Subthalamotomy for advanced Parkinson disease

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Object. The aim of this study was to determine if subthalamotomy is effective in treating advanced Parkinson disease (PD).

Methods. The authors performed microelectrode mapping–guided stereotactic surgery on the subthalamic nucleus in eight patients with PD. Lesioning was performed using radiofrequency heat coagulation and confirmed with magnetic resonance imaging. Three patients who underwent unilateral and four with bilateral subthalamotomy were evaluated for up to 18 months according to the Unified PD Rating Scale (UPDRS). One patient who underwent unilateral subthalamotomy died 6 months postsurgery.

At 3 months into the “off” period after surgery, there were significant improvements in contralateral bradykinesia (p < 0.0002), rigidity (p < 0.0001), tremor (p < 0.01), axial motor features (p < 0.02), gait (p < 0.03), postural stability (p < 0.03), total UPDRS scores (p < 0.05), and Schwab and England scores (p < 0.04). The benefits were sustained at 6, 12, and 18 months, except for the improvement in tremor. At 12 months into the “on” period, significant benefits were present for motor fluctuation (p < 0.04), on dyskinesia (p < 0.006), off duration (p < 0.05), total UPDRS score (p < 0.02), and contralateral tremor (p < 0.05). Benefits for motor fluctuation, off duration, and off-period tremor were lost after the 18-month follow-up period. The levodopa requirement was reduced by 66% for the unilateral and 38% for the bilaterally treated group. Bilateral subthalamotomy offered more benefits than did unilateral surgery for various parkinsonian features in both the on and off periods. Three patients suffered hemiballismus, two recovered spontaneously, and one died of aspiration pneumonia after discontinuation of levodopa.

Conclusions. These findings indicate that subthalamotomy can ameliorate the cardinal symptoms of PD, reduce the dosage of levodopa, diminish complications of the drug therapy, and improve the quality of life.

KEY WORDS • Parkinson disease • hemiballismus • subthalamotomy • ablative therapy • subthalamic nucleus • microelectrode

In the advanced stage of PD, drug-related complications such as dyskinesia, psychosis, and unpredictable motor fluctuations become difficult management problems. Several stereotactic neurosurgical targets have been investigated for potential therapeutic interventions in advanced PD refractory to medical treatment. In the early 1990s, PVP for advanced PD was found to be helpful in eliminating some of these complications,5,19,20,22 especially dyskinesia. Nevertheless, PVP has its limitations, because bilateral surgery may produce serious speech disturbances. Furthermore, PVP does not have the benefit of reducing levodopa dosage, as does STN surgery.27 With advances in stereotactically guided functional neurosurgery, targeting the STN has become easier and it has been advocated as a better choice than PVP.17

Although the size of the STN is small, there are reciprocal connections with the cortex, striatum, thalamus, and brainstem. The outputs of the STN project to the GPI, the SNr,1,29,36 and the pedunculopontine nucleus.28 The STN receives inputs from the globus pallidus externus, cortex, and thalamus.1,28,29,36 With such vast connections, the STN exerts significant influence on the basal ganglia. Hyperactive STN neurons were found in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–treated primates35 and confirmed in patients with PD.15 A current pathophysiological model of PD raises the possibility that a hyperactive STN is the culprit that is largely responsible for PD symptomatology.1,29,36

In primates, lesioning of the STN reversed parkinsonian symptoms caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.7 Inactivation of the STN by the injection of γ-aminobutyric acid agonists directly into it,8 or by high-frequency electrical stimulation inside it,9 improved the symptoms of parkinsonism in primates. Thus, the STN is an effective target for neurosurgical interventions for parkinsonism.1,4,7

Although DBS of the STN has been generally favored in patients with PD,15 ablation of the STN may represent a safe, technically feasible, and less costly alternative.2,3,4,33 Using FDG-PET scans obtained after unilateral STN ablation in six patients, Su, et al.,32 found a highly significant reduction in glucose utilization in the ipsilateral SNr, GPI,pons, and ventral thalamus. In the lesioned hemisphere, the PD-related regional metabolic covariance pattern declined significantly after surgery, but it was unaltered in the con-
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Clinical Material and Methods

Eight patients with advanced PD (mean age 61 years, mean disease duration 11 years) underwent unilateral subthalamotomy. The diagnosis was made in the absence of a history of known causes of PD, such as encephalitis or vascular infarction. None of the patients had dementia, gaze abnormalities, incontinence, or ataxia, which might suggest a PD-plus syndrome such as progressive supranuclear palsy. All patients had responded well to levodopa early in the course of their disease but currently suffered from complications of levodopa therapy, with unpredictable motor fluctuations, shortening of drug efficacy, or dyskinesia refractory to medical management.

