Neuropsychological functioning before and after unilateral thalamic stimulating electrode implantation in Parkinson's disease


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One theoretical advantage of chronic thalamic stimulation compared with thalamotomy for the treatment of refractory Parkinson's disease (PD) entails the avoidance and reversibility of potential cognitive morbidity. Support for the cognitive safety of thalamic stimulation remains largely anecdotal; empirical data are limited to the neuropsychological findings published for one small series of patients. The purpose of this study was to supplement those published findings that pertain to the mean changes in neuropsychological test scores and to extend previous findings by evaluating cognitive changes in individual cases from preoperative baseline to 4 months after electrode implantation. Nine patients with tremor-dominant, refractory PD underwent unilateral implantation of a deep brain stimulating electrode in the ventralis intermedius thalamic nucleus (five patients on their left and four patients on their right sides). A neuropsychological test battery was administered to each patient to evaluate attention, language, memory, and visuoperceptual and executive functions during their best "on" state before surgery, while on a medication regimen, and with the stimulator turned on after surgery. As a group, the patients attained significantly higher scores on word list recognition (discriminability) and delayed recall of prose passages after surgery than before surgery. In addition, there was a trend toward higher scores on a visual confrontation naming test after surgery. Examination of individual patient data indicated gains and losses in test scores exceeding two standard deviations to be very rare. Changes of one standard deviation were also relatively rare, but gains were more likely to occur than losses. These observations provide preliminary support for the cognitive safety of thalamic stimulation for PD.

Key Words * neuropsychology * Parkinson's disease * thalamus * electrical stimulation

Attempts to ameliorate movement disorders by neurosurgical means date to the early 1900s, but stereotactic lesioning of the ventralis lateralis (VL) nucleus of the thalamus to alleviate the motor abnormalities of Parkinson's disease (PD) was not performed until the 1950s.[20,27] The popularity of stereotactic thalamotomy waned considerably following the introduction of levodopa treatment in the 1960s, but the stereotactic neurosurgical treatment of refractory PD has experienced a recent resurgence.[21,33] Contemporaneous advances in neuroimaging, neurosurgical techniques, and scientific knowledge about basal ganglia physiology, in tandem with a growing awareness of the limitations of pharmacotherapies for parkinsonism, have catalyzed not only a renaissance of thalamotomy and
Among newer surgical therapies for refractory PD is the implantation of chronic electrical stimulating devices in a variety of targets, including the ventralis intermedius (VIM) nucleus of the thalamus,[1,2,5-8,11,14,17,32,40-42] the subthalamus,[29] and the internal globus pallidus.[40,41] Although the benefits of acute, intraoperative stimulation on motor function had been already observed during "early" thalamotomies, Andy[4] was probably the first to describe the beneficial effects of chronic electrical stimulation of a variety of thalamic nuclei (including VIM) in a small series of patients with movement disorders. Benabid and coworkers[5-7] subsequently published the first reports of the effects of VIM stimulation in a large series of patients with PD.

Ventralis intermedius stimulation has been held to be efficacious in the treatment of parkinsonian motor symptoms, particularly for tremor, and involves little or no cognitive morbidity.[1,2,5-8,11,18,32] Indeed, the apparent lack of cognitive morbidity, the creation of a smaller lesion, and the theoretical reversibility and adaptability over time of stimulation effects have been postulated to be major advantages of thalamic stimulation versus thalamotomy.[28] More specifically, although only a few studies of cognitive outcome in thalamotomy have used formal or standardized neuropsychological evaluations,[3,15,16,34,35,36,38,43,44] cognitive morbidity in early thalamotomy series has been estimated to be considerable. Burchiel[12] estimated that significant changes in memory and language might occur in up to 39% of patients who underwent thalamotomy (60% of bilateral and 31% of unilateral thalamotomy cases), although there is tentative evidence that complications assessed via neuropsychological tests might be relatively uncommon in modern thalamotomy, and indeed, that some aspects of memory might improve following unilateral VL thalamotomy.[30]

