Improvement in Parkinson Disease by Subthalamic Nucleus Stimulation Based on Electrode Placement

Effects of Reimplantation

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Background: The misplacement of electrodes is a possible explanation for suboptimal response to bilateral subthalamic nucleus (STN) stimulation in patients with Parkinson disease.

Objective: To evaluate whether reimplantation of electrodes in the STN can produce improvement in patients with poor results from surgery and with suspected electrode misplacement based on imaging findings.

Design: Prospective follow-up study.

Setting: Academic research.

Patients: A 1-year postoperative study was undertaken in 7 consecutive patients with Parkinson disease who, despite bilateral STN stimulation, experienced persistent motor disability and who were operated on for reimplantation a median of 16.9 months later.

Main Outcome Measures: The primary outcome was measured as the change in the Unified Parkinson Disease Rating Scale (UPDRS) motor score 1 year after reimplantation. The secondary outcome was measured as the extent of pharmacologic and electrical treatments required and the threshold at which the first stimulation-induced adverse effect appeared. The distances between the electrode contacts used for chronic stimulation and the STN theoretical effective target, defined as the mean position of the clinically efficient contact from 193 previously implanted electrodes, were compared.

Results: Except for a single patient, all patients displayed improvement following reimplantation. Under off-medication (ie, the patient is taking no medication) condition, STN stimulation improved the basal state UPDRS motor score by 26.7% before reimplantation and by 59.4% at 1 year after reimplantation. The median off-medication Schwab and England score improved from 51% to 76%. The median levodopa equivalent daily dose was reduced from 1202 mg to 534 mg. The stimulation variables changed from a mean of 2.6 V/73.0 µs/163.0 Hz to 2.8 V/60.0 µs/140.0 Hz. The mean threshold of the first stimulation-induced adverse effect increased from 2.6 to 4.4 V. The mean distance between the contacts used for chronic stimulation and the theoretical effective target decreased from 5.4 to 2.0 mm. This distance correlated inversely with the percentage improvement in the UPDRS motor score.

Conclusion: Patients demonstrating poor response to STN stimulation as a result of electrode misplacement can benefit from reimplantation in the STN closer to the theoretical target.

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principal objective of this study was to evaluate whether reimplantation of electrodes in the STN can produce an improved outcome in patients with poor results from surgery and with suspected electrode misplacement based on imaging findings.

Benabid et al. defined the theoretical effective target (TET) for STN implantation as the mean position of the contacts for clinical stimulation taken from 193 successfully implanted electrodes; statistically, the mean (SD) location is 5.02 (0.71) twelfths of the anteroposterior commissure (AC-PC) line anterior to the posterior commissure, 1.5 (0.66) eighths of the height of the thalamus below the AC-PC line, and 11.98 (1.12) mm lateral to the midline. The coordinates of the TET are reproducible at our center and are similar to those found by other groups.

## METHODS

### DESIGN AND PATIENTS

The first 7 consecutive patients with PD who were treated with bilateral STN stimulation, who demonstrated limited benefits from the method, and who were subsequently reoperated on at our center were studied. Limited benefit was defined as improvement of less than 40% in the UPDRS motor score, despite trials to optimize stimulation variables, for patients in whom the levodopa-induced motor score was higher than 60%. The 7 patients came from different centers, including 1 patient from our center. All patients satisfied criteria to qualify for surgery and for initial STN stimulation treatment. Each patient had a minimal decrease in the LEDD following surgery, an STN stimulation response that was markedly lower than the corresponding levodopa response, and the occurrence of an initial stimulation-induced adverse effect at a voltage prohibitive to obtaining a fair antiparkinsonian effect. Of 14 electrodes implanted, 12 fulfilled criteria characteristic of misplacement (Figure 1). These electrodes, visualized with minimal artifact on T1-weighted sequences, were positioned outside of the STN hypointense signal on T2-weighted magnetic resonance (MR) images.

### SURGICAL TECHNIQUE

Neurosurgical targeting of the STN was based on contrast ventriculography, enabling precise situating of the AC-PC line and on indirect TET localization by teleradiography. The Talairach method, for which the x-ray tube is positioned 4.5 m from the radiographic plate, was used for teleradiography. The x-ray tube and frame are fixed to the ground to improve precision. Data from stereotactic MR imaging revealing the STN as a hypointense signal on T2-weighted coronal views were also considered. For each patient, the misplaced original electrode was not explanted because of the risk of hemorrhage; its presence did not hinder the use of 5 microelectrodes that provided a series of parallel trajectories through which intraoperative electrophysiologic microrecordings and stimulation were performed simultaneously under local anesthesia to physiologically locate the sensorimotor STN.

