

## Impaired Frontostriatal Cognitive Functioning Following Posteroventral Pallidotomy in Advanced Parkinson's Disease

Glenn T. Stebbins,\* John D. E. Gabrieli,\*† Kathleen M. Shannon,\*  
Richard D. Penn,‡ and Christopher G. Goetz\*

\**Department of Neurological Sciences and †Department of Neurosurgery, Rush Medical College; ‡Department of Psychology, Stanford University*

We investigated the long-term effects of posteroventral pallidotomy on tests sensitive to the functional integrity of frontostriatal neural systems in a sample of 11 patients with advanced Parkinson's disease (PD). Patients were assessed within 1 month prior to surgery and at 12 months following pallidotomy. Changes in outcome measures were compared to a control sample of equally performing PD patients receiving nonsurgical medical management assessed over a 12-month period. Measures of cognitive abilities sensitive to frontostriatal functional integrity tested psychomotor processing speed, executive components of working memory, and reasoning. Additional tests of general mental status and semantic memory ability were utilized to assess the specificity of the effect of pallidotomy on cognitive function. Significant declines in performance on all measures sensitive to frontostriatal integrity were found for the surgery group but not the PD control group. No significant changes in performance were found on the measures of general mental status or semantic memory for either the surgery or PD control samples. These results suggest that the posteroventral pallidotomy selectively impairs performance on tests of frontostriatal cognitive abilities. © 2000 Academic Press

Recent insights into the functional architecture of the striatum have led to a resurgence of ablative surgery for the treatment of the motor impairments associated with Parkinson's disease (PD) (reviewed in Goetz & Diederich, 1996). A common neural target is the posteroventral aspect of the internal globus pallidus (GPi), a structure that has an inhibitory output to the thalamus. Pallidal inhibition of the thalamus is usually modulated through inhibitory stimulation of the GPi by the direct pathway emanating from the puta-

Portions of this research were supported by a grant from the Office of Naval Research (N00014-92-J-184) and the United Parkinson Foundation.

Address correspondence and reprint requests to Glenn T. Stebbins, Department of Neurological Sciences, Rush Medical College, 1645 W. Jackson, Suite 450, Chicago, IL 60612. Fax: (312) 432-9332. E-mail: [gstebbin@rpslmc.edu](mailto:gstebbin@rpslmc.edu).



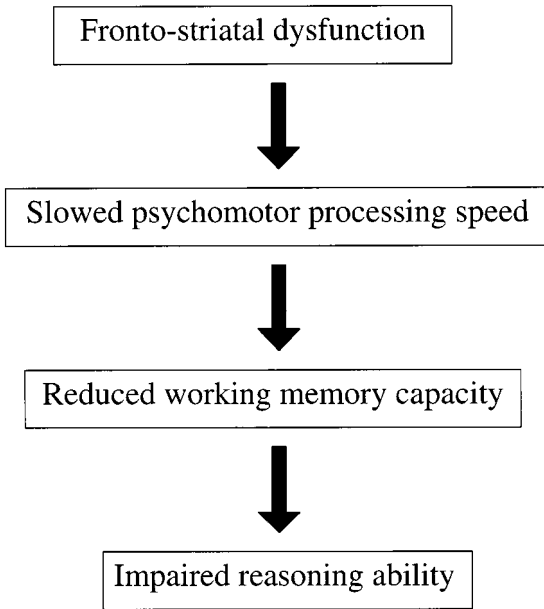
men and excitatory stimulation by the indirect pathway emanating from the putamen through the external aspect of the global pallidus (GPe) (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986). The loss of dopamine producing cells in the substantia nigra pars compacta in PD results in decreased inhibition of the GPi from the direct pathway and increased excitation of the GPi from the indirect pathway, with a net result of excessive GPi inhibition of the thalamus (DeLong, 1990). This excessive GPi inhibition of the thalamus decreases thalamic stimulation of the motor cortex which is thought to produce the motor impairments of PD.

These concepts seem to explain why surgically placed lesions in the GPi might improve motor performance by reducing inhibition of the thalamus. However, the situation appears to be more complex. Posteroventral pallidotomy (PVP) improves the motor symptoms of PD (e.g., Dogali, Fazzini, Kolodny, et al., 1995; Iacono & Lonser, 1994; Laitinen, Bergenheim, & Hariz, 1992; Lang, Lozano, Montgomery, et al., 1997; Shannon, Penn, Kroin, et al., 1998). The most common report is of an improvement of motor function during the "off" state, when patients are withdrawn from levodopa medications. However, movement speed is not improved (Pfann, Penn, Shannon, et al., in press) and dyskinesias are markedly reduced (e.g., Lang et al., 1997; Shannon et al., 1998); these are the opposite of what would be predicted by releasing GPi inhibition of the thalamus.