Patients underwent FDG-PET studies before their first STN surgery. Additionally, all patients underwent neuropsychological testing. Only patients without dementia and who demonstrated hyperactivity in the basal ganglia on FDG-PET scans were accepted for surgery. Patients were considered for unilateral subthalamotomy if they had severe disabling rigidity, tremor, or akinesia refractory to medical management and/or severe motor fluctuations or disabling dyskinesias. The STN contralateral to the more clinically affected side was selected for surgery. All patients understood the nature of the risks involved and gave informed consent. Staged subthalamotomy was performed on the other side in four of the eight patients 4 to 6 months after their first STN surgery (Cases 5–8); the other four underwent only a unilateral subthalamotomy. Patients who underwent bilateral subthalamotomy have been followed for at least 12 months (three patients), and 4 months after the second operation (one patient); the three who underwent unilateral procedures and survived have been followed for 12 to 20 months. (One of the unilaterally lesioned patients had persistent hemiballismus 35 days after the subthalamotomy, later died of aspiration pneumonia, and was excluded from the analysis). The characteristics of all eight patients are listed in Table 1.

Clinical Evaluation and Data Analysis

After unilateral subthalamotomy, all seven patients were given their preoperative dosages of levodopa, and subsequent adjustments were made based on clinical need. Patients were assessed at 3, 6, 12, and 18 months postsurgery according to the Core Assessment Program for Intracerebral Transplantation with timed tests, the UPDRS, and a home diary made 1 week before each follow-up visit. The following neuropsychological tests were performed before and 9 to 12 months after surgery: Mini-Mental State Examination, Wisconsin Card Sorting Test–Short Form, Wisconsin Memory Scale, Benton Visual Retention Test, Token Test, and a verbal fluency test.

In the patients who underwent bilateral subthalamotomy, each contralateral limb was assessed separately at the scheduled time and the follow-up period was classified as such. We did this because we have found no significant effects on the ipsilateral limb after unilateral subthalamotomy. The evaluations were performed in the practically defined on and off states. Different parkinsonian symptoms were evaluated using subscores of the UPDRS III for tremor (Items 20 and 21), rigidity (Item 22), bradykinesia (Items 23–26), axial motor features (Items 18, 19, 20a, 22a, 27, 28, and 31), gait (Item 29), and postural stability (Item 30). Complications of therapy with dyskinesia (Items 32–35) and clinical fluctuations (Items 36–39) were also evaluated. Data from the 3-, 6-, 12-, and 18-month postoperative assessments were compared with preoperative values, using either the paired Student t-test or the Wilcoxon signed-rank test.

### TABLE 1

**Characteristics of eight patients with advanced PD**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (yrs), Sex</th>
<th>Dura-</th>
<th>Follow-</th>
<th>Lesion Side</th>
<th>S &amp; E†</th>
<th>Total UPDRS Score‡</th>
<th>Levodopa Dosage (mg)</th>
<th>Complications</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>58, M</td>
<td>4</td>
<td>21</td>
<td>rt</td>
<td>NA</td>
<td>50 80 60 36</td>
<td>300 0</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>64, M</td>
<td>8</td>
<td>20</td>
<td>lt</td>
<td>NA</td>
<td>40 70 107 74</td>
<td>550 300</td>
<td>small asymmetrical intracerebral hematoma</td>
</tr>
<tr>
<td>3</td>
<td>63, F</td>
<td>8</td>
<td>5</td>
<td>lt</td>
<td>NA</td>
<td>30 50 91 17</td>
<td>1000 400</td>
<td>severe rt hemiballismus for 2 mos</td>
</tr>
<tr>
<td>4</td>
<td>67, M</td>
<td>9</td>
<td>12</td>
<td>lt</td>
<td>NA</td>
<td>30 60 103 63</td>
<td>600 200</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>62, M</td>
<td>16</td>
<td>21/16</td>
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<td>30 70 86 26</td>
<td>1625 1000</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>63, F</td>
<td>10</td>
<td>20/14</td>
<td>lt</td>
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<td>30 60 90 48</td>
<td>800 600</td>
<td>none</td>
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<tr>
<td>7</td>
<td>48, F</td>
<td>15</td>
<td>19/15</td>
<td>lt</td>
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<td>30 70 57 40</td>
<td>740 300</td>
<td>rt upper-extremity ballismus for 4 wks</td>
</tr>
<tr>
<td>8</td>
<td>63, M</td>
<td>15</td>
<td>8/4</td>
<td>lt</td>
<td>NA</td>
<td>10 50 145 125</td>
<td>1500 1000</td>
<td>none</td>
</tr>
<tr>
<td>mean</td>
<td>61</td>
<td>11</td>
<td>1</td>
<td></td>
<td></td>
<td>31 66 93 59</td>
<td>874 486</td>
<td>none</td>
</tr>
</tbody>
</table>

* Months after first surgery/months after second surgery. Abbreviations: NA = not applicable; S & E = Schwab and England.
† Scores of functional independence in the worst and best conditions, according to the Schwab and England ADL scale.
‡ Composite UPDRS motor ratings obtained 12 hours after the cessation of medication (off), and the best on condition after taking medication (on).
test as appropriate. The significance level was set at a probability value of less than 0.05. Because of the exploratory nature of these analyses and the small number of patients, correction for multiple comparisons was not done.