The theoretical advantage of VIM stimulation in minimizing (or, allowing for the reversal of) cognitive morbidity remains largely supported by anecdotal rather than empirical data. Only one study[13] has published formal neuropsychological evaluation data relating to thalamic stimulation in PD. In examining neuropsychological test performances in nine PD patients before and 4 to 10 days after VIM stimulating electrode implantation, Caparros-Lefebvre, et al.,[13] found no significant changes in average test scores in language, attention, memory, visuoperceptual functions, executive functions, and praxis. However, they did note that on almost all tests administered, some patients showed decrements in scores, others showed increases in scores, and yet others showed no change.[13] This raises the possibility that mean test scores mask potential cognitive declines or improvements, in that decrements in some patients' scores are offset by gains in other patients' test scores. One purpose of the present study was thus to evaluate not only potential changes in mean scores but also to address how many patients showed changes in test scores of given magnitude (that is, of one, two, or more standard deviations [SDs]). Because Caparros-Lefebvre, et al., evaluated patients relatively soon after surgery, it is possible that some individual patients' changes in test scores might represent transient changes in cognition. To determine whether potential cognitive changes persist beyond the more immediate postoperative period, we evaluated patients approximately 4 months after surgery.

**CLINICAL MATERIAL AND METHODS**

**Patient Population**

Nine of 12 patients with PD who underwent thalamic-stimulating electrode implantation at the specialty movement disorders center of an academic medical center also underwent neuropsychological evaluation
before and after stimulator implantation. One patient did not undergo neuropsychological evaluation because English was not his native language, and two patients were not evaluated because of scheduling difficulties. All patients had a diagnosis of PD based on the presence of two of three cardinal signs (tremor, rigidity, bradykinesia); all had tried dopamine agents that either failed to provide adequate symptomatic relief or produced intolerable side effects. The predominant parkinsonian symptom in all patients was tremor. Demographic and disease characteristics of the patient sample are presented in Table 1.

### Table 1: Demographic and Disease Characteristics in Nine Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>64.56 (10.54)</td>
</tr>
<tr>
<td>education</td>
<td>13.33 (1.80)</td>
</tr>
<tr>
<td>estimated verbal IQ</td>
<td>105.75 (13.42)</td>
</tr>
<tr>
<td>gender</td>
<td>8 men / 1 woman</td>
</tr>
<tr>
<td>handedness</td>
<td>9 right</td>
</tr>
<tr>
<td>age at diagnosis</td>
<td>56.56 (10.49)</td>
</tr>
<tr>
<td>disease duration (yrs)</td>
<td>8.00 (3.32)</td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td>48.89 (16.50)</td>
</tr>
<tr>
<td>history of treatment for depression</td>
<td>2</td>
</tr>
<tr>
<td>baseline surgery interval (mos)</td>
<td>0.22 (0.67)</td>
</tr>
<tr>
<td>postsurgery test interval (mos)</td>
<td>4.11 (1.27)</td>
</tr>
<tr>
<td>pre- to postsurgery test interval (mos)</td>
<td>4.44 (1.51)</td>
</tr>
<tr>
<td>side of implant</td>
<td>Lt / Rt</td>
</tr>
<tr>
<td>stimulation parameters</td>
<td></td>
</tr>
<tr>
<td>amplitude (V)</td>
<td>3.42 (0.91)</td>
</tr>
<tr>
<td>pulse width (µsec)</td>
<td>76.67 (26.46)</td>
</tr>
<tr>
<td>rate (pulses/sec)</td>
<td>156.11 (27.81)</td>
</tr>
</tbody>
</table>

* Data are presented as the mean ± SD in parentheses.

### Surgical Procedure

After the application of a local anesthetic, a Cosman-Roberts-Wells frame (Radionics, Inc., Burlington, MA) was attached to the patient's head. Following attachment of the head frame, a localizing computerized tomography (CT) scan was obtained, with the gantry angled to approximate the anterior commissure-posterior commissure (AC-PC) plane. Computerized tomography scans were acquired at 1.5-mm intervals through the thalamic region. The thalamic VIM nucleus target location was calculated as follows: the anteroposterior target coordinate was the AC-PC length divided by 12, the quotient of which was multiplied by 2.5. The lateral target coordinate was calculated as the sum of one-half the third ventricle width and 11.5. The initial target depth was the AC-PC plane.