One possible explanation for the effects of PVP on motor function in PD is that it eliminates abnormal signals coming from the damaged GPi which interfere with movement. The "noise" from a malfunctioning basal ganglion circuit is removed by destroying its major outflow path. Whatever the final explanations are for the effects of PVP on movement, it is clearly a focal lesion in or near circuits that are important to cognitive function. Specifically, the striatum constitutes part of a feedback "loop" to the dorsolateral prefrontal cortex. Projections from this frontal region converge on the caudate nucleus which then project to the direct (GPi) and indirect (GPe) pathways (Alexander, Crutcher, & De Long, 1990; Cummings, 1993). Striatothalamic projections close the feedback "loop" by connecting with the dorsolateral prefrontal cortex. Disruption of this frontostriatal loop results in deficits of specific cognitive abilities contained under the rubric of working memory (Cooper, Sagar, Jordan, & Harvey, 1991; Gabrieli, Singh, Stebbins, et al., 1996; Goldman-Rakic, 1987).

Working memory is a limited-capacity psychological system that is used to temporarily store and transform information in a goal-directed manner (Waters & Caplan, 1996). It is a multicomponent system variously conceptualized as comprising a central executor (Baddely, 1986), or executors (Goldman-Rakic, 1986; Wilson, O. Scalaidhe, & Goldman-Rakic, 1993), with associated buffer storage systems for speech-based information (the phonological loop) and visuospatial information (visuospatial sketchpad).

The limitations of working memory are thought to be due to constraints



**FIG. 1.** Hypothesized model of impaired cognitive function resulting from striatal dysfunction.

on how much information can be maintained in each of its component parts. The capacities of the buffer storage systems are operationalized as performance on tests measuring span in speech-based (e.g., digit span) or visuospatial (e.g., Corsi block span) domains. In most studies, the buffer storage components of working memory are minimally affected in patients with striatal damage such as PD (Cooper, Sagar, Doherty et al., 1992; Taylor, Saint-Cyr, & Lang, 1987) and Gilles de la Tourette's syndrome (Stebbins et al., 1995). Therefore, the deficit in striatal diseases appears to be due to impairments of executive components of working memory.

We have proposed a model delineating the effects of striatal diseases such as PD (Gabrieli et al., 1996), Huntington's disease (Singh et al., 1992), Gilles de la Tourette's syndrome (Stebbins et al., 1995), and potentially schizophrenia (Stone, Gabrieli, Stebbins, et al., 1998) on the executive components of working memory (Fig. 1). According to this model, damage to the striatum reduces psychomotor processing speed, which in turn diminishes the capacity of executive working memory operations. Because the executive components of working memory require the simultaneous and synchronized processing and storage of information, decrements in psychomotor processing speed may disrupt parallel processes and limit working memory capacity. Furthermore, reduced working memory capacity impairs reasoning ability

because reasoning taxes the limits of working memory (Carpenter, Just, & Shell, 1990).

In support of this model, many studies report selectively impaired performance on tests assessing each of these components in patients with striatal disease. For example, PD patients are usually found to be impaired on tests of (1) psychomotor processing speed (Gabrieli et al., 1996; Mortimer, Pirozolo, Hansch, et al., 1982; Rafal, Posner, Walker, et al., 1984; Stebbins, Gabrieli, Masciari, et al., 1999); (2) working memory tasks which require the simultaneous and synchronized processing and storage of information (Cooper et al., 1991, 1992; Gabrieli et al., 1996; Stebbins et al., 1999); and (3) reasoning, such as the Raven Progressive Matrices (Cronin-Golomb & Braun, 1997; Stebbins, Gabrieli, Burton, et al., 1994) and the Wisconsin Card Sorting test (Lees & Smith, 1983; Stebbins, Gabrieli, Burton, et al., 1994; Taylor et al., 1986). These three deficits are highly intercorrelated (Gabrieli, 1996; Gabrieli et al., 1996; Stebbins et al., 1999).

In contrast to these impairments in cognitive function, patients with PD often perform normally on memory tests that do not place great demands on the executive components of working memory. For example, the performance of patients with PD on tests of semantic memory, such as measures of vocabulary knowledge, is often found to be intact (Flowers, Pearce, & Pearce, 1984; Gabrieli et al., 1996; Stebbins et al., in press). PD patients also perform well on tests of immediate recognition memory, which places little demand on working memory, but are impaired on other declarative memory tasks, such as recall, that tax working memory resources (Breen, 1993; Gabrieli et al., 1996; Stebbins et al., in press; Taylor et al., 1986). Thus, PD patients do not show impairments on cognitive tasks that make few demands on working memory processes, but fail tasks that require working memory resources in excess of their limited capacity.

Unlike the extensive literature on motoric effects of PVP, there are only a limited number of studies examining the effects of PVP on cognition (Baron, Vitek, Bakay, et al., 1996; Samuel, Caputo, Brooks, et al., 1998; Scott, Gregory, Hines, et al., 1998; Soukup, Ingram, Schiess, et al., 1997; Uitti, Wharen, Turk, et al., 1997). The majority of these studies have employed a wide range of cognitive performance measures designed to assess multiple cognitive functions, such as general intelligence, memory, language, and visuospatial abilities. Such an approach to testing is useful for assessing the safety of PVP on such cognitive functions. Such an approach, however, does not provide a specific and sensitive assessment of the cognitive functions that have been shown to be impaired in PD.

