Cognitive outcome following pallidotomy: the influence of side of surgery and age of patient at disease onset

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Object. The authors studied the neuropsychological correlates of stereotactically guided lesioning of the right and left posteroventral globus pallidus internus (GPi) in a prospective series of patients suffering from Parkinson’s disease (PD).

Methods. Eighteen patients with PD who underwent stereotactically guided lesioning of the GPi (left side in 10 patients and right side in eight) completed neuropsychological evaluations before and after surgery. Patients served as their own controls. Multiple two-by-two repeated-measures analyses of variance were used to assess neuropsychological changes as a function of the side in which lesioning was performed (lesioning on the left side compared with that on the right) and surgery (presurgery compared with postsurgery). Relationships between cognitive variables and patient age at disease onset, age at surgery, and disease duration were examined using a linear regression model.

The most striking findings were evident from results of a phonemic word fluency test in which patients in whom a left-sided pallidotomy had been performed achieved a mean performance score that was lower than the score of patients in whom a right-sided pallidotomy had been performed; this score declined even more as a result of surgery. Change in performance on the word fluency test across pre- and postoperative assessments was also related to patient age at onset of PD in those who had undergone left-sided pallidotomy, with patients of an older age at disease onset showing the greatest decline in performance.

Conclusions. These preliminary findings indicate that the side on which surgery was performed and patient age at onset of PD are important in the prediction of postoperative cognitive outcome. The findings also indicate that stereotactically guided lesioning of the GPi presents a relatively mild cognitive risk.

Key Words • pallidotomy • Parkinson’s disease • cognitive impairment • neuropsychological function • posteroventral internal globus pallidus
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TABLE 1
Preoperative and postoperative scores on cognitive tests in 18 patients who underwent left- or right-sided pallidotomy*

<table>
<thead>
<tr>
<th>Test</th>
<th>Preop</th>
<th>Postop (~ 6 Wks)</th>
<th>Postop (~ 8 Mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R, Digit Span Test</td>
<td>9.2 ± 2.7</td>
<td>8.8 ± 2.7</td>
<td>9.4 ± 2.4</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>28.9 ± 12.2</td>
<td>25.3 ± 8.4</td>
<td>39.6 ± 10.0</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td>90.5 ± 12.4</td>
<td>92.7 ± 18.1</td>
<td>90.6 ± 15.8</td>
</tr>
<tr>
<td>MAE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naming Test†</td>
<td>57.5 ± 3.9</td>
<td>55.4 ± 4.0</td>
<td>55.7 ± 3.1</td>
</tr>
<tr>
<td>COWA Test‡</td>
<td>30.1 ± 5.5</td>
<td>16.1 ± 6.6</td>
<td>42 ± 10.5</td>
</tr>
<tr>
<td>Repetition Test</td>
<td>12.8 ± 3.2</td>
<td>11.6 ± 2.1</td>
<td>12.1 ± 2.2</td>
</tr>
<tr>
<td>Token Test</td>
<td>41.8 ± 2.8</td>
<td>39.6 ± 3.6</td>
<td>42.9 ± 2.2</td>
</tr>
<tr>
<td>Rey AVLT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summation of Trials 1–5</td>
<td>37.7 ± 7.9</td>
<td>36.4 ± 6.2</td>
<td>42.9 ± 6.5</td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>7.2 ± 3.4</td>
<td>7.1 ± 2.4</td>
<td>8.4 ± 2.7</td>
</tr>
<tr>
<td>Delayed Recognition</td>
<td>13.8 ± 1.8</td>
<td>13.3 ± 1.9</td>
<td>12.6 ± 1.7</td>
</tr>
<tr>
<td>False-Positive Errors</td>
<td>5.9 ± 5.4</td>
<td>6.2 ± 3.7</td>
<td>3.8 ± 3.5</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>9.3 ± 4.6</td>
<td>9.4 ± 5.5</td>
<td>8.7 ± 3.1</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard deviations. Abbreviations: AVLT = Auditory Verbal Learning Test; MAE = Multilingual Aphasia Examination; WAIS-R = Wechsler Adult Intelligence Test–Revised.
† Significant (p = 0.006) main effect for time.
‡ Significant interaction effect (p = 0.006) on two- (side of surgery) by-two (pre- or postoperative) repeated-measures ANOVA.

able to assess. The goal of the present investigation was to study prospectively the neuropsychological correlates of right- and left-sided stereotactically guided pallidotomies in a series of patients with PD.