A total equivalent levodopa dose was calculated for each patient by using the following conversion: 100 mg of standard-release levodopa was equivalent to 125 mg of sustained-release levodopa, 1 mg of pergolide, or 10 mg of bromocriptine.

**Surgical Procedure**

After overnight fasting and forgoing levodopa for a minimum of 24 hours, a CRW stereotactic frame was secured to the cranium of the patient after application of local anesthesia. A 1.5-tesla MR imager was used to produce 3-mm-thick nonoverlapping slices in the axial, sagittal, and coronal planes. Standard T1-weighted sagittal views obtained parallel to the interhemispherical fissure were used to delineate the AC and PC on a midsagittal slice. To assess the medial–lateral coordinate of AC and PC more accurately, T1-weighted axial MR images were acquired parallel to the AC–PC line. Coronal T2-weighted spin-echo images obtained perpendicular to the AC–PC line were used for direct visualization of the STN (TR 2700 msec, TE 45 and 90 msec). Occasionally, if the STN was not well visualized, we used an inversion-recovery technique (TR 3500 msec, TE 60 msec, TI 200 msec) as reported by Starr, et al.31 The MR imaging data were then transferred to a Stereoplan workstation. The AC and PC were measured either on sagittal or axial T1-weighted MR images. We calculated the length of the AC–PC line and tentatively set the STN target at 12 mm lateral, 4 mm posterior, and 4 mm ventral to the midpoint of the intercommissural line. The fiducial marker for the STN target derived by this method was then compared with the direct target visualized in the coronal plane. Often we found a discrepancy between the two methods, which was probably due to magnetic distortion. Under such circumstances, a composite STN target37 was derived from all the methods used, which enabled us to locate the STN electrophysiologically with the microelectrode on first penetration 70% of the time.

One percent xylocaine was used to infiltrate the scalp in the region of the coronal suture 3 cm from the midline on the side of surgery. A 14-mm burr hole was drilled and the dura was opened for the introduction of the microelectrodes. An X-Y microdrive assembly consisting of an adjustable-base Stepper Drive mounted on the frame of the CRW apparatus was used for both the microelectrode and lesioning electrodes. A motorized drive unit that could advance or retract the electrode in steps of 0.25 to 10 μ was connected to the Stepper Drive. The Stepper Drive, with its attached cables for the controller and amplifier, as well as the microelectrode and lesioning electrode, were gas-sterilized before use and assembled on the operating table. The head stage preamplifier was embedded inside the Stepper Drive, which was connected to the stand-alone physiological units.

**Neurophysiological Technique**

Commercially available 1- to 5-μ tungsten-tipped, disposable microelectrodes with 0.3 to 1 mΩ impedance at 1000 Hz were used to map the STN and surrounding structures in a similar fashion to the described methods.15 Single-cell action potentials were filtered and amplified through an isolated microelectrode amplifier and simultaneously recorded on the videotapes through interface and NeuroMap workstations. An audio and oscilloscope system was used to hear and view the data in real time. This provided instant analysis of the frequency and characteristics of neuronal activity.
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discharges, as well as a permanent record on tapes and hard disc. We started recording 30 mm above the proposed target, allowing an additional 5-mm perimeter beyond it. Four to five tracts were needed for satisfactory assessment of the border of the STN. The Schaltenbrand and Wahren stereotactic atlas was used to evaluate anatomical landmarks of the microelectrode trajectories. We observed neuronal responses to eye movement as well as passive and active motion of the joints once STN-like signals were seen. At least three tracts of 3.5 mm or more of the STN were identified before planning the ablation. In addition, we delineated the boundary of the corticospinal tract anterior and lateral to the STN if it had not yet been found prior to the lesioning.

Lesioning Procedure

A radiofrequency lesioning electrode with a diameter of 1.2 mm and a 3-mm exposed tip was used to create a single lesion in the STN. We aimed to ablate the dorsolateral efferent part of the STN because the lesion was typically 5 mm but some tracts contained less than 5 mm of STN. In this circumstance, we would then allow the lesion to extend 1 to 2 mm dorsal to the border of the STN. Once the tip entered the upper border of the STN, we applied a continuous 1-V, 1-msec pulse at 100 Hz and observed the clinical response. The effects on contralateral bradykinesia, tremor, and rigidity as well as side effects such as tonic muscle contraction, levator inhibition, and speech and cognitive impairment were evaluated by a neurologist. We also used low-frequency stimulation (2 Hz, 0.2-msec pulse width, 1–5 V) when involuntary muscle contraction was encountered. This was used to differentiate a capsular response from stimulation-induced dystonia. Finally, the tip was advanced to the target site as determined electrophysiologically. We proceeded to make a lesion if the following conditions were met: 1) no muscle contraction occurred in the contralateral limb; 2) contralateral tremor, rigidity, and akinesia improved; 3) no eye deviation or levator inhibition occurred; and 4) speech and cognitive function remained intact.