The purpose of the present study was to assess the effects of PVP on frontostriatal cognitive functions in patients with advanced PD. Specifically, we administered one test of psychomotor processing speed, two tests of the executive components of working memory, and one test of reasoning ability to a sample of 11 patients with advanced PD prior to and 12 months follow-

ing PVP. We also administered tests of general mental status and semantic memory, cognitive processes which place fewer demands on frontostriatal cognitive function, to assess the specificity of PVP effects on frontostriatal cognitive function. We hypothesized PVP would adversely affect performance on the frontostriatal cognitive tests, but not on the measures of general mental status or semantic memory. A sample of 10 PD patients, of equivalent parkinsonian severity but not part of the PVP study, were tested to assess performance changes on these measures in best medically managed patients over a 12-month period.

## METHODS

### *Participants*

*PVP participants.* Eleven participants with PD were recruited from an ongoing study of the safety and efficacy of PVP surgery at Rush-Presbyterian-St. Luke's Medical Center Movement Disorder's Clinic (Shannon et al., 1998). Each met Core Assessment Protocol for Intercerebral Transplantation (CAPIT) criteria for the diagnosis of PD (Langston, Widner, Goetz, et al., 1992). These criteria include the presence of at least two of the following clinical signs: resting tremor, cogwheel rigidity, bradykinesia, and postural reflex impairment, with either resting tremor or bradykinesia as one of the two signs. Additional entry criteria for the PVP study included the presence of motor fluctuation, loss of dopaminergic medication effect (off period) at least 25% of waking hours, Hoehn and Yahr (HY; Hoehn & Yahr, 1967) stage IV while in the off period, and HY stage III or better when dopaminergic medications were effective (on period). Patients with clinically diagnosed dementia or psychosis were not enrolled in the study.

*Clinical comparison participants.* Ten participants with PD were tested with the same cognitive measures as those used with the PVP cohort. The comparison participants were not enrolled in the PVP study, but were part of a study of changes in cognitive function in PD over time. They were matched to the PVP cohort for age, education, Unified Parkinson's Disease Rating Scale (UPDRS: Fahn, Elton, the UPDRS Development Committee, 1987) motor score during the on period, and HY score during the on period. Their data are included in this report to provide a comparison of changes in frontostriatal cognitive function over a 1-year interval in a sample of best medically managed PD patients of equal disease severity.

### *Neurosurgical Procedure*

Full discussion of the surgical procedure is provided in Shannon et al. (1998). Briefly, the ventral posterior target in the GPi was located using MR imaging and microelectrode mapping. Microelectrode mapping of the GPi was accomplished with two to five passes of a 0.9- to 1.5-M $\Omega$  recording electrode. Following mapping, a 1.3-mm-diameter radiofrequency lesioning electrode was placed in the best tract or tracts and used to create the lesion in the GPi target. Lesioning was performed contralateral to the side with more severe parkinsonian signs. MR imaging was performed the day after surgery to localize the site of the lesion. Immediately following surgery preoperative medications were reinstated and all patients were discharged within 48 h following surgery.

### *Assessment of Motor Function*

Full discussion of the methods and results of clinical assessment of motor function is provided in Shannon et al. (1998). Briefly, clinical assessments were performed 1 month prior

to surgery and at 1, 6, and 12 months following surgery. Motor assessment followed the recommendations of CAPIT (Langston et al., 1992) including testing during off periods (when antiparkinsonian medications had been withdrawn for a period of at least 12 h) and on periods (following the first morning dose of antiparkinsonian medications). Measures of motor function included the complete UPDRS (Fahn et al., 1987), a reliable measure of parkinsonian motor signs (Stebbins & Goetz, 1998), and timed motor tests recommended by CAPIT.

### *Assessment of Cognitive Function*

To accomplish the aim of studying the effects of PVP on cognitive function, we limited our primary outcomes measures to four tests that measure frontostriatal cognitive abilities. To assess the specificity of changes in frontostriatal cognitive function, we included one test of general cognitive function and two tests that measure semantic memory function.

Testing of cognitive function was performed in conjunction with assessment of motor function at the baseline visit one month prior to surgery and the 12-month follow-up visit after surgery for the PVP cohort. Cognitive testing of the comparison group was conducted at two intervals separated by 12 months. Testing of cognitive function for all participants was conducted while the patient was in the on period.

### *Tests of Frontostriatal Cognitive Ability*

*Psychomotor processing speed.* The Symbol Digit Modalities Test (SDMT: Smith, 1986) was employed as our measure of psychomotor processing speed. Participants were presented with a "key" consisting of nine simple geometric designs (e.g., a plus sign, a circle, an inverted T) with each design matched to a unique digit from 1 to 9. The test form consisted of a series of the nine designs, and the participant's task was to identify the corresponding number for each design according to the key. The key was available to the participant throughout the task. Participants were instructed to perform the task quickly but accurately. They were allowed 90 s to complete as many targets as possible. The score was the number of correctly completed targets in the allotted time. The oral version of this test was chosen because it is minimally affected by motoric slowing per se. In this version, participants verbally reported their answer to the examiner as opposed to writing their answer on the test form. The examiner recorded the participant's response on a separate answer form.

