Effects of Bilateral Subthalamic Stimulation on Cognitive Function in Parkinson Disease

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Background: Chronic bilateral subthalamic deep brain stimulation (STN-DBS) is known to improve motor function in patients with Parkinson disease (PD). However, the possible effects of STN-DBS on neuropsychological functions have been studied less.

Objectives: To investigate the effects of STN-DBS on neuropsychological functions in PD.

Design: Before-after trial.

Patients and Methods: Fifteen consecutive patients were assessed before and 3 months after implantation of stimulators for STN-DBS (postsurgical assessment with the stimulators switched on). Both assessments were performed with patients in a drug-free condition. The neuropsychological battery consisted of tests measuring memory and visuospatial and frontal functions.

Results: The comparison between presurgical and postsurgical performance showed a moderate deterioration in verbal memory and prefrontal and visuospatial functions, and a moderate improvement in a prefrontal task and obsessive-compulsive traits. The motor state improved in all patients.

Conclusion: Therapy with STN-DBS improves motor symptoms in PD without any clinically relevant neuropsychological deterioration.

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In the 1990s, surgical stimulation techniques were introduced to treat patients with Parkinson disease (PD) in whom pharmacological treatment failed.1 Although there is growing evidence of the beneficial effects of chronic bilateral subthalamic deep brain stimulation (STN-DBS) on PD motor symptoms,2-7 its influence on neuropsychological functions has not yet been investigated thoroughly. Although STN-DBS does not produce a global frontal deterioration,6,8 a negative effect in specific prefrontal functions (eg, phonetic verbal fluency)8,9 and verbal and visuospatial memory9 has been described. However, reports of performance on a prefrontal measure, the Trail-Making B Test, are contradictory. Although Trépanier et al8 found poorer performance, Ardouin et al8 found improvement after STN-DBS, a discrepancy that may be due to methodological differences. For instance, in the study by Trépanier et al,8 the neuropsychological assessment was performed while patients were under the effects of levodopa, whereas in the study by Ardouin et al,8 it was performed while some patients were receiving and others were free of levodopa.

In this study, we systematically investigated the effects of bilateral STN-DBS on neuropsychological functions that have been reported to change after surgical procedures in PD, such as pallidotomy, globus pallidus internus (GPI) stimulation, subthalamotomy, and STN-DBS. To minimize the influence of changes in levodopa dosage, we compared performance before and after surgery while patients were free of medication overnight. The neuropsychological assessment performed is similar to and the group of patients are comparable with those described in a previous study of pallidotomy from our laboratory.10

In comparison with the presurgical baseline assessment, STN-DBS produced a statistically significant deterioration in performance on the RAVLT, the Line Orientation Test, phonetic and semantic verbal fluency, and the Stroop color test. A statistically significant improvement was observed in the Trail-Making B Test and MOCI scores (Table 1).

Despite these changes, few patients with normal presurgical performance demonstrated postsurgically impaired performance, according to the cutoff determined by normative scores, ie, 3 patients on the RAVLT, 2 patients on the Line Ori-
patients and methods

Unless otherwise indicated, data are given as mean ± SD.

patients

We studied 15 consecutive patients (7 men and 8 women) with advanced PD undergoing STN-DBS therapy. Inclusion criteria were age younger than 75 years and the presence of disabling motor fluctuations and drug-induced dyskinesias that were resistant to medical therapy. Exclusion criteria were the presence of dementia (scores below 25/30 on the Mini-Mental State Examination),35 major depression, or marked cerebral atrophy on results of neuroimaging studies.