Stimulation via the reimplanted electrode induced fair clinical improvement of rigidity at low intensity without causing adverse effects at far higher intensities. The quadripolar electrodes (Medtronic, Minneapolis, Minnesota) were implanted bilaterally or unilaterally (left electrodes in 2 patients) during a single session. All patients underwent postoperative MR imaging to check for surgical complications and to verify electrode placement. Fusion of postimplantation ventriculography with MR imaging permitted precise localization of the electrode contacts without electrode-induced artifacts. Electrodes were connected to the extension lead previously established and were linked to a programmable implanted pulse generator (Medtronic).

### EVALUATIONS

The following evaluations were made before reimplantation (basal state) and at 1 year after operation: (1) the UPDRS motor scores under off-medication condition with and without STN stimulation, (2) the results of calculations for the percentage stimulation-induced improvement [(100 × (basal state–stimulated state)/basal state)], (3) the LEDD and Schwab and England (UPDRS VI) scores, and (4) the threshold for the initial stimulation-induced adverse effect. The electrical variables of stimulation were studied, and a comparison was made of the distances between the electrode contacts used for long-term stimulation and the STN TET before and at 12 months after reimplantation.

### MAIN OUTCOME MEASURES

The primary outcome was measured as the change in the percentage of stimulation-induced improvement in the off-medication UPDRS motor score obtained 1 year after reimplantation. Multiple secondary outcomes were measured as the reduction of the LEDD, the improvement in the Schwab and England score, the mean threshold of stimulation for adverse effects induced by the electrode contacts, and their distance from the TET. Distribution-based statistical analysis was used for primary and secondary outcome evaluation, and Spearman rank correlation was used to assess the relationship between the UPDRS motor score improvement and the distance between the electrode contact and the TET.
RESULTS

Seven patients, 2 women and 5 men, were reoperated on at our center for STN stimulation. Their median age at reimplantation was 56 years (age range, 49-70 years), and the median duration between the 2 implantations was 16.9 months (range, 12-23 months). The mean UPDRS motor score under on-medication on-stimulation (ie, while receiving both medication and stimulation) condition before reimplantation was 11.9. Five patients had bilateral reimplantation, and 2 patients had unilateral (left electrode) reimplantation.

Except for 1 patient, all patients demonstrated improvements for the primary and secondary outcomes. The results are summarized in Table 1. The median UPDRS motor scores under off-medication on-stimulation condition were 40.1 before reimplantation and 22.2 at 1 year after reimplantation. An LEDD reduction of 55.6% was noted. The therapeutic contact was, on average, 3.4 mm closer to the TET after the second operation. The left-sided therapeutic contact of the patient who showed no improvement following reimplantation remained 4.2 mm from the TET. The Talairach coordinates (x, y, and z) of the electrode contacts and the distance between the center of the electrode contacts before and after reimplantation are given in Table 2. Fourteen electrodes were stimulated after reimplantation, while only 11 had been stimulated before reimplantation. Before reimplantation, 3 electrodes were not used for long-

Table 1. Comparison of the United Parkinson Disease Rating Scale (UPDRS) Motor Scores Under Off-Medication On-Stimulation Condition Before Reimplantation and 1 Year After Reimplantation

<table>
<thead>
<tr>
<th>UPDRS Motor Score</th>
<th>Levodopa Equivalent Daily Dose, Median (Range), mg</th>
<th>Schwab and England Score, Median (Range), %</th>
<th>Distance Between the Therapeutic Electrode Contact and the Theoretical Effective Target, Mean (SD), mm</th>
<th>Generator Setting Voltage/ Pulse Width in Microseconds/ Mean (SD) Range Frequency in Hertz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Reimplantation</td>
<td>54.7 (42-66)</td>
<td>1202 (400-1600)</td>
<td>51 (30-70)</td>
<td>5.4 (3.4)</td>
</tr>
<tr>
<td>1 y After Reimplantation</td>
<td>22.2 (8-43)</td>
<td>534 (0-1500)</td>
<td>76 (30-90)</td>
<td>2.0 (0.9)</td>
</tr>
</tbody>
</table>

Table 2. Talairach Coordinates (x, y, and z) of the Electrode Contacts Used for Long-term Stimulation and Distance (Δx, Δy, and Δz) Between the Center of the Electrode Contacts Before Reimplantation and 1 Year After Reimplantation