The initial lesion was made at 60°C for 60 seconds, and clinical monitoring was performed to assess the immediate effects. If no adverse effects were observed, higher-temperature lesioning at 75°C for 60 seconds was performed at the same target location. This resulted in a roughly 5 × 5-mm spherical lesion as seen on a postoperative MR image (Fig. 1). The MR studies were performed within 5 to 7 days postsurgery to confirm the location of the STN lesion and to estimate its volume.

Sources of Supplies and Equipment

The Signa MR imager was purchased from General Electric Medical Systems, Milwaukee, WI. The CRW stereotactic frame, the Stereoplan workstation, and the radiofrequency lesioning electrode were acquired from Radionics, Inc., Burlington, MA. The adjustable-base Stepper Drive, the motorized drive unit (TMS Controller), the disposable microelectrodes, and the microelectrode amplifier were all obtained from FHC, Inc., Bowdoinham, ME. The interface workstation was purchased from Neuro Data Instruments Corp., New York, NY, and the NeuroMap workstation was supplied by Radionics Software Applications, Inc., Burlington, MA.

Results

Significant improvement was seen in the contralateral rigidity, tremor, and bradykinesia while the patient was still on the operating table, and it persisted throughout the follow-up period. We also observed immediate but less robust improvement postsurgery in the bradykinesia of the ipsilateral lower limb but not in the upper limb. Nonetheless, the ipsilateral benefits lasted less than 3 months. At the 3-month evaluation postsurgery, ipsilateral rigidity was 4.5 ± 1.9 compared with presurgical values of 5.5 ± 2.4 (p > 0.05); ipsilateral tremor was 2.6 ± 3.3 compared with presurgical values of 3.2 ± 3.8 (p > 0.4); and ipsilateral bradykinesia was 11 ± 3.4 compared with presurgical values of 11.8 ± 3.8 (p > 0.07).

Contralateral bradykinesia, rigidity, and tremor improved 37% (p < 0.0002), 56% (p < 0.0001), and 63% (p < 0.003), respectively, in the off period at 3 months postsurgery. The benefits were sustained throughout the 18-month follow-up period for bradykinesia and rigidity, but not for tremor. Five patients with contralateral tremor improved markedly even off medication during the first 3 months postsurgery (p < 0.003). There was decline in benefits after 6 months, however (p < 0.02), and by 12 (p > 0.06) and 18 months (p > 0.8) no statistical significance was noted during the off state. During the on state, contralateral tremor was significantly ameliorated from 3 months (p < 0.02) up to 12 months (p < 0.04). Figure 2 shows the improvement in contralateral tremor and bradykinesia in the on and off states at the different evaluation periods. During the on state there was also significant improvement in rigidity, tremor, and bradykinesia in the contralateral limbs from 3 to 18 months (see Table 2). The percentage of improvement from the off to the on state was 62% for rigidity, 71% for tremor, and 48% for bradykinesia at 12 months of follow up. Preoperatively, the percentage of improvement from off to on was 29% for rigidity, 40% for tremor, and 30% for bradykinesia.

Axial motor features, including speech, facial expression, facial tremor, neck rigidity, ability to rise from a chair, posture, and body bradykinesia improved by 30% (p < 0.01),
Effects of subthalamotomy on parkinsonian features in seven patients

Table 2

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score Range</th>
<th>Off-Period Score (mean ± SD, % improved)</th>
<th>On-Period Score (mean ± SD, % improved)</th>
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<tbody>
<tr>
<td></td>
<td>Preop</td>
<td>6 Mos</td>
<td>12 Mos</td>
</tr>
<tr>
<td>total score</td>
<td>0–160</td>
<td>92.6 ± 30.1</td>
<td>66.3 ± 18.4, 28†</td>
</tr>
<tr>
<td>ADL</td>
<td>0–52</td>
<td>25.4 ± 10.1</td>
<td>16.7 ± 5.3, 34†</td>
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<td>motor score</td>
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<td>67.1 ± 20.8</td>
<td>49.6 ± 14.9, 26†</td>
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<tr>
<td>S &amp; E level</td>
<td>0–100</td>
<td>37.1 ± 19.8</td>
<td>51.4 ± 19.5, 38†</td>
</tr>
<tr>
<td>gait</td>
<td>0–4</td>
<td>3.0 ± 0.8</td>
<td>2.3 ± 0.8, 24†</td>
</tr>
<tr>
<td>axial motor</td>
<td>0–28</td>
<td>14.9 ± 7.1</td>
<td>9.9 ± 3.8, 34†</td>
</tr>
<tr>
<td>postural stability</td>
<td>0–4</td>
<td>3.3 ± 0.8</td>
<td>2.1 ± 0.9, 35</td>
</tr>
<tr>
<td>contralat bra-</td>
<td>0–16</td>
<td>11.8 ± 3.4</td>
<td>7.1 ± 3.7, 45†</td>
</tr>
</tbody>
</table>
dykiniesia
| rigidity         | 0–8         | 6.4 ± 2.0 | 3.0 ± 2.2, 57‡ | 2.3 ± 1.5, 63‡ | 3.7 ± 0.5, 42† | 4.5 ± 2.2 | 2.1 ± 1.8, 62† | 1.0 ± 1.1, 80† | 1.0 ± 1.1, 78† |
| tremor           | 0–12        | 5.2 ± 5.0 | 2.0 ± 2.4, 65† | 2.3 ± 3.0, 54 | 3.5 ± 2.9, 32 | 3.1 ± 3.3 | 0.9 ± 1.4, 74† | 0.7 ± 1.3, 78† | 0.5 ± 1.2, 84† |