*Executive components of working memory.* The Listening Span test (Salthouse & Babcock, 1991) was employed as one measure of the executive components of working memory. Participants were instructed to listen to simple sentences, to immediately afterward select from among three choices the correct answer to a question about the sentence, and to remember the last word from each sentence for later recall. Participants were told that the questions had to be answered correctly. The number of sentences presented on each trial increased successively from one to seven, with three trials presented at each series length. The sentences were 6 to 10 words long. The final word from each sentence was one or two syllables, common enough to be found in a children's dictionary (Simon & Schuster, 1984), and appeared only once as a final word in the sentences. The question and answer alternatives for each sentence did not contain the final word of the sentence.

Participants were provided an answer booklet in which they marked their answers. Participants heard each sentence read aloud by the examiner at a normal speaking rate (e.g., "The boy ran with the dog"). Participants then selected one of three alternatives in response to a question about the sentence (e.g., "Who ran? \_\_\_ boy; \_\_\_ man; \_\_\_ girl"). After selecting the answer for the question about each sentence in a trial, participants were asked to turn the page and orally report the last word of each sentence, in the order they had been presented. Only trials on which the participant provided correct answers to the multiple-choice questions were counted. The span score (maximum = 7) was the maximum number of sentences for which

a participant recalled all final words of the sentences in the correct order for at least two of the three trials. Participants were given as much time as they required to produce their answers. Alternate forms of this test were used at baseline and follow-up testing, with order of form counterbalanced across participants.

The Digit Ordering test (Cooper et al., 1991) was employed as a second measure of the executive components of working memory. Participants were instructed to listen to seven single-digit numbers orally presented in random order and repeat them to the examiner in ascending order. Thus, if the participant was presented with the series 7-3-4-2-0-9-1, they had to repeat the series as 0-1-2-3-4-7-9. Digits were presented at the rate of approximately one digit per second. Fifteen series of digits were presented. Scoring awarded 1 point for each digit placed in the correct order that maintained an ascending sequence. Responses that were not part of the presented sequence, but maintained ascending order were tolerated but not considered in scoring. If a participant reported more than seven digits, only the first seven digits were considered. Thus, the maximum attainable score was 105 points. Alternate forms of this test were used at baseline and follow-up testing, with order of form counterbalanced across participants.

*Reasoning.* The Raven's Progressive Matrices—Advanced Matrices (Raven, Court, & Raven, 1976) were employed as a measure of reasoning ability. Participants were presented with multiple designs that are linked by a common conceptual pattern. The final design was missing, and the patient had to choose which of six to eight alternative final designs was correct. The test is divided into two sections: Set I has 12 problems and Set II has 36 problems. Participants were allowed 45 min to complete as many problems as possible.

### *Test of General Mental Status*

*Mini-Mental State Examination (MMSE).* The MMSE (Folstein, Folstein, & McHugh, 1975) is a widely used test of general mental status. Test items include orientation to time and place, attention, memory, repetition, verbal comprehension, and constructional abilities. Points were awarded for correct performance of testing items. Participants were allowed as much time as required to complete the test. The maximum score on this test is 30 points.

### *Tests of Semantic Memory*

*Vocabulary.* This measure of semantic memory is one subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1981). Participants were presented orally and visually with 35 words and asked to provide a definition for each word in the standard administration. Two points were awarded for complete definitions, 1 point for incomplete definitions, and 0 points for incorrect definitions, with a maximum score of 70 points. Participants were allowed as much time as necessary to complete this test.

*Peabody Picture Vocabulary Test—Revised (PPVT) Forms A and B.* The PPVT (Dunn & Dunn, 1981) is a visual-verbal test of semantic memory. Participants were presented with four line drawings depicting objects and scenes. Definitions were orally presented to the participants, and they were asked to choose which of the four drawings best matches the definition. Participants completed as many trials as possible until they failed six of eight consecutive trials. Form A and B were used as alternate forms with order of presentation counterbalanced across participants.

### *Data Analyses*

Resulting data from each of these tests were analyzed in a series of two-way (PVP/comparison group) repeated measures analysis of variance (ANOVA) models with time of assessment (baseline vs. 12 month follow-up) as the repeated measure. Because multiple comparisons

were required for this analytic approach, we sought to assess the level of independence between measures to gauge possible inflation of Type I error. Correlations among the four frontostriatal cognitive measures and among the two semantic memory measures in both samples were all significant (working memory: all  $r$ 's  $> .44$ , all  $p$ 's  $< .05$ ; semantic memory correlation:  $r = .622$ ,  $p < .002$ ). The lack of independence among these measures decreased our concerns regarding inflation of Type I error due to multiple comparisons. Thus, no correction for multiple comparisons was employed and a significance level of  $\alpha < .05$  was adopted for all analyses to avoid Type II error.

