient 21 and GPe in patient 3). However, stimulation of the dorsal area of the structure (either GPi or GPe) was less efficient than stimulation of the ventral area.

Two other patients who did not exhibit any benefit from stimulation of the ventral contacts (GPi-GPi) demonstrated aggravation of their condition by stimulation...
of the dorsal contacts with at least 1 contact in the GPe (GPe-Lam, patient 11; GPe-GPe, patient 2). Two other patients (patients 8 and 14) in whom either bilateral ventral (Gpi-Gpi or Gpi-Lam) or dorsal (GPe-Lam in both) pallidal stimulation significantly improved the BFM scores had, preoperatively, a hyperkinetic form of dystonia.

### Table 2. Effects of Bilateral Ventral vs Dorsal High-Frequency Pallidal Stimulation on Dystonia Motor Disability According to Intrapallidal Locations of Stimulating Contacts (Talairach Coordinate System x, y, z) in 22 Patients With Primary Generalized Dystonia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Baseline</th>
<th>BFM Movement Subscale Scores</th>
<th>Location of Talairach Coordinate System Contacts (x, y, z)</th>
<th>Patient No.</th>
<th>Baseline</th>
<th>BFM Movement Subscale Scores</th>
<th>Location of Talairach Coordinate System Contacts (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>17.5</td>
<td>Gpi (22.2, 15.2, −3.5) Gpi (23, 13, −6)</td>
<td>7</td>
<td>7</td>
<td>Lam (23, 16, 0.5)</td>
<td>Lam (22, 16, −1.5)</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>40</td>
<td>Gpi (18, 13, −3.5) Gpi (20, 16, −1.5)</td>
<td>53</td>
<td>53</td>
<td>Gpi (18, 16, 0.5)</td>
<td>Gpi (20, 20, 2)</td>
</tr>
<tr>
<td>3</td>
<td>61.5</td>
<td>28.5</td>
<td>Gpe (22.5, 13.3, 0) Gpi (23, 14.5, 0.7)</td>
<td>55.5</td>
<td>55.5</td>
<td>Gpe (22.5, 16, 2)</td>
<td>Gpe (23, 17, 2)</td>
</tr>
<tr>
<td>4</td>
<td>38.5</td>
<td>13</td>
<td>Gpi (22.3, 14, −3.5) Gpi (20, 13, −2.6)</td>
<td>32</td>
<td>32</td>
<td>Lam (22.5, 16.5, 1.2)</td>
<td>Gpe (21, 17, 3.1)</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>37.5</td>
<td>Gpi (21, 14, −4.9) Gpi (21, 13.1, −4)</td>
<td>62</td>
<td>62</td>
<td>Gpi (21, 16, −0.5)</td>
<td>Gpi (21, 15, −0.5)</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>33.5</td>
<td>Lam (22, 15, −0.6) Gpi (20, 17.2, −2)</td>
<td>39.5</td>
<td>39.5</td>
<td>Gpe (22, 18, 1.5)</td>
<td>Gpe (20, 18.7, 0.5)</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>40.5</td>
<td>Lam (18, 15, −1.7) Gpi (18, 14.8, −1.1)</td>
<td>65</td>
<td>65</td>
<td>Gpi (18, 17.9, 0.5)</td>
<td>Gpi (18, 17.9, 0.5)</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>8</td>
<td>Gpi (19.2, 18.8, −2.4) Gpi (16.5, 17.5, −2.4)</td>
<td>8</td>
<td>8</td>
<td>Gpi (19.9, 18, 1.6)</td>
<td>Lam (16.8, 18.1, 6)</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>15</td>
<td>Lam (21.9, 14.8, −3) Lam (22, 15.9, 0.6)</td>
<td>40.5</td>
<td>40.5</td>
<td>Gpi (22, 18, 0.6)</td>
<td>Gpe (22, 19, 3.5)</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>45</td>
<td>Gpi (24, 12, −3.5) Gpi (20, 12, −3.5)</td>
<td>43</td>
<td>43</td>
<td>Gpe (24, 19.5, 2.8)</td>
<td>Gpe (20, 20.2)</td>
</tr>
<tr>
<td>11</td>
<td>60.5</td>
<td>47</td>
<td>Gpi (18, 15, −4) Lam (16.5, 17.5, −3)</td>
<td>NA</td>
<td>NA</td>
<td>Gpi (19.5, 20, 0.5)</td>
<td>Lam (17.4, 19.8, 0.5)</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>45</td>
<td>NA</td>
<td>25</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>102</td>
<td>46.5</td>
<td>Gpi (20, 17, −4) Lam (20, 16, 0.5)</td>
<td>65</td>
<td>65</td>
<td>Lam (20, 19, −0.4)</td>
<td>Gpe (20, 18.4, 3)</td>
</tr>
<tr>
<td>14</td>
<td>32.5</td>
<td>4</td>
<td>Gpi (22, 16, −3.9) Lam (21.2, 14, −2.8)</td>
<td>13.5</td>
<td>13.5</td>
<td>Gpi (22, 16.2, 8)</td>
<td>Lam (21, 14.8, 2)</td>
</tr>
<tr>
<td>15</td>
<td>41</td>
<td>43</td>
<td>Lam (22, 13, −2.8) Gpi (22, 13.5, −3.8)</td>
<td>44</td>
<td>44</td>
<td>Gpi (22, 13.2, 4)</td>
<td>Lam (22, 13.5, 0)</td>
</tr>
<tr>
<td>16</td>
<td>39</td>
<td>28</td>
<td>Lam (22, 13, −1.1) Gpi (22, 14, −3.7)</td>
<td>30</td>
<td>30</td>
<td>Gpe (24, 16.5, 3.7)</td>
<td>Gpe (23.17, 5.2)</td>
</tr>
<tr>
<td>17</td>
<td>29</td>
<td>4</td>
<td>Gpi (21.2, 15, −0.5) Lam (21.2, 14, −0.5)</td>
<td>16</td>
<td>16</td>
<td>Gpi (23, 20.7)</td>
<td>Lam (21.5, 17.1)</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>26</td>
<td>Gpi (19, 15, −3.4) Gpi (19, 13, −1.1)</td>
<td>46</td>
<td>46</td>
<td>Lam (21, 19, 1.2)</td>
<td>Gpe (21, 15.3)</td>
</tr>
<tr>
<td>19</td>
<td>22</td>
<td>7</td>
<td>Gpi (19.7, 16.1, −4.5) Gpi (20, 17, −4.5)</td>
<td>13</td>
<td>13</td>
<td>Gpe (22.5, 19.5, 2)</td>
<td>Lam (19.5, 20.2)</td>
</tr>
<tr>
<td>20</td>
<td>34</td>
<td>22.5</td>
<td>Gpi (22.9, 18.8, −4) Gpi (19.2, 16.2, −4)</td>
<td>27</td>
<td>27</td>
<td>Gpe (23.5, 16.5, 1.5)</td>
<td>Gpe (20.5, 17.5, 1.5)</td>
</tr>
<tr>
<td>21</td>
<td>32</td>
<td>20</td>
<td>Lam (22, 15.6, −5.7) Gpi (18.5, −15.5, 5.7)</td>
<td>37</td>
<td>37</td>
<td>Lam (23.5, 17.5, −3.5)</td>
<td>Gpi (19.5, 14.8, −3.5)</td>
</tr>
<tr>
<td>22</td>
<td>38</td>
<td>15.5</td>
<td>Gpi (18.7, 14, −2.3) Gpi (19.4, 16, −2.3)</td>
<td>22</td>
<td>22</td>
<td>Lam (19.8, 16, 0.5)</td>
<td>Lam (20, 18.5)</td>
</tr>
</tbody>
</table>