Clinical Material and Methods

Patient Population

All patients with advanced PD underwent microelectrode-guided radiofrequency lesioning of the GPi. Patients were included in the present study if they were native English speakers, did not suffer from dementia (based on the criteria established by the American Psychiatric Association1), and had completed pre- and postoperative neuropsychological assessments. The final sample included 18 patients (10 of whom underwent surgery on the left side and eight of whom underwent surgery on the right). The patients’ mean age was 61.1 years (range 35–77 years) and the average educational level completed was 11.83 years (range 8–16 years). There were five women and 13 men. Two patients were left handed.

Surgical Procedure

The preliminary target in the GPi was determined on the basis of a volumetric magnetic resonance image that was acquired after the patient had been placed in a Leksell frame. Microelectrode exploration (stimulation and recording) through a parasagittal trajectory angled 55 to 75° to the anterior commissure–posterior commissure line confirmed the target location in the GPi and identified the adjacent optic tract and internal capsule. Several (three–four) contiguous radiofrequency lesions were made in the pallidum. A magnetic resonance image obtained 24 hours later confirmed lesion location in each patient.

Neuropsychological Testing

All patients underwent preoperative and postoperative neuropsychological examinations during their “on” state. The majority of patients were assessed on an outpatient basis and many had traveled a significant distance to attend the appointment. These factors, as well as other patient variables (extreme fluctuations in motor function and fatigue), precluded the use of an extensive 7- to 8-hour-long neuropsychological battery of tests. Consequently, a screening battery was designed with specific emphasis on functions known to be influenced by PD. Neuropsychological function in the following domains was assessed using the tests3,10,18 listed in Table 1: attention (Digit Span Test, age-corrected scaled score); processing speed (Symbol Digit Modalities Test, oral version, raw score); concept formation and problem solving (Wisconsin Card Sorting Test, perseverative responses, standard score); language (Multilingual Aphasia Examination [Naming, COWA, Sentence Repetition, and Token Tests; corrected raw scores]); verbal memory (Rey Auditory Verbal Learning Test, Summation of Trials 1–5, Delayed Recall, and Delayed Recognition [raw scores]); and number of false-positive errors on recognition testing); and depression (Geriatric Depression Scale, raw score). In addition, all patients completed the Neurobehavioral Cognitive Status Examination, a cognitive screening instrument used to assess the following independent areas of function: orientation and attention, language, construction, memory, calculation, and reasoning. Finally, all patients and most of their spouses were interviewed together, with specific reference given to perceived cognitive changes as a direct result of the surgery. Perceived cognitive changes were assigned a global rating, with a score of 1 reflecting no change or improvement, a score of 2 reflecting questionable or mild decline, and a score of 3 reflecting a clear decline.
Because of early reports in which postoperative language deficits were described in patients who had undergone left-sided pallidotomy, a comprehensive language assessment was repeated when such patients returned to see the neurosurgeon for their first postoperative appointment. This assessment permitted researchers to determine any language deficits in the immediate postoperative period that might not be apparent at a long-term follow-up review. Typically, language assessment occurred between 6 and 8 weeks after surgery (mean 6.5 weeks, range 4–8 weeks) and was performed using the four tests included in the Multilingual Aphasia Examination listed in Table 1. All patients completed the full battery of tests following surgery and the majority of patients (72%) were assessed within the 6- to 12-month period following surgery (in months: mean 8.7, mode 7.5, standard deviation 3.1, range 3.5–14).

Statistical Analyses

Patients served as their own controls. Because of the exploratory nature of the study and the small sample sizes, multiple two-by-two repeated-measures ANOVAs were used to assess changes in each of the aforementioned measures as a function of group (left-sided pallidotomy or right-sided pallidotomy) and surgery (presurgery or postsurgery). Significant effects were then analyzed using post hoc paired t-tests. The relationships between cognitive variables and age at disease onset, age at surgery, and disease duration were examined using a linear regression model. Given the number of analyses, a more conservative α value of 0.01 was chosen to reduce the likelihood of making a type I error.

Results

There were no differences in age at surgery, age at onset of PD, duration of disease, education, or sex between patients who underwent left-sided pallidotomy and those who underwent right-sided pallidotomy.

Repeated-measures analyses revealed significant effects involving only two of the dependent variables (Table 1). Most striking were scores from the phonemic word fluency test, the COWA test, which requires the patient to generate within 1 minute as many different words as possible that begin with a specific letter of the alphabet. Unacceptable responses include proper nouns and derivatives of previously stated words (such as “box” followed by “boxes”). We found a significant group effect, with significantly lower scores achieved by patients who underwent left-sided pallidotomy compared with those who underwent right-sided pallidotomy (F[1,16] = 22.99, p < 0.001). In addition, we noted a significant interaction effect in which scores attained by patients who underwent a left-sided pallidotomy declined following surgery, whereas scores of those who underwent a right-sided pallidotomy were unchanged (F[1,16] = 8.861, p < 0.009; Fig. 1).