*See Table 1 for definition of off and on periods and Fig. 3 for definition of percentage of clinical improvement. Abbreviations: SD = standard deviation; % improved = percentage of clinical improvement.

† p < 0.05 and > 0.01.

‡ p < 0.01 and > 0.001.

34% (p < 0.04), 47% (p < 0.03), and 48% (p < 0.04) at 3, 6, 12, and 18 months, respectively, in the off period. Four patients with staged bilateral surgery were counted according to the date of their initial unilateral surgery. This might account for the higher percentage of improvement in the 12- and 18-month evaluations, because the second surgeries were performed 4 to 6 months after the first one. There were no significant benefits achieved during the on state with regard to axial motor features (p > 0.16). The benefits for gait and postural stability were significant only during the off and not in the on state. Figure 3 illustrates the effects of surgery on different items on the UPDRS in the off state at various time points.

The total UPDRS scores (UPDRS II and III) improved 30% in the off state (p < 0.006) and 35% in the on state (p < 0.02) at 3 months, and they remained improved at 6, 12, and 18 months (p < 0.02 for each period). The ADL scores (UPDRS II) and the total motor scores (UPDRS III) improved significantly at each follow-up visit from 3 to 18 months in the on and off states (p < 0.005 to p < 0.05).

Compatible with such an improvement, the Schwab and England level of independence during the off state at various assessment periods. Three patients who needed assistance for one or more ADL preoperatively became independent after subthalomotomy and remained independent at the last follow-up visit.

Neuropsychological tests conducted before and 9 to 12 months after surgery were available in one of the unilaterally and three of the bilaterally treated patients. Data in three bilaterally treated patients showed no significant change in the Mini-Mental State Examination (mean 10.9%, p > 0.09), Wisconsin Memory Scale (mean −10.1%, p > 0.08), verbal fluency scores (mean −6.9%, p > 0.29), Wisconsin Card Sorting Test–Short Form perseverative errors (mean 7.6%, p > 0.42), Token Test (mean −7.8%, p > 0.09), or Benton Visual Retention Test results (mean 6.7%, p > 0.42).

In the off state, the pronation and supination and finger dexterity test results improved 34 and 31%, respectively, at 3 months (p < 0.002). The benefits remained significantly present at 6 (p < 0.002) and 12 months (p < 0.001). Results of the stand-walk-sit test were also significantly improved at 3, 6, and 12 months (p < 0.01 at each time point). Ipsilateral timed tests did not show improvement at 3 months for the pronation and supination (p > 0.49) or finger dexterity tests (p > 0.73). Table 3 shows the effects of unilateral subthalomotomy on several timed tests during the off period.

At 3 months, drug-induced dyskinesias were reduced 75% (p < 0.01) in four patients who had suffered from them preoperatively. The benefits were maintained at 6 (p < 0.01), 12 (p < 0.006), and 18 months (p < 0.03). Three of four patients with bilateral on-period dyskinesias...
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reported no further contralateral or ipsilateral dyskinesia, even though their levodopa dosage was kept at preoperative levels for a period of up to 3 months postsurgery. One patient who had complete cessation of dyskinesia in the first 12 months experienced the return of milder and nondisabling unilateral dyskinesia at 18 months. Five patients who had suffered painful early morning dystonia preoperatively reported complete relief of the symptoms after surgery and remained free of painful dystonia throughout the follow-up period.

The duration of the off period was reduced 86% at 3 months (p < 0.003), and the benefits remained significantly improved at 6 (p < 0.0004) and 12 months (p < 0.01), but not at 18 months (p < 0.09), as judged by UPDRS Item 39. Significantly less on/off fluctuation as defined by UPDRS Items 36 to 38 was seen at 3 (p < 0.02), 6 (p < 0.01), and 12 months (p < 0.04). The benefits did not last in the longer postsurgical period, however, and by 18 months (p < 0.12), they became statistically nonsignificant. Figure 4 shows the scores for motor fluctuation and off duration after surgery at different time points.