Abbreviations: BFM, Burke-Fahn-Marsden Dystonia Rating Scale; GPe, external globus pallidum; Gpi, internal globus pallidum; Lam, medullary lamina; NA, not applicable.

Figure 2. Example of the locations of the dorsal (A; white circles) and ventral (B) stimulating contacts in 1 patient after 3-dimensional atlas–magnetic resonance imaging coregistration. The levels of atlas sections are indicated with reference to the posterior commissure (PC). The dorsal contacts are in the external globus pallidus and the ventral contacts are in the internal globus pallidus.
COMMENT

To our knowledge, this is the first prospective, double-blind, video-controlled study investigating the effects of ventral vs dorsal high-frequency pallidal stimulation in patients with primary generalized dystonia. We confirmed that bilateral high-frequency ventral stimulation of the GP significantly improved the baseline BFM movement subscore by 42% at 1 month after surgery. Moreover, half of the patients exhibited improvement of more than 50% compared with the preoperative scores. In these patients, the ventral contacts were preferentially localized in the GPi or Lam, with at least 1 contact in the GPi in 18 of 21 patients. In contrast, bilateral high-frequency dorsal pallidal stimulation had variable effects among patients. Overall, half of the patients exhibited little or no improvement (<25%) or their condition worsened compared with the preoperative state. In most of the patients, bilateral high-frequency dorsal pallidal stimulation was less efficient because the BFM score improved more than 50% in only 4 patients compared with 11 patients who received ventral pallidal stimulation. Most of the patients who obtained either fewer beneficial effects or little improvement or whose condition worsened had at least 1 contact in the GPe. On the whole, patients who were good responders with ventral stimulation did not obtain further benefit from dorsal stimulation, and most patients experienced a less remarkable effect. This was even more deleterious for poor responders; only 1 had a beneficial effect from dorsal stimulation.