Controlled Oral Word Association test scores across the three testing sessions were also examined using a repeated-measures ANOVA in patients who underwent a left-sided pallidotomy (that is, presurgery, approximately 6 weeks postsurgery, and approximately 8 months postsurgery). This analysis reveals a pattern in which there is a sharp decline in phonemic word fluency scores evident at the 6-week assessment and a mild improvement from this level (but not to preoperative levels) at the 8-month assessment (F[2,14] = 10.682, p = 0.002; Table 1).

Furthermore, when we examined individual patient assessment protocols, 70% of patients who had undergone a left-sided pallidotomy exhibited a decline in phonemic fluency when assessed approximately 8 months following surgery (mean drop 15 points, range 10–23 points). Two patients who underwent left-sided pallidotomy retained consistent scores (change of ≤ 5 points) and one patient’s scores improved. The three patients who had undergone left-sided pallidotomy in our series had no clinically significant drop in COWA scores and had presented with early onset PD (onset at age ≤ 40 years). We infer from the data that there is a highly significant relationship between the age of a patient at onset of PD (using age at disease onset as a continuous variable) and change in COWA scores from the pre- to postoperative assessment (r = −0.941, p < 0.001; Fig. 2). Figure 2 illustrates that patients in whom PD was diagnosed later in life had the biggest decline in COWA test scores. This relationship is not simply an artifact of extreme outliers because when the same correlation was computed without the two most extreme cases (that is, the patients with the youngest and oldest ages at PD onset) a significant relationship was still evident (r = −0.933, p = 0.001).

Not surprisingly, patient age at surgery was related to age at PD onset (r = 0.842, p = 0.002) and, therefore, age at surgery was also significantly related to a decline in COWA test scores (r = −0.925, p < 0.001). To determine whether patient age at onset of PD or age at surgery is the more critical variable in predicting change in the COWA test score, the relationship between patient age at PD onset and change in COWA test score was examined while controlling for the effects of age at surgery by using a partial correlation technique. This correlation was significant (r = −0.791, p = 0.006), whereas the relationship between patient age at surgery and change in COWA test score did not meet the study’s threshold for statistical significance.
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when the effects of age at PD onset were controlled \((r = -0.725, p = 0.027)\). This outcome indicates that the more critical variable is patient age at onset of PD rather than age at surgery. Finally, duration of disease was unrelated to change in COWA test score \((r = 0.051, p = 0.889)\).

The only other significant repeated-measures finding was evidence of a mild decline in confrontation naming across both groups as a function of surgery \((F[1,13] = 10.8, p = 0.006; \text{Table 1})\).

The majority (67%) of patients and spouses denied any significant subjective changes in cognition (attention/concentration, language, or memory) as a result of surgery. Four (22%) of the patients or family members described mild or questionable cognitive decline following surgery but were uncertain if the perceived decline reflected surgery or PD progression. These four patients were evenly split between those who had undergone left-sided pallidotomy and those who had undergone right-sided pallidotomy. The final two patients (11%), both of whom had undergone left-sided pallidotomy, believed that they suffered a definite decline in cognitive function as a result of the surgery. The proportion of patients in each category (no change, questionable/mild decline, and definite decline) did not differ as a function of the side on which surgery was performed \((\chi^2[2 \text{ df}, 18 \text{ patients}] = 1.8, p = 0.407)\). Notably, none of the four patients in our series with early-onset PD experienced postoperative cognitive declines. Attention/concentration, memory, naming, and mental arithmetic skills were those areas most frequently identified as weaker after surgery in those patients who acknowledged either a questionable or a definite cognitive decline. Other important noncognitive difficulties such as alterations in speech, including hypophonia and transient dysarthria, were reported by some patients, as well as transient difficulties in writing.

Discussion

Patients who underwent a left-sided pallidotomy procedure performed more poorly on a phonemic word fluency test than those who underwent a right-sided pallidotomy. Furthermore, a significant decline in test performance was evident as a function of surgery in patients following left- but not right-sided pallidotomy. This finding is consistent with other reports in the literature in which a decline was evident as a function of surgery in patients following left-sided pallidotomy. In many of these studies, changes demonstrate any change in word fluency scores as a result of lesioning of the GPi. In no other study has undergone right-sided pallidotomy and those who underwent left-sided pallidotomy. In addition, in no other study has the role of age at disease onset been assessed in relation to postpallidotomy cognitive outcome. It is possible that a failure to examine both of these variables might have obscured true postoperative declines in word fluency in patients with late-onset PD following left-sided pallidotomy. It is also possible that variability in cognitive outcome is partially related to differences in surgical technique at different centers (for example, use of microelectrode or macroelectrode guidance). Gross and colleagues have demonstrated that variable clinical effects can be attributed to lesion location within the GPi. Although the specific neuropsychological sequelae of pallidotomy have not been analyzed with respect to lesion location, it is possible that a slight variability in lesion location within the GPi may account for some of the differences in patients’ cognitive outcomes.