Mean age of patients was 61.1 ± 8.3 years; mean age at onset of illness, 45.1 ± 9.1 years; and mean disease duration, 16.1 ± 8.3 years. Mean educational level was 7.7 ± 4.0 years. All patients were right-handed. All patients were taking levodopa, and 9 of them were also taking dopamine agonists (pergolide mesylate or ropinirole hydrochloride). The average levodopa equivalent dose was 1349.6 ± 589.2 mg/d at the time of presurgical evaluation. Electrical variables were set at a pulse width of 60 milliseconds, a frequency of stimulation of 130 Hz, and a mean voltage intensity of 3.1 ± 0.7 V. All patients gave informed consent to participate in our study.

neuropsychological assessment

The neuropsychological battery selected examined the integrity of the frontal-subcortical circuits and included tests in which scores were reported to change after current surgical procedures in PD (eg, pallidotomy, GPi stimulation, subthalamotomy, and STN-DBS). Declarative memory was evaluated by means of a version of the Rey Auditory Verbal Learning Test (RAVLT).36 We recorded the number of words learned during 5 consecutive presentations of a list of 15 words and the number of words recalled after a 20-minute delay with the interference of other tests. The percentage of words forgotten after the delay indicated long-term retention. Recognition was assessed by means of the total words correctly identified from a set of 30 (15 presented stimuli and 15 new words). To keep practice effects in memory tasks to a minimum, we used a modified version of the RAVLT in the follow-up. We randomized both versions of the RAVLT such that 50% of patients underwent assessment using one version initially, and the other 50% used the same version postoperatively. We used parallel lists of 15 nouns in each examination, following the procedure proposed by Jones-Gotman (and described by Lezak) in the presurgical and postsurgical examination of epileptic patients. Visuospatial function was evaluated using the Line Orientation Test of Benton et al.37 The subjects were instructed to estimate the inclination of each pair of lines shown on a page, taking as reference the representation on another page of 11 lines, numbered from 1 to 11, each separated by an angle of 18°. The test included a total of 30 items.

We examined prefrontal functions using the Trail-Making Test and phonetic and semantic verbal fluency tests. Patients were instructed to join the numbers from 1 to 25 in the Trail-Making A Test, and to join numbers and letters following a number-letter sequence ordered from 1-A to 13 in the Trail-Making B Test. The time taken to join the items was recorded. In the phonetic and semantic verbal fluency tests, patients had to supply as many words as they could that begin with the letter p (phonetic clue) and names of animals (semantic clue), with 1 minute for each task. The Stroop color and word-color tests were also administered. In the first, patients had to name the color of each group of crosses, whereas in the second they had to say the color in which the name of another color was printed. In both tasks, patients had to give as many correct answers as possible within 45 seconds. We also assessed the obsessive-compulsive traits using the Maudsley Obsessional Compulsive Inventory (MOCl),18 which consists of 30 sentences measuring obsessive-compulsive traits. Subjects were instructed to answer true or false.

All patients were examined before and after surgery by the same neuropsychologist (M.A.). The preoperative baseline examination was performed 3 days before implantation of stimulators, and postsurgical evaluation was performed 3 months after the operation (with the stimulators switched on). Both examinations were performed in the morning (8-9 AM), with patients free of medication for a minimum of 12 hours (overnight).

comment

This study shows that bilateral STN-DBS, which provides impressive motor benefits in patients with medically intractable PD, produces both beneficial and detrimental neuropsychological changes. In the 3-month postoperative assessment, we found deterioration on phonetic and semantic verbal fluency, Stroop color test, Schwab and England, and Activities of Daily Living scales (Table 2). Levodopa dose was postsurgically reduced by a mean of 57.9% (±34.5%), and in 3 patients, levodopa therapy was withdrawn. Neuropsychological changes did not correlate with motor changes or with clinical or demographic data.
MOTOR ASSESSMENT

Motor performance was assessed by means of a levodopa challenge, following the instructions devised by the Core Assessment Program for Intracerebral Transplantations. Clinical evaluation was performed by means of the Unified Parkinson's Disease Rating Scale version 3.0. Patients also underwent assessment using the staging system of Hoehn and Yahr,21 the rating system of Schwab and England,22 and the Activities of Daily Living Scale. These scales were administered 3 days before and 3 months after STN-DBS.