Some methodologic issues may limit the validity of our findings. The relatively small sample size and the fact that patients were previously treated with ventral chronic stimulation for a few weeks, along with the lack of a washout off-stimulation period between each test stimulation condition, could have contributed to modification of our findings. The feasibility of the study justified our sample size, and the use of blind assessments on videotape of the BFM findings. The relatively small sample size and the fact that patients were previously treated with ventral chronic stimulation for a few weeks, along with the lack of a washout off-stimulation period between each test stimulation condition, could have contributed to modification of our findings. The feasibility of the study justified our sample size, and the use of blind assessments on videotape of the BFM findings. Furthermore, administration of a washout off-stimulation period between the test stimulation condition was impossible because of the severity of dystonia in the patients.

The 42% amelioration in symptoms obtained with ventral stimulation 1 month after surgery was consistent with results of other open studies10,11 and demonstrated that, except for the speech and swallowing features, a significant improvement in facial, limb, and axial symptoms can be achieved after a short duration of stimulation. These results confirm that the therapeutic target is the posterolateral and ventral areas of the pallidum.11,13 Although the ventral contacts were preferentially within the GPi, some variability in response was observed in our study. The prospect to identify in individual patients a correlation between the precise intrapallidal location of a contact and clinical improvement seems to be too simplistic as to the variability and complexity of dystonia. The abnormal involuntary movements may result from dynamic phenomena such as abnormal patterned activity superimposed on a slow rate of firing and abnormal oscillations in regions of the GPi, variable from one patient to another.12 Nevertheless, inasmuch as the GPi is the primary output of the basal ganglia, the suppression of aberrant activities within the basal ganglia–thalamic-cortical pathway via stimulation of the ventral and posterolateral areas of the pallidum may account for the robust, even if not constant, beneficial effect on dystonia.2,3,14,15

The results obtained from dorsal contact stimulation are more difficult to interpret. Despite the variable effect of dorsal contact stimulation across patients, the total baseline BFM score and the axial subscore improved by 23% and 34%, respectively. Because the mean amplitude of electrical current applied through the dorsal contacts was higher than that applied through the ventral contacts, one cannot rule out that, in patients who exhibited improvement from stimulation in the dorsal area of the pallidum, spread of the electrical current toward the internal segment could have contributed to the favorable effects of stimulation, particularly if their stimulating sites were at the ventral border of the GPe. However, this hypothesis seems unlikely because stimulation applied through at least 1 contact within the GPe ameliorated dystonia in some patients but failed to ameliorate it in others. It cannot be ruled out that chronic dorsal stimulation in an experimental condition different from that used in the present study (using other parameters) would have changed our results in favor of dorsal stimulation.

The model of the basal ganglia–thalamic-cortical motor circuit, previously proposed to explain hypokinetic and hyperkinetic movement disorders, cannot account for our results.5 That stimulation of the GPe in patients with dystonia may elicit choreic movements,16 lead to improvement of motor disability, or worsen the dystonia, as shown in the present study, is hard to reconcile. As previously suggested for pallidotomy and GPi stimulation in dystonia,7 we speculate that stimulation-induced change in the discharge pattern of the GPe, along with degree of desynchronization of neurons, could account for the effect of stimulation. In line with this hypothesis, GPi and GPe firing features in patients with dystonia were shown to be closely similar, suggesting that the abnormally patterned output from the GPi could not result from increased differential inhibitory or excitatory input arising from the direct or indirect pathway but is transmitted from the GPe.17,18 The reasons why symptoms were ameliorated in some patients but not in others are not known. We suggest that factors such as both anatomical19 and cellular20 characteristics of GP, along with potential heterogeneity in intrinsic physiologic functioning of GP across patients,5,18 may account for these discrepancies. In support of the latter hypothesis, in the present study, symptoms not ameliorated by stimulation in the ventral area also were not improved by stimulation in the dorsal area, indicating that unknown factors associated with the dystonia itself may have a role in the response to the effects of stimulation.

In conclusion, our data confirm that ventral pallidal stimulation, primarily in the GPi and Lam, is the optimal treatment of dystonia and results in early improvement, that is, in the first month postoperatively, although some variability across patients is observed. In addition, the various effects of dorsal (GPe) stimulation in dystonia, with clinical benefit, absence of improvement, or worsening of dystonic posturing, suggests that
modifications via neurostimulation of the GPe ouput (closely interconnected with the subthalamic nucleus) may strongly influence the clinical expression of the aberrant patterns of activity in the sensorimotor loops, on an individual basis, depending on the complexity and variability of dystonia. That some patients respond to neither GPI nor GPe stimulation suggests that still unknown factors associated with dystonia itself could also have a role.

Accepted for Publication: January 12, 2007.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by national grant PHRC 98 from the Direction Régionale de la Recherche Clinique (DRRC) Assistance-Publique-Hôpitaux de Paris, an unrestricted grant from Medtronic Inc, and by INSERM French Dystonia Network and GIS Maladies Rares.

Additional Contributions: The nurses at Centre d’Investigation Clinique provided care for the patients during the study.

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