After application of local anesthetic, a burr hole was placed just anterior to the coronal suture and 2.5 cm from the midline. Using the Cosman-Roberts-Wells arc system and a microdrive, an electrode 300 mm in length, 1.1 mm in diameter, with an uninsulated tip of 3 mm, was inserted into the brain through the burr hole. At several levels above and below the calculated target, electrical stimulation was initiated to provoke contralateral arm and face paresthesias and then to determine the effect of stimulation on tremor. Stimulation parameters were 100 pulses per second, 200 µsec pulse width, with the voltage varied from 0 to 10 V. The optimal location for the deep brain stimulating (DBS) electrode was defined as that where stimulation at the lowest voltage produced transient paresthesias and good tremor control, but not motor or speech deficits. The DBS electrode (model 3382; Medtronic, Inc., Minneapolis, MN) was next positioned in this location. This electrode had four contacts that were 2.5 mm in length and separated
from each other by 1 mm. Stimulation was again used to ensure efficacy of the DBS electrode before its final implantation.

Following placement of the DBS electrode and with the patient anesthetized, a pulse generator (ITREL II; Medtronic, Inc.) was implanted in the subcutaneous tissue of the subclavicular region. The generator was connected to the DBS electrode subcutaneously. After the patient recovered, the generator was adjusted and programmed to deliver stimulation producing optimal tremor control. The stimulation parameters could be further adjusted on subsequent outpatient visits.

**Neuropsychological Evaluation**

Typically, patients received a neuropsychological evaluation 1 week before surgery and 4 months after surgery, with the test-retest interval spanning an average of 4.5 months (see Table 1). Before surgery, patients were evaluated while receiving medication and during their self-reported best "on" state. Following surgery, patients were reevaluated with the stimulator turned on and while receiving medication. The mean stimulation parameters at time of neuropsychological evaluation are presented in Table 1. The neuropsychological test battery was selected to evaluate different domains of cognition, emphasizing attention/executive function, language, and memory, while being relatively brief (the battery took 2-3 hours to administer).

**Cognitive Screening.** The Mattis Dementia Rating Scale (DRS),[31] a cognitive screening test yielding scores in five domains of cognition: attention, initiation and perseveration, visuoconstructional function, conceptualization, and memory, was administered.

**Attention and Executive Functions.** The Brief Test of Attention (BTA),[37] a test of auditory selective and divided attention, and the Wisconsin Card Sorting Test (WCST),[23] a card sorting task demanding rule conceptualization and modification of response strategy to verbal feedback, were administered.

**Language Function.** The Controlled Oral Word Association Test (COWAT; letter fluency),[9] the BDAE Animal Naming test (category or semantic verbal fluency),[22] and the Boston Naming Test (BNT; visual confrontation naming)[25] were administered. Alternate forms of the verbal fluency tasks were used before and after surgery, with order of test administration randomized.

**Visuoperceptual Functions.** The Hooper Visual Organization Test (VOT), a visuoperceptual gestalt formation task,[24] the Judgment of Line Orientation (JLO), a task of matching lines of similar spatial orientation,[10] and the Facial Recognition test, a facial matching assessment[10] were administered.

**Learning and Memory.** The California Verbal Learning Test (CVLT), a word list learning, recall, and recognition test,[19] the Wechsler Memory Scale-Revised (WMS-R),[45] the Logical Memory (prose recall) and Figural Memory (recognition of nonverbal stimuli) subtests, and the Kaufman Adolescent and Adult Intelligence Test (KAIT)[26] Famous Faces subtest for remote memory and general knowledge were administered. Because of time constraints, one patient did not receive the BTA and WCST, and two patients were not evaluated on the VOT and JLO.

**Statistical Analysis**

Given the small sample size and nonnormal distribution of data, pre- and postoperative neuropsychological test scores were compared using the nonparametric Wilcoxon Signed-Rank test, which considers both the direction and magnitude of the differences among paired observations.[39] To
evaluate individual patient change, standard (z) scores were computed for each test score, using published, age- (and in relevant instances, education- and gender-) appropriate normative data. A change in test score of between 1 and 1.99 SDs was defined a priori as indicating "possible change," and a change in test score of 2 SDs or greater was defined as indicating "probable change."