SURGICAL PROCEDURE

Antiparkinsonian medication therapy was withdrawn the night before surgery. A model-G Leksell stereotactic frame (Elekta Instruments, Inc, Atlanta, Ga) was placed with the patient under local anesthesia. Images through the region of the intercommissural line were acquired at 1-mm-thick slices obtained using cranial computed tomography. After selection of a slice with the anterior and posterior commissures, the theoretical anatomic target was placed 2 mm posterior and 5 mm ventral to the midcommissural point, and 12 mm lateral to the intercommissural line. The target was approached with an anteroposterior angle of 60° with respect to the intercommissural line and a sagittal angle of 10°. The stereotactic coordinates were calculated by means of a computer program containing a digitized brain atlas based on the atlas of Schaltenbrandt and Wahren.21

With the use of local anesthesia, a single 15-mm burr hole was made in the skull 2 cm from the midline at the coronal suture. Recording of single-unit neuronal activity was performed using neurologic registering equipment (Neurorack; TPM Servicios Medicos, Madrid, Spain). A platinum-iridium microelecrod (extended microelecrod, H-Tracc export) was inserted through the burr hole. Microelecrod recording was started 20 mm above the theoretical target and conducted using an electronic microdrive device. By means of the microelecrod recording, the discharge pattern of the neurons of the thalamus, subthalamicus, and substantia nigra pars reticularis could be identified. The sensorimotor area of the subthalamicus was distinguished by modifying neuronal activity in response to active and passive movements or palpation and light touch of individual contralateral body parts. Microstimulation within the subthalamicus (bipolar pulses at 40-80 µA, 300 Hz, and 500-1000-millisecond duration) was applied to determine the threshold for beneficial and adverse effects. A minimum of 1 and a maximum of 4 parallel exploration tracks in the parasagittal and coronal planes were needed for localization of the sensorimotor subthalamicus area and its anatomic boundaries. Brief general anesthesia was induced using intravenous propofol, 2.5 mg/kg, during the procedure, except when patient collaboration was needed.

Once the sensorimotor area of the subthalamicus was determined, an electrode for long-term stimulation (DBS 3389 electrode; Medtronic, Minneapolis, Minn) was inserted at this location. An external stimulation device connected to the stimulation electrode was then used to confirm that there were not any limiting adverse effects, such as diplopia, tonic contraction of a limb, paresthesias, dyskinesias, or vegetative symptoms, and that motor response was adequate. Cranial magnetic resonance imaging was performed in all patients immediately before lead implant to rule out hemorrhagic complications and electrode misplacement. Programmable pulse generators (titer II; Medtronic) were implanted in the subclavicular region ipsilateral to the electrode 1 week after surgery.

RAVLT, and Line Orientation Test performances, and improvement on Trail-Making B Test and MOCI scores.

The deterioration in verbal fluency and global speed of naming (measured by the Stroop color test) is consistent with the results reported by 2 other groups that performed neuropsychological assessment in patients undergoing STN-DBS. Since a loss of phonetic and/or semantic verbal fluency was also found after pallidotomy and GPi stimulation, decrease in verbal fluency seems to be an adverse effect of all of the surgical procedures presently used to treat PD.

The ANOVA analyses demonstrated a postoperative decrease in learning ability, as can be observed in the curve of the RAVLT. By contrast, immediate memory and recognition did not change. The verbal learning decline may be due to an inability to retrieve information resources. Using the same test, Crowe et al obtained similar results in a group of 13 PD patients after left-side pallidotomy, and McCarter et al reported that small lesions of the left subthalamic nucleus can produce deterioration of verbal learning. By the use of other tests, verbal memory deficits were also observed in PD patients after left-side pallidotomy and bilateral GPi stimulation, and STN-DBS. All surgical procedures involving the left or both hemispheres seem to negatively influence verbal memory. Since pallidotomy, GPi stimulation, subthalamotomy, and STN-DBS produce functional changes of the GPi and thalamus, and since these nuclei are related to memory processes (such as associative memory), changes in learning ability may be expected.

We found a deterioration in Line Orientation Test performance. Previous studies found an improvement in...
this test performance after pallidotomy. Since this is the first investigation, to our knowledge, of the effects of STN-DBS on visuospatial function, further research into this topic is required.