## RESULTS

Participant demographics and disease history variables are presented in Table 1. Matching of PVP and control PD patients was successful for age ( $t(19) = 1.04$ ,  $p > .30$ ), education ( $t(19) < 1.0$ ), UPDRS Motor Examination score during on period ( $t(19) < 1.0$ ), and HY stage during on period ( $U = 48.00$ ,  $p > .61$ ). Changes in levodopa dose across the study period between the PVP and PD control groups were similar [ $F(1, 19) < 1.0$ ].

Postsurgery MRI results indicated successful placement of the lesions within the GPI of all participants. Postsurgical adverse events, including mild facial weakness, increased dysarthria, and transient hallucination, resolved in all patients within 1 month following surgery.

Mean scores for the baseline and follow-up assessments are listed in Table 2. At baseline assessment the PVP and control PD patients showed the typical pattern of impaired performance on tests of frontostriatal cognitive function and intact performance on tests of non-frontostriatal cognitive function. Additionally, there were no significant differences between the PVP and control PD patients on any of the cognitive assessment tests at baseline (all  $t$ 's  $< 1.29$ ,  $p > .21$ ).

### *Psychomotor Processing Speed*

There was a significant decrease in performance between the baseline and follow-up assessments on the Symbol Digit Modalities Test [ $F(1, 19) = 12.50$ ,  $MSe = 11.73$ ,  $p < .005$ ]. The time of assessment (baseline vs. 12 month follow-up) by group interaction was reliable [ $F(1, 19) = 5.31$ ,  $MSe = 11.73$ ,  $p < .05$ ], due to a significant decline for the PVP group (Wilcoxon  $Z = 2.45$ ,  $p < .05$ ), but not the PD control group (Wilcoxon  $Z < 1.0$ ).

### *Tests of Executive Component of Working Memory*

There were significant decreases in performance between the baseline and follow-up assessments on the Listening Span test [ $F(1, 19) = 9.83$ ,  $MSe = .225$ ,  $p < .01$ ] and the Digit Ordering test [ $F(1, 19) = 5.48$ ,  $MSe = 119.24$ ,  $p < .05$ ]. The time of assessment by group interactions were reliable [Listening Span— $F(1, 19) = 6.01$ ,  $MSe = .225$ ,  $p < .05$ ; Digit Ordering— $F(1, 19) = 4.55$ ,  $MSe = 119.24$ ,  $p < .05$ ], due to significant

TABLE 1  
Patient Demographic and Disease Characteristics

Patient number	Age	Education	Lesion side	UPDRS		HY		Levodopa dose (mg)	
				On	Off	On	Off	Baseline	Follow-up
Pallidotomy sample									
1	70	10	Left	36	83	2.5	5	1250	1250
2	68	12	Left	44	76	3	4	650	800
3	52	19	Right	31	71	2	4	1000	1000
4	67	12	Left	20	63	3	4	900	1100
5	60	12	Left	24	69	2.5	4	1250	1250
6	63	8	Right	32	64	2.5	4	1150	1100
7	59	13	Left	22	111	3	5	850	850
8	64	9	Left	33	49	3	4	850	850
9	45	12	Right	15	77	2	4	1000	1000
10	45	14	Left	—	—	—	—	600	700
11	44	14	Right	23	55	2.5	4	750	800
Means ( $\pm$ standard error)	57.9 (3.0)	12.3 (0.9)	—	26.7 (2.8)	71.8 (5.4)	2.5 (0.1)	4 (0.1)	931.82 (67.17)	972.73 (56.55)
PD control sample means ( $\pm$ standard error)	62.4 (3.2)	12.9 (1.0)	—	30.1 (2.5)	—	2.5 (0.1)	—	935 (65.0)	990 (57.64)

Note. Education is years of formal education; UPDRS, Unified Parkinson's Disease Rating Scale Motor Examination section; HY, Hoehn and Yahr stage.

TABLE 2

Mean ( $\pm$  Standard Error) Performance on Cognitive Assessment Measures at Baseline and 12-Month Follow-up

Measure	Group			
	Pallidotomy		PD control	
	Baseline	Follow-up	Baseline	Follow-up
Tests of frontostriatal cognitive ability				
Symbol Digit Modalities Test	41.64 (3.27)	35.46 (4.00)	40.90 (2.23)	39.60 (2.06)
Listening Span	1.91 (0.39)	1.09 (0.25)	1.90 (0.18)	1.90 (0.20)
Digit Ordering Test	72.82 (5.10)	57.73 (7.00)	70.30 (6.53)	69.60 (7.73)
Raven's Progressive Matrices	11.73 (2.58)	8.36 (2.92)	12.00 (1.82)	11.40 (1.93)
Test of general mental status				
Mini-Mental Status Examination	27.46 (0.78)	27.36 (0.80)	28.00 (0.49)	28.50 (0.43)
Tests of semantic memory				
Vocabulary	41.18 (4.68)	40.73 (4.12)	42.08 (4.07)	42.50 (4.22)
Peabody Picture Vocabulary Test	152.27 (3.98)	153.46 (3.72)	158.51 (2.55)	161.20 (2.29)

declines for the PVP group (Listening Span Wilcoxon  $Z = 2.19$ ,  $p < .05$ ; Digit Ordering Wilcoxon  $Z = 2.41$ ,  $p < .05$ ), but not for the PD control group (Listening Span Wilcoxon  $Z < 1.0$ ; Digit Ordering Wilcoxon  $Z < 1.0$ ).