<table>
<thead>
<tr>
<th>Patient No./Side</th>
<th>Time</th>
<th>x (Anteroposterior)</th>
<th>y (Lateral)</th>
<th>z (Vertical)</th>
<th>Δx</th>
<th>Δy</th>
<th>Δz</th>
<th>Distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/Right</td>
<td>Before</td>
<td>5.36</td>
<td>−9.88</td>
<td>1.99</td>
<td>0.85</td>
<td>2.91</td>
<td>0.36</td>
<td>3.05</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.97</td>
<td>−12.79</td>
<td>−1.40</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1/Left</td>
<td>Before</td>
<td>4.73</td>
<td>0.90</td>
<td>0.13</td>
<td>−0.49</td>
<td>−2.85</td>
<td>−0.11</td>
<td>2.89</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.95</td>
<td>11.84</td>
<td>−1.65</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2/Right</td>
<td>Before</td>
<td>3.47</td>
<td>−6.62</td>
<td>−2.17</td>
<td>−1.74</td>
<td>4.34</td>
<td>0.31</td>
<td>4.68</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.24</td>
<td>−13.96</td>
<td>−0.73</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>3/Left</td>
<td>Before</td>
<td>6.31</td>
<td>8.04</td>
<td>−0.34</td>
<td>1.77</td>
<td>−3.82</td>
<td>0.08</td>
<td>4.22</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>5.46</td>
<td>11.86</td>
<td>−0.69</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>4/Right</td>
<td>Before</td>
<td>1.77</td>
<td>−8.97</td>
<td>−4.94</td>
<td>−6.10</td>
<td>3.37</td>
<td>3.30</td>
<td>7.71</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.84</td>
<td>−12.34</td>
<td>−0.61</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>4/Left</td>
<td>Before</td>
<td>3.10</td>
<td>5.91</td>
<td>−6.69</td>
<td>−6.04</td>
<td>−7.63</td>
<td>3.80</td>
<td>10.45</td>
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<tr>
<td></td>
<td>After</td>
<td>6.14</td>
<td>13.54</td>
<td>−1.65</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>5/Right</td>
<td>Before</td>
<td>3.74</td>
<td>−12.52</td>
<td>−2.34</td>
<td>−4.41</td>
<td>0.88</td>
<td>0.61</td>
<td>4.54</td>
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<tr>
<td></td>
<td>After</td>
<td>5.71</td>
<td>−13.40</td>
<td>−1.23</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>5/Left</td>
<td>Before</td>
<td>1.63</td>
<td>7.23</td>
<td>−1.91</td>
<td>−8.80</td>
<td>−4.13</td>
<td>1.29</td>
<td>9.81</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>5.57</td>
<td>11.36</td>
<td>−0.74</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6/Left</td>
<td>Before</td>
<td>4.18</td>
<td>9.27</td>
<td>−2.46</td>
<td>−1.77</td>
<td>−2.37</td>
<td>0.27</td>
<td>2.97</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.94</td>
<td>11.64</td>
<td>−1.26</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>7/Right</td>
<td>Before</td>
<td>5.46</td>
<td>−11.92</td>
<td>−1.08</td>
<td>1.27</td>
<td>5.22</td>
<td>0.16</td>
<td>5.37</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.91</td>
<td>−17.14</td>
<td>−2.06</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>7/Left</td>
<td>Before</td>
<td>5.17</td>
<td>10.67</td>
<td>−1.35</td>
<td>−0.75</td>
<td>−4.96</td>
<td>0.11</td>
<td>5.01</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>5.50</td>
<td>15.83</td>
<td>−0.14</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Overall mean (SD)</td>
<td>...</td>
<td>−2.38 (3.47)</td>
<td>−0.82 (4.33)</td>
<td>0.93 (1.35)</td>
<td>5.52 (2.66)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
term stimulation because of an indicated lack of benefit, while 3 electrodes were used with bipolar stimulation and 1 with tripolar stimulation. One year after reimplantation, all electrodes were operational, 13 as single monopolar contacts, with the other one used for monopolar stimulation of 2 adjacent contacts. After reimplantation, there was an increase in the threshold voltage for the first induced adverse effect from the contact used for long-term stimulation (Table 3). In general, the only adverse effect of reimplantation was transient postoperative infection necessitating removal of the stimulator and extension lead, followed by reimplantation 2 months later with no sequelae. The improvement in the UPDRS motor score from STN reimplantation correlated with the distance between the center of the electrode contact and the TET (Figure 2), with closer proximity of the contact to the target associated with more effective stimulation, resulting in greater reduction of the motor score.