Our patients improved their performance on Trail-Making B Test after surgery, suggesting a specific positive effect of STN-DBS on dorsolateral prefrontal cortex. This finding is in accordance with the results obtained in other reports describing patients with PD after STN-DBS, GPI stimulation, and pallidotomy. The positive change in the Trail-Making Test performance could be explained by the dramatic improvement in the motor state. However, the postsurgical improvement in Trail-Making B Test performance was not statistically related to the motor improvement, and we did not find any change in Trail-Making A Test performance, which has a similar motor component.

In the present study, STN-DBS improved obsessive-compulsive traits. The effects that we found in obsessive-compulsive traits after STN-DBS are similar to those previously obtained after pallidotomy. Several surgical procedures involving the frontolimbic basal ganglia circuitry have been reported to be effective for idiopathic obsessive-compulsive disorder. These changes in obsessive-compulsive scores suggest that the subthalamic nucleus might influence limbic circuit, as suggested by Alexander et al.

The neuropsychological assessment is similar to and the group of patients in the present study are comparable with those reported in a previous study of pal-

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD) Score</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total trials</td>
<td>41.20 (8.69)</td>
<td>36.47 (10.20)</td>
<td>2.62†</td>
<td>.02</td>
</tr>
<tr>
<td>Forget, %</td>
<td>28.46 (18.87)</td>
<td>31.67 (19.07)</td>
<td>−0.52</td>
<td>.61</td>
</tr>
<tr>
<td>Recognition</td>
<td>25.93 (2.89)</td>
<td>26.60 (3.89)</td>
<td>−0.73</td>
<td>.475</td>
</tr>
<tr>
<td>Line Orientation Test</td>
<td>15.00 (6.93)</td>
<td>13.67 (7.59)</td>
<td>2.35†</td>
<td>.03</td>
</tr>
<tr>
<td>Trail-Making A Test</td>
<td>99.00 (72.06)</td>
<td>93.60 (52.95)</td>
<td>0.44</td>
<td>.67</td>
</tr>
<tr>
<td>Trail-Making B Test</td>
<td>291.58 (193.83)</td>
<td>252.33 (179.69)</td>
<td>2.44†</td>
<td>.03</td>
</tr>
<tr>
<td>Trail-Making B-A Test</td>
<td>102.00 (41.6)</td>
<td>77.33 (3.94)</td>
<td>3.32†</td>
<td>.005</td>
</tr>
<tr>
<td>Semantic verbal fluency</td>
<td>17.53 (4.47)</td>
<td>14.67 (4.86)</td>
<td>3.12†</td>
<td>.008</td>
</tr>
<tr>
<td>Phonemic verbal fluency</td>
<td>46.27 (11.42)</td>
<td>41.40 (9.37)</td>
<td>2.33†</td>
<td>.04</td>
</tr>
<tr>
<td>Word-color</td>
<td>26.54 (6.24)</td>
<td>22.85 (8.64)</td>
<td>2.16</td>
<td>.05</td>
</tr>
<tr>
<td>Interference</td>
<td>19.92 (7.36)</td>
<td>17.85 (6.08)</td>
<td>1.54</td>
<td>.15</td>
</tr>
<tr>
<td>Stroop test</td>
<td>8.40 (3.70)</td>
<td>5.47 (3.16)</td>
<td>4.11§</td>
<td>.001</td>
</tr>
</tbody>
</table>

RAVLT indicates Rey Auditory Verbal Learning Test; MOCI, Maudsley Obsessional Compulsive Inventory.
†P < .05.
‡P < .01.
§P < .005.
In this sense, the effects of levodopa on cognition are maximal alterations in these areas of cognition exist. Further implications in some patients in whom borderline presurgical alterations in these areas of cognition exist. Further research is needed to determine how to obtain maximal motor improvement with minimal neuropsychological alterations with STN-DBS.

CONCLUSIONS

Our results further support previous studies indicating that STN-DBS does not result in clinically important neuropsychological deterioration. However, the moderate decline in verbal memory and prefrontal and visuospatial functions and the improvement on a prefrontal task and of obsessive-compulsive traits could have clinical implications in some patients in whom borderline presurgical alterations in these areas of cognition exist. Further research is needed to determine how to obtain maximal motor improvement with minimal neuropsychological alterations with STN-DBS.

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