### *Test of Reasoning*

There was a significant decline in performance between the baseline and follow-up assessments on the Raven's Progressive Matrices [ $F(1, 19) = 9.15$ ,  $MSe = 4.50$ ,  $p < .01$ ]. The time of assessment by group interaction was reliable [ $F(1, 19) = 4.45$ ,  $MSe = 4.50$ ,  $p < .05$ ], due to a significant decline in performance for the PVP group (Wilcoxon  $Z = 2.31$ ,  $p < .05$ ), but not the PD control group (Wilcoxon  $Z < 1.0$ ).

### *Consistency of Impaired Performance*

To measure the consistency of frontostriatal cognitive impairment we assessed the frequency with which decreased performance met or exceeded 2  $SD$  of the mean on at least two tests. Seven of the 11 PVP patients and only 1 of the 10 comparison PD patients met this impairment criterion [ $\chi^2 (1, N = 21)$ ,  $p < .05$ ].

### *Test of General Mental Status*

There was no significant difference in performance between the baseline and follow-up assessments on the MMSE [ $F(1, 19) < 1.0$ ]. The time of assessment by group interaction was marginal [ $F(1, 19) = 3.69, MSe = .25, p = .07$ ], due to a slight improvement in performance on this measure for the comparison group, but not the PVP group.

### *Tests of Semantic Memory*

There was a significant improvement in performance between baseline and follow-up assessments on the Peabody Picture Vocabulary Test [ $F(1, 19) = 5.82, MSe = 6.78, p < .05$ ]. There was no significant difference in performance between baseline and follow-up assessments on the Vocabulary test [ $F(1, 19) < 1.0$ ], however. The time of assessment by group interactions for both measures of semantic memory were not reliable (both  $F$ 's  $< 1.0$ ).

## DISCUSSION

We found a significant decrease in performance on measures of psychomotor processing speed, the executive components of working memory, and reasoning at 1 year following PVP in our series of 11 PD patients. The declines in performance occurred only in the PVP group; there was no decline in the 10 PD patients assessed over the same interval of time in whom PVP was not performed. The impairments were not due to a general decline in cognitive function because patients' performance on a measure of mental status remained unchanged following PVP. Changes in levodopa doses were consistent between the PVP and PD control groups, so the impairments were not due to medication effects. In addition, impaired performance was limited to the frontostriatal cognitive measures, because performance on measures of semantic memory either remained unchanged or improved slightly following PVP. Thus, PVP appeared to have a specific and selective detrimental effect on psychomotor processing speed, the executive components of working memory, and reasoning.

These conclusions must be viewed cautiously for several reasons. First, we studied a small sample of PD patients, and the representativeness of our sample to all PD patients is not known. Second, although our use of a comparison group provides some control for changes in cognitive function due to disease progression, our patients were neither randomly assigned to group nor blinded to treatment. Third, the small sample size of the study precludes our ability to investigate the relationship of specific demographic (e.g., age) and surgical procedures (side of lesion) to the outcome measures. Finally, our results demonstrate statistically significant decreases in performance on tests sensitive to frontostriatal functional integrity following PVP. Their clinical significance, however, is not clear. Compared to healthy elderly partici-

pants, both the PVP and PD control groups were impaired on the measures of psychomotor processing speed, executive components of working memory, and reasoning (Cooper et al., 1991; Gabrieli et al., 1996; Stebbins et al., in press), so additional impairment may not have been noticeable to the PVP participants. None of our patients spontaneously reported difficulties with cognitive abilities, other than a common complaint of "slowed" thinking. Whether the statistically significant changes in frontostriatal cognitive test performance following PVP translates into clinically significant deficits remains to be seen.

There are divergent reports from other investigators on the effects of PVP on cognitive function. Short-term follow-up studies, those assessing cognitive functioning at baseline and 3 months after PVP, report either no change in cognitive status (Soukup et al., 1997) or decrements in performance on measures of verbal fluency (Scott et al., 1998; Uitti et al., 1997). One long-term follow-up study, assessing cognitive function at baseline and 12 months after PVP, reported decrements in performance on tests of frontal lobe function and memory (Baron et al., 1996). The decline in functioning was not present 3 months after surgery, suggesting a delayed effect on cognition. Additionally, when two subjects with postoperative frontal subdural hematomas were excluded from the analyses, significant differences in frontal lobe function and memory were not found for the remaining 10 patients. A second long-term follow-up study reported deterioration on tests of verbal working memory, although no data were presented on these measures (Sammuel et al., 1998).

The discrepancy of results between the present study and previous reports may be due to multiple causes. First, the short-term studies may not have allowed sufficient time to pass following the procedure for decrements in cognitive performance to manifest. A lack of significant change may have been due to sustained placebo effects (Goetz, Laurgens, & Stebbins, submitted for publication) or to a delayed effect of PVP on cognitive function.