Their results suggest that the critical variable is the patient’s age at disease onset. Qualitatively, in predicting individual patient outcome, this appears to be the case in our sample as well. Further studies are needed to confirm this impression. Within this context, it is important to note that patient age at PD onset is not synonymous with age at diagnosis. Thus, future studies must be conducted in a way that carefully distinguishes between these two variables.

As noted previously, other investigators \((11,14,17)\) failed to demonstrate any change in word fluency scores as a result of lesioning of the GPi. In many of these studies, changes were assessed in combined groups of patients who underwent right-sided pallidotomy and those who underwent left-sided pallidotomy. In addition, in no other study has the role of age at disease onset been assessed in relation to postpallidotomy cognitive outcome. It is possible that a failure to examine both of these variables might have obscured true postoperative declines in word fluency in patients with late-onset PD following left-sided pallidotomy. It is also possible that variability in cognitive outcome is partially related to differences in surgical technique at different centers (for example, use of microelectrode or macroelectrode guidance). Gross and colleagues have demonstrated that variable clinical effects can be attributed to lesion location within the GPi. Although the specific neuropsychological sequelae of pallidotomy have not been analyzed with respect to lesion location, it is possible that a slight variability in lesion location within the GPi may account for some of the differences in patients’ cognitive outcomes.

A mild decline in score on a confrontation naming test was also evident in our sample of patients following pallidotomy. This decline was unrelated to the side of surgery. We question the clinical significance of this finding because the absolute magnitude of the decline was 2.5 points, which corresponds to missing approximately one more item on the confrontation naming test following surgery.

It is possible that more striking declines in scores on the confrontation naming test and, perhaps, the other lan-
Trépanier and colleagues, who found that up to 25% of patients acknowledged cognitive declines following surgery. Series with early-onset PD acknowledged cognitive declines as well. Notably, none of the four patients in our study denied any declines in thinking skills as a result of surgery. This possibility is judged to be unlikely. Nonetheless, the potential role of practice effects cannot be completely ruled out.

Finally, the majority (66%) of patients and spouses denied any declines in thinking skills as a result of surgery. Two patients (11%) reported a definite decline in their thinking skills following stereotactically guided pallidotomy, which was corroborated by their spouses or other family members. Notably, none of the four patients in our series with early-onset PD acknowledged cognitive declines following surgery.

These data differ slightly from the results reported by Trépanier and colleagues, who found that up to 25 to 30% of their sample of pallidotomy patients demonstrated definite postsurgical declines in executive cognitive functions, according to spouse reports. Differences between our data and those of Trépanier and colleagues most likely reflect the different variables assessed and differences in informants. Trépanier and colleagues noted that a number of our patients demonstrated decreased insight after pallidotomy. Our data might represent an underestimation of the actual prevalence of perceived cognitive decline following pallidotomy because of the possibility of limited patient insight into postoperative changes and the lack of a witness to provide additional information in all cases. We must address these issues and examine potential risk factors (such as side of surgery and patient age at disease onset) that can further identify those patients who are more likely to exhibit cognitive deficits after undergoing pallidotomy.

**Conclusions**

In summary, a clinically significant decline was apparent by using a measure of phonemic word fluency, the COWA test, in our patients following left-sided pallidotomy. Furthermore, this decline was evident only in patients with late-onset PD who underwent left-sided pallidotomy. These preliminary findings indicate that the side of lesioning and patient age at PD onset are important in predicting cognitive outcome and should be explored further. Note that the majority of our patients and their spouses denied any significant cognitive declines associated with stereotactically guided lesioning of the GPi; this supports the results of statistical analyses, which suggest relatively mild cognitive deficits associated with the procedure. Furthermore, at least in our series, the overwhelming majority of our patients (17 [94%] of 18 patients) strongly believed that their surgery was worthwhile, despite any cognitive declines. From the patients’ perspectives, the neurological improvements clearly outweighed potential cognitive and behavioral risks. Overall, our findings indicate that unilateral lesioning of the GPi presents a relatively mild cognitive risk, particularly for patients with early-onset PD who are undergoing procedures in the nondominant hemisphere.

**References**

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