The three patients with unilateral subthalamotomy were grouped together to compare them with the four patients with bilateral subthalamotomy. Additional improvements in PD features were seen after the second surgery in the bilateral group. Off-state improvement in the axial motor features, gait, and total motor scores was 24, 29, and 23%, respectively, at 12 months for the unilateral compared with the bilateral group, which showed improvement of 50, 52, and 59%, respectively. Table 4 illustrates the additional benefits in the bilateral group. Figure 5 illustrates the evolution over time in total UPDRS scores, axial motor features, and levodopa usage for each patient in the bilateral group. Benefits were seen after the first operation and further improvement was seen after surgery on the contralateral STN.

In the patients as a group, the mean dosage of levodopa was 874 mg before surgery and 486 mg at the last evaluation, a 44% reduction. Table 1 shows the levodopa dosage of each individual before and after surgery. In the unilaterally treated group, the mean dosage was 483 mg before surgery and 167 mg at the last evaluation, a reduction of 66%. In the bilateral group, the mean dosage was 1167 mg before surgery and 725 mg at the last evaluation, a reduction of 38%. Two of the three unilaterally treated patients had predominantly tremor with good response to levodopa after subthalamotomy. This might account for the greater reduction in the unilateral than in the bilateral group.

### Postoperative Complications

Hemiballismus occurred in three patients after 12 subthalamotomy procedures (25%), and one died. Measured 5 to 7 days after surgery, the group with hemiballismus had a mean lesion volume of 180 mm³, in contrast with the mean lesion volume in the five operations that did not result in hemiballismus, which measured 100 mm³. This difference was not statistically significant (p > 0.38). The patient in Case 7 (see Table 1) developed a mild choreic movement of the upper extremity 3 days after left subthalamotomy. Her lesion volume, measured 6 days after surgery, was 80 mm³; the lesion was located at the dorsolateral STN extending into the zona inserta. She recovered in 4 weeks without

### TABLE 3

<table>
<thead>
<tr>
<th>Test</th>
<th>Preop</th>
<th>3 Mos</th>
<th>6 Mos</th>
<th>12 Mos</th>
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<tr>
<td>stand-walk-sit†</td>
<td>70 ± 31</td>
<td>33 ± 12‡</td>
<td>26 ± 10‡</td>
<td>30 ± 11‡</td>
</tr>
<tr>
<td>contralat pronation &amp; supination§</td>
<td>33 ± 9</td>
<td>22 ± 5§</td>
<td>21 ± 6*</td>
<td>21 ± 6*</td>
</tr>
<tr>
<td>contralat finger dexterity</td>
<td>38 ± 10</td>
<td>26 ± 5‡</td>
<td>25 ± 5‡</td>
<td>26 ± 5‡</td>
</tr>
<tr>
<td>ipsilat pronation &amp; supination§</td>
<td>26 ± 7</td>
<td>27 ± 4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ipsilat finger dexterity</td>
<td>29 ± 7</td>
<td>23 ± 7</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SD in seconds. Abbreviation: — = not done.
† Starting with the patient seated in a chair, the time required to stand, walk 23 feet, turn, walk back to the chair, and sit down.
‡ p < 0.01, according to paired Student t-tests, presurgery compared with postsurgery.
§ Twenty successive cycles of complete contact of the palmar and dorsal surfaces of the hand with the knee.
¶ Performed by tapping the thumb with each finger 10 times in rapid succession.

TABLE 4

Comparison of various PD features in the unilaterally and bilaterally treated groups at 12 months postsurgery*

<table>
<thead>
<tr>
<th>Score</th>
<th>Off-Period Score (% improved)</th>
<th>On-Period Score (% improved)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilat</td>
<td>Bilat</td>
</tr>
<tr>
<td>axial motor†</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>gait</td>
<td>29</td>
<td>52</td>
</tr>
<tr>
<td>UPDRS total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II (motor)</td>
<td>25</td>
<td>56</td>
</tr>
<tr>
<td>II (ADL)</td>
<td>23</td>
<td>59</td>
</tr>
<tr>
<td>S &amp; E (ADL)</td>
<td>32</td>
<td>49</td>
</tr>
</tbody>
</table>

* Percentage of clinical improvement and the off and on periods are defined in Fig. 3 and Table 1, respectively. In this table, UPDRS scores were obtained before surgery and 12 months postsoperatively.
† Axial motor score consists of speech, facial expression, neck rigidity, facial tremor, ability to rise from chair, posture, and body bradykinesia.

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treatment. Her evaluation at 12 months during the off period revealed normal function of the right upper extremity with no dyskinesia, rigidity, or bradykinesia.

The patient in Case 4 had a lesion volume of 140 mm$^3$ involving all of the lateral STN, and he was noted to have extensive edema in the midbrain 5 days after left subthalamotomy. Three days after the procedure he developed severe disabling right hemiballismus, which lasted for 2 months. An MR image obtained 53 days postoperatively revealed that the lesion was located at the dorsolateral STN; the lesion volume was 40 mm$^3$. At the 6-month evaluation in the off period, there was a 75% improvement compared with presurgical scores in terms of right bradykinesia, rigidity, and tremor. At that time, he was leading an independent life without medication.