A second putative cause for the discrepant results is the use of differing assessment strategies. The previous studies did not specifically assess psychomotor processing speed, the executive components of working memory, or reasoning, but rather sought to assess the effects of PVP on general cognitive function. Such an assessment approach is important to elucidate the safety of PVP in regards to cognitive function, but may lack the statistical power (due to multiple tests and few participants) and specificity to assess effects on frontostriatal cognitive function.

Our finding of significantly greater decline in frontostriatal cognitive function in PVP PD patients, compared to best medically managed PD patients, presents a potentially serious adverse effect of the procedure. This is in contrast to reports of positive effects of PVP on motor functioning and suggests a functional dissociation of GPi effects on motor and cognitive performance. Although the GPi is not typically thought of as a pivotal neural structure

for cognitive function, recent evidence of specific GPi dysfunction during a frontostriatal cognitive task in PD has been reported. Using positron emission tomography (PET) neuroimaging, and H<sub>2</sub><sup>15</sup>O labeling, regional cerebral blood flow was measured in six PD patients and six normal controls while they performed a task requiring the executive components of working memory and a control task (Owen, Doyon, Dagher et al., 1998). The only consistent difference in regional blood flow occurred in the right GPi. Across all comparisons, PD patients showed decreased right GPi blood flow, while the control participants showed increased blood flow in this region. The authors suggest that increased GPi blood flow represents increased inhibitory outflow to the cortex which in turn suppresses extraneous cortical activity and selectively enhances pertinent cortical activity essential to the cognitive task. The loss of dopamine in PD appears to increase the inhibitory outflow from the GPi which may excessively inhibit cortical activity at the cost of cognitive performance on tasks requiring the executive components of working memory. The effect of ablating the GPi during PVP may be an overcompensation of this cortical inhibition and lead an inability to suppress extraneous cortical activity during working memory tasks. This would suggest that PD patients who have received PVP would evidence decreased ability to suppress irrelevant stimuli compared to PD patients of equal disability who have not received ablative GPi surgery. Additional studies are needed test this hypothesis.

These findings provide new insights into the cognitive neuroscience of the frontostriatal system and, perhaps, normal aging. We have proposed that there is a frontostriatal syndrome characterized by correlated deficits in psychomotor processing speed, executive components of working memory, reasoning, and strategic declarative memory (Gabrieli et al., 1996; Gabrieli, 1996; Stebbins et al., in press). This syndrome is evident in PD, Huntington's disease, and Gilles de la Tourette's syndrome (Gabrieli et al., 1996; Singh et al., 1992; Stebbins et al., 1995). Normal aging is also characterized by disproportionate decreases in these mental abilities across the lifespan (reviewed in Prull, Gabrieli, & Bunge, in press), and these three declines are highly intercorrelated (Salthouse, 1982, 1992). It is difficult, however, to make direct links between neural structures and cognitive declines because normal aging and striatal degenerative diseases involve, to varying extents, multiple neural systems. It is unclear, therefore, whether the frontostriatal syndrome reflects the cumulative consequence of degeneration across multiple neural systems or can result from focal injury. The present results show that a focal striatal lesion can, by itself, produce the entire frontostriatal syndrome by selectively compromising psychomotor speed, executive components of working memory, and reasoning.

## REFERENCES

- Alexander, G. E., & Crutcher, M. D. 1990. Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. *Trends in Neuroscience*, **13**, 266–271.

- Alexander, G. E., Crutcher, M. D., & DeLong, M. R. 1990. Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. *Progress in Brain Research*, **85**, 119–146.
- Alexander, G. E., DeLong, M. R., & Strick, P. L. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, **9**, 357–381.
- Baddeley, A. 1986. *Working memory*. Oxford: Clarendon Press.
- Baron, M. S., Vitek, J. L., Bakay, R. A. E., Green, J., Kaneoke, Y., Hashimoto, R., Turner, R. S., Woodard, J. L., Cole, S. A., McDonald, W. M., & DeLong, M. R. 1996. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. *Annals of Neurology*, **40**, 355–366.
- Breen, E. K. 1993. Recall and recognition memory in Parkinson's disease. *Cortex*, **29**, 91–102.
- Carpenter, P. A., Just, M. A., & Shell, P. 1990. What one intelligence test measures: A theoretical account of the processing in the Raven Progressive Matrices test. *Psychological Review*, **97**, 404–431.
- Cooper, J. A., Sagar, H. J., Doherty, S. M., Jordan, N., Tidswell, P., & Sullivan, E. V. 1992. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in PD a follow-up study of untreated patients, *Brain*, **115**, 1701–1725.
- Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. V. 1991. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain*, **114**, 2095–2122.
- Cronin-Golomb, A. & Braun, A.E. 1997. Visuospatial dysfunction and problem solving in PD. *Neuropsychology*, **11**, 44–52.
- Cummings, J. L. 1993. Frontal-subcortical circuits and human behavior. *Archives of Neurology*, **50**, 873–880.
- DeLong, M. R. 1990. Primate models of movement disorders of basal ganglia origin. *Trends in Neuroscience*, **13**, 281–285.
- Dogali, M., Fazzini, E., Kolodny, E., Eidelberg, D., Sterio, D., Devinsky, O., & Beric, A. 1995. Stereotactic ventral pallidotomy for Parkinson's disease. *Neurology*, **45**, 753–761.
- Dunn, L. M. & Dunn, L. M. 1981. *Peabody Picture Vocabulary Test—Revised. Manual*. Circle Pines, MN: American Guidance Service.
- Fahn, S., Elton, R. L., & the UPDRS Development Committee. 1987. Unified Parkinson's Disease Rating Scale. In S. Fahn, C. D. Marsden, D. Calne, & M. Goldstein (Eds.), *Recent developments in Parkinson's disease*, Vol. 2. Florham Park, NJ: Macmillan Healthcare Information. Pp. 153–163.
- Flowers, K. A., Pearce, I., & Pearce, J. M. S. 1984. Recognition memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **47**, 1174–1181.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. 1975. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.
- Gabrieli, J. D., E. 1996. Memory systems analysis of mnemonic disorders in aging and age-related diseases. *Proceedings of the National Academy of Sciences*, **93**, 13534–13540.
- Gabrieli, J. D. E., Singh, J., Stebbins, G. T., & Goetz, C. G. 1996. Reduced working memory span in Parkinson's disease: Evidence for the role of a frontostriatal system in working and strategic memory. *Neuropsychology*, **10**, 322–332.
- Goetz, C. G., & Diederich, N. J. 1996. There is a renaissance of interest in pallidotomy for Parkinson's disease. *Nature Medicine*, **2**, 510–514.
- Goetz, C. G., Leurgans, S., & Stebbins, G. T. Objective changes in motor function during placebo treatment in Parkinson's disease. *Neurology*. (in press).