COMMENT

A prospective 1-year follow-up analysis is presented of 7 patients with PD who were operated on for reimplantation of suspected misplaced electrodes used for long-term stimulation of the STN following poor results after initial surgery. In all but a single patient, the second operation improved the motor score and the Schwab and England score and permitted a reduction of the LEDD. The threshold voltage of stimulation inducing an adverse effect increased, and the reimplanted electrodes were situated closer to the TET. The UPDRS motor score under off-medication on-stimulation condition decreased in parallel with the distance between the electrode contact in use and the TET. Bilateral STN stimulation is considered the surgical therapy of choice for PD. However, some patients have little or no clinical relief from the cardinal motor symptoms, including levodopa-induced dyskinesias and fluctuations. A response to stimulation far weaker than that to levodopa 1 year after the initial surgery may be considered a failure of STN stimulation because preoperative levodopa responsiveness of the motor score has been reported to be predictive of postsurgical improvement. The reasons for STN stimulation suboptimal responses should be examined and may be related to 1 or more of the following: patient selection, precision of electrode placement, and postoperative follow-up. A study described 41 patients who were operated on consecutively and who exhibited suboptimal results. Lack of symptomatic relief was associated with inadequate preoperative screening, including the absence of neuropsychological testing (34%) and misdiagnosis by a practitioner not specializing in movement disorders (27%). In the present study, all patients were selected for initial implantation at experienced centers with interdisciplinary approaches. The 7 patients satisfied necessary criteria, had no reason to be excluded from the study, and exhibited good responses to levodopa treatment.

Although appropriate patient selection is important for the desired surgical outcome, the key to marked improvement following STN stimulation is optimal surgical technique for precise implantation of stimulation electrodes in the target. Although neurosurgeons aim to minimize shifts from the originally planned electrode positions, this does not exclude the possibility that inadequate surgical technique may be responsible for postoperative lack of benefit. No consensus exists regarding technique or surgical procedure, and those used are particularly complex. Whether ventriculography is necessary or MR imaging is sufficient is a controversial issue, as well as the use of microelectrode recording. The neurosurgical procedure used by our group aims to decrease imprecision of targeting by adding several methods such as teleradiography, microrecording through 5 parallel microelectrodes, and microstimulation with careful examination of stimulation-induced beneficial and adverse effects. This enables x-ray visualization of the electrodes with minimal parallax error and no magnetic artifact relative to the AC-PC line. The position of the electrode contacts can be obtained by superimposing the final intraoperative teleradiograph on the preoperative MR image. So, it is possible to achieve localization of the STN within millimeters and to implant electrodes as close as possible to the TET, with closer proximity to the TET associated with better results.
Our results support the interest in using the TET for STN targeting, with the Cartesian coordinates of the target being calculated with great accuracy from data acquired among many patients with PD who gained benefit from STN stimulation. In a retrospective analysis of 41 patients with STN stimulation failure, Okun et al reported 46% electrode misplacement. Despite our procedural analysis, 1 patient among 7 in our study had unexplained poor results from STN stimulation after reimplantation, while another patient (despite statistical targeting) had a misplaced electrode following initial surgery at our center because of the STN being situated in a more lateral position than our statistical target. The second operation comprised electrode implantation closer to the STN target as visualized on MR imaging and successfully improved the outcome, although (intriguingly) the distance between the contact and the TET had increased. Unusual STN position examples such as this one highlight the interest in MR imaging and intraoperative electrophysiologic methods.

In our study, the final pulse width was narrower and the frequency was lower than the initial ones, while the voltage thresholds for induction of adverse effects and the applied potentials for long-term stimulation were higher than before reimplantation. Electrode placements closer to the TET are one of the causes of these effects. This possibility of increasing the voltage broadened the therapeutic window and, consequently, the percentage improvement in the UPDRS motor score. Subthalamic nucleus stimulation is known to be a safe procedure with low permanent morbidity. In our study, no permanent morbidity and 1 transient adverse event was noted following reimplantation.

We have reported that the proximity between the contact for stimulation and the STN target correlated with STN stimulation efficacy. Therefore, for well-selected and levodopa-responsive patients with poor results following STN stimulation and with suspected electrode misplacement on imaging, reimplantation closer to the TET should be considered. However, there will remain rare patients for whom no clear explanation is found for poor results of the STN stimulation technique.

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Author Contributions: Dr Anheim had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Anheim, Silem, and Pollak. Acquisition of data: Anheim, Batir, Fraix, Chabardes, Krack, and Benabid. Analysis and interpretation of data: Anheim, Batir, Chabardes, Seigneuret, Krack, and Benabid. Drafting of the manuscript: Anheim, Batir, and Silem. Critical revision of the manuscript for important intellectual content: Anheim, Fraix, Chabardes, Seigneuret, Krack, Benabid, and Pollak. Statistical analysis: Batir. Obtained funding: Benabid. Administrative, technical, and material support: Anheim, Silem, Chabardes, Benabid, and Pollak. Study supervision: Chabardes, Seigneuret, Benabid, and Pollak.
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