The patient in Case 3 had a lesion volume of 140 mm$^3$ involving all of the lateral STN, and he was noted to have extensive edema in the midbrain 5 days after left subthalamotomy. Three days after the procedure he developed severe disabling right hemiballismus, which lasted for 2 months. An MR image obtained 53 days postoperatively revealed that the lesion was located at the dorsolateral STN; the lesion volume was 40 mm$^3$. At the 6-month evaluation in the off period, there was a 75% improvement compared with presurgical scores in terms of right bradykinesia, rigidity, and tremor. At that time, he was leading an independent life without medication.

The patient in Case 3 developed right hemiballismus 35 days after left subthalamotomy. The lesion volume, measured 5 days postoperatively, was 320 mm$^3$ and involved the entire STN. For the first 4 months after the onset of hemiballismus, her involuntary movement was mild to moderate. Although she needed some assistance in ADL, she could walk on her own. Starting 5 months postoperatively, the hemiballismus became violent and disabling. An MR image obtained 150 days post-surgery revealed that the lesion volume was 60 mm$^3$ adjacent dorsolaterally to the substantia nigra. Levodopa was discontinued in an attempt to control the hemiballismus, and the patient subsequently developed aspiration pneumonia and sepsis. She died 6 months after surgery.

One patient (Case 2) had a small asymptomatic intracerebral hemorrhage in the frontal subcortical area from the needle track. None of the eight patients had impairment in eye movement or in motor, sensory, speech, or cognitive function.

**Discussion**

Our data clearly demonstrate that unilateral and bilateral subthalamotomy can ameliorate the cardinal symptoms of PD, decrease the required dosage of levodopa, and reduce the complications of therapy (dyskinesia and off duration), as well as improve the patient’s quality of life.

**Efficacy of Subthalamotomy Compared With DBS**

Unilateral subthalamotomy has effects similar to unilateral DBS of the STN. Kumar, et al.,\textsuperscript{18} reported that contralateral bradykinesia improved by 30.1%, tremor by 86.3%, and rigidity by 30.6% with unilateral DBS, whereas we report improvement in contralateral bradykinesia of 37%, tremor of 63%, and rigidity of 56% at the 3-month follow-up review. Gait improved by 29% and the axial motor score improved by 24% in our series, comparable with the data of Kumar, et al.,\textsuperscript{18} who reported a 12% improvement for gait and an 18.6% improvement for axial motor score after unilateral DBS of the STN. Bilateral subthalamotomy had a greater effect than unilateral surgery. In our series, during the off state, total UPDRS scores improved 56% for bilateral and 25% for unilateral procedures. In the series reported by Kumar, et al.,\textsuperscript{18} DBS of the STN improved total UPDRS scores by 54% for bilateral and by 23% for unilateral stimulation. In other series,\textsuperscript{24,27} similar degrees of improvement were reported for bilateral DBS. Our data also showed significant improvements in all aspects of parkinsonian features after subthalamotomy while patients were on levodopa, except in gait, postural stability, and axial motor function.

**Long-Term Clinical Benefits**

Except for tremor, all cardinal symptoms of parkinsonism improved significantly after subthalamotomy during the off period, and the benefits were sustained throughout the 18-month evaluation period. The postsurgical improvements in the complications of drug therapy, that is, motor fluctuation and off duration, were significant between 3 and 12 months but returned to nonsignificance at 18 months. Contralateral tremor was markedly improved in the immediate postoperative off period, but the benefits were not sustained at 12 months. Even though the off-period benefits for tremor were lost, the patients were quite satisfied with the excellent response of tremor to levodopa. This effect remained at the 18-month evaluation. It is interesting that all the patients with tremor did not experience complete relief in the on state preoperatively, but the tremors were amelio-

**Fig. 5.** Graphs showing evolution of total UPDRS scores (upper), axial motor features (center), and levodopa dosages (lower) in each patient in the bilaterally treated group after first and second surgeries. Arrow or asterisk indicates second, contralateral surgery. See Fig. 3 for explanations of axial motor features and percentage of improvement.
Unilateral and bilateral subthalamotomy for advanced PD