RESULTS

Changes in Test Scores in the Sample Group

The patient group's mean test scores (and SDs) are presented in Table 2. As a group, patients attained statistically significantly higher scores after surgery than before it on two memory measures: delayed recognition (discriminability) of a word list (CVLT) and delayed recall of two prose passages (WMS-R Logical Memory II). There was also a trend (p = 0.06) for the group to attain higher scores after surgery than before it on a visual confrontation naming test (Boston Naming Test). No statistically significant decrements in test scores were observed.

![Table 2: Neuropsychological Test Scores Before and After Thalamic Stimulator Implantation and Number of Patients Showing Test Score Changes Exceeding 1 and 2 SDs](image-url)
Frequency of Changes in Test Scores Among Individual Patients

The frequency with which changes in test scores exceeding one and two or more SDs was observed and these changes are presented in Table 2. Probable gains and losses in test scores (that is, changes of 2 SDs) from baseline were rarely observed. Possible changes (those > 1 SD but < 2 SDs) were observed relatively rarely. However, such "possible changes" were most often noted to occur on the word list learning and memory task (CVLT). These changes were more often gains than losses, with the exception of free recall intrusion errors (incorrect recall of words not on the list), in which losses (increased errors) were more common after than before surgery. These "possible" changes, however, need to be interpreted very conservatively, because published normative data for the CVLT provide ranges of raw scores corresponding to a given z-score, rather than precise raw-to-z score conversions. Thus, if a baseline score is at the upper end of the range of raw scores corresponding to a given z-score, then a relatively small change in raw score can result in a z-score change of 1 SD.

DISCUSSION

The results obtained in this small patient series are congruent with those reported by Caparros-Lefebvre, et al.[13] in another small patient series. That is, statistically significant changes in neuropsychological test scores following thalamic stimulator implantation are rarely observed when group results are considered. The absence of any statistically significant decrements in test scores is encouraging, but given the small sample sizes in this and the study by Caparros-Lefebvre, et al., these data should be considered only preliminary and tentative support for the cognitive safety of thalamic stimulation for refractory PD.

The statistically significant gains observed in two memory scores (delayed word list recognition discriminability and delayed prose recall) after surgery might similarly be interpreted conservatively, although the consistency of improved delayed recall/recognition across two verbal memory tasks, particularly when also accompanied by a trend toward improved visual confrontation naming, is noteworthy. Statistically significant changes observed in a group's tests scores do not reveal whether such changes are clinically meaningful. A statistically significant score change is unlikely to have occurred by chance, but statistical significance does not reveal whether such a change is unusual. The 3% average improvement in word list recognition discriminability is small in absolute terms. However, the fact that two of nine patients showed improvements in excess of 2 SDs suggests that at least some patients may demonstrate meaningful improvements in recognition. The average gain of four story units on delayed prose recall, on the other hand, probably reflects consistent but small gains across patients, because no patients demonstrated gains of 2 SDs or more. Indeed, the small change may reflect practice effects, because a subset of the test normative sample aged 55 to 64 years, tested twice within a 4- to 6-week period, showed an average gain of approximately seven points on retesting[45] (one might assume a
smaller practice effect at a 4.5-month test-retest interval as used in this study). Of course, the clinical significance of test score change could be addressed more directly by having a PD control group closely matched to the surgical treatment group in terms of age, education, gender, baseline disease, and cognitive characteristics.

Studies of large patient series in the United States will not be possible until thalamic stimulation becomes an approved treatment for refractory PD symptoms. However, our observation that "probable" test score changes might occur in a minority of patients, highlights the need for future studies in large series of patients so as to identify potential demographic, disease, and cognitive characteristics that might reliably predict which patients will experience significant changes (either improvements or decrements) in cognitive function. Such studies might also address the temporal stability of the cognitive effects of thalamic stimulator implantation in PD, potential laterality effects, and also elucidate the effects on cognition of stimulation per se by evaluating cognitive function with the stimulator turned on and off.

References


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