rated by levodopa after subthalamotomy, a similar observation to that made by Alvarez, et al. In previous FDG-PET studies, PD is associated with the presence of a specific abnormal metabolic brain network. This PD-related regional covariance pattern is characterized by pallidothalamic and pontine hypermetabolism associated with relative metabolic decrements in cortical motor regions. Expression of the PD-related regional covariance pattern is abnormally increased in multiple populations of unmedicated patients with PD and correlates consistently with independent clinical measures of disease severity. Significant declines in PD-related regional covariance pattern activity in response to effective medical and surgical antiparkinsonian therapy were reported. Loss of benefit observed during long-term follow-up evaluations after unilateral pallidotomy has been well documented. In our series, we have observed deterioration in the benefits achieved in motor fluctuation, off duration, and off-state tremor within 12 to 18 months postsurgery. The mechanism is not fully understood. Studies such as FDG-PET scanning in the patients who undergo subthalamotomy or pallidotomy both in the short and long term might be useful to investigate the mechanism of lost benefits. It is possible that subthalamotomy does not prevent the reemergence of complications of levodopa treatment in the long term or does not halt the progression of the disease. Less optimal lesion sitting in the pallidotomy is unlikely to be due to the small size of the STN. We studied FDG-PET scans obtained at different postoperative periods in six patients with unilateral subthalamotomy, and the pattern of changes at 3 months and 12 months (unpublished data) was quite different. Plasticity of brain function might be responsible for some loss of benefits.

Levodopa Dosage

Our data document that unilateral and bilateral subthalamotomy have the advantage of reducing the required levodopa dosage. Alvarez, et al., purposely kept the dosage of levodopa the same for 12 months after unilateral subthalamotomy except in one patient who discontinued medication at 6 months without losing the benefits of surgery. After 12 months, five patients in the series reported by Alvarez, et al., reduced the dosage of levodopa by 59%, a figure similar to the 66% reduction in the levodopa dosage in our bilaterally treated group. Our bilaterally treated group had a 38% reduction in medication dosage, which was comparable with the 40 to 60% reduction seen in the bilateral STN stimulation. In our series, the bilaterally treated group had more advanced disease and required more levodopa treatment (Table 1). This might account for the discrepancy between the two groups.

Drug-Induced Dyskinesia

We created a 5 × 5-mm lesion in the STN by using the procedure described. The lesion involved part of the STN but also the pallidofugal fibers, which adjoin the dorsal surface of the STN. Lesioning of the pallidofugal fibers will interrupt the pallidal outflow coursing through the lenticular fasciculus and the ansa lenticularis. This has the effect of a pallidotomy, which might explain the dramatic effects on drug-induced dyskinesia seen in our series. We observed the complete elimination of bilateral on-state dyskinesia, even with unilateral subthalamotomy. The benefits were sustained throughout 18 months of follow up. We cannot rule out the reduced levodopa dosage might have contributed to this effect.

Incidence of Hemiballismus

One of the dreaded side effects from the destruction of the STN is the creation of hemiballismus. Gill and Heywood reported that three of their 21 patients experienced hemiballismus after subthalamotomy. Alvarez, et al., reported that in one of 11 patients with unilateral subthalamotomy persistent hemiballismus occurred, and a secondary pallidotomy was required. Overall, the incidence of hemiballismus from lesioning of the STN appears small according to the literature; the total reported cases were fewer than 50.

To develop hemiballismus in normal monkeys, Carpenter, et al., showed that more than 20% of the STN had to be destroyed, and that the lesions should not extend into adjacent structures. In advanced PD, the STN neurons are hyperactive, with a discharge rate of 37 ± 17 Hz, which is twice the rate in normal monkeys (19 Hz). The threshold for producing hemiballismus by lesioning part of the STN in patients with PD would be more than 20% of its size. If a lesion in the STN extended outside the boundary dorsally to involve pallidofugal fibers, one would expect a low incidence of hemiballismus, as proposed by Lozano. Two of three patients with hemiballismus in our series recovered completely after 1 to 2 months, although the factors leading to their recovery remain uncertain. Lang found that hemiballismus resulting from a vascular infarct could resolve if the lesion was confined to the STN, but not if the lesion extended outside this structure. For the patient who died of aspiration pneumonia, we probably should have performed pallidotomy after 2 months of persistent hemiballismus as Alvarez, et al., did. Further studies of the factors leading to hemiballismus and its spontaneous solution, as well as larger series of patients, will be necessary before subthalamotomy can be recommended for widespread use. For the time being, subthalamotomy remains an experimental procedure but a viable therapeutic option for patients in the areas where DBS is not appropriate.

Conclusions

Unilateral or bilateral subthalamotomy results in moderate improvement in all aspects of parkinsonian features, and it also reduces the required dosage of levodopa and improves the quality of life. Drug-induced dyskinesia is remarkably ameliorated after surgery, similar to the improvements seen after pallidotomy. The benefits from surgery are sustained up to the last assessment performed at 18 months. At follow-up reviews performed 12 months or more postsurgery, some loss of improvement is noted with regard to off-state tremor, and in relation to the complications from drug therapy such as off duration and motor fluctuation. Bilateral subthalamotomy offers greater improvement than unilateral procedures, with additional benefits for the various features of parkinsonism. Hemiballismus is a serious complication occurring after subthalamotomy. Subthalamotomy should be regarded as an experimental procedure until all the factors leading to the occurrence of and recovery from hemiballismus have been clearly defined.
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References


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