- Goldman-Rakic, P. S. 1987. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In V. F. Plum (Ed.), *Handbook of physiology—The nervous system*. Bethesda, MD: Am. Physiol. Soc. Pp. 373–417.
- Hoehn, M., & Yahr, M. 1967. Parkinsonism: Onset, progression and mortality. *Neurology*, **17**, 427–442.
- Iacono, R. P., & Lonsler, R. R. 1994. Reversal of Parkinson's akinesia by pallidotomy. *Lancet*, **343**, 418–419.
- Laitinen, L. B., Bergenheim, A. T., & Hariz, M. I. 1992. Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms. *Stereotactic and Functional Neurosurgery*, **58**, 14–21.
- Lang, A. E., Lozano, A. M., Montgomery, E., Duff, J., Tasker, R., & Hutchinson, W. 1997. Posteroventral medial pallidotomy in advanced Parkinson's disease. *New England Journal of Medicine*, **337**, 1036–1042.
- Langston, J. W., Widner, H., Goetz, C. G., Brooks, D., Fahn, S., Freeman, T., & Watts, R. 1992. Core assessment program for intracerebral transplantations (CAPIT). *Movement Disorders*, **7**, 2–13.
- Lees, A. J., & Smith, E. 1983. Cognitive deficits in the early stages of Parkinson's disease. *Brain*, **106**, 257–270.
- Mortimer, J. A., Pirozzolo, F. J., Hansch, E. C., & Webster, D. D. 1982. Relationship of motor symptoms to intellectual deficits in Parkinson's disease. *Neurology*, **32**, 133–137.
- Owen, A. M., Doyon, J., Dagher, A., Sadikot, A., & Evans, A. C. 1998. Abnormal basal ganglia outflow in Parkinson's disease identified with PET implications for higher cortical functions. *Brain*, **121**, 949–965.
- Pfann, K. D., Penn, R. D., Shannon, K. M., & Corcos, D. M. 1998. Pallidotomy and bradykinesia: Implications for basal ganglia function. *Neurology*, **51**, 796–803.
- Prull, M. W., Gabrieli, J. D. E., & Bunge, S. A. 1999. Memory and aging: A cognitive neuroscience perspective. In F. I. M. Craik & T. A. Salthouse (Eds.), *Handbook of aging and cognition II*. Mahwah, NJ: Erlbaum.
- Rafal, R. D., Posner, M. I., Walder, J. A., & Friedrich, F. J. 1984. Cognition and the basal ganglia: Separating mental and motor components of performance in Parkinson's disease. *Brain*, **107**, 1083–1094.
- Raven, J. C., Court, J. H., & Raven, J. 1976. *Manual for Raven's Progressive Matrices*. London, UK: HK Lewis.
- Salthouse, T. A. 1982. *Adult cognition: An experimental psychology of human aging*. New York: Springer-Verlag.
- Salthouse, T. A. 1992. What do adult age differences in the Digit Symbol Substitution Test reflect? *Journal of Gerontology: Psychological Sciences*, **47**, P121–128.
- Salthouse, T. A., & Babcock, R. L. 1991. Decomposing adult age differences in working memory. *Developmental Psychology*, **27**, 763–776, 1991.
- Samuel, M., Caputo, E., Brooks, D. J., Schrag, A., Scaravilli, T., Branston, N. M., Rothwell, J. C., Marsden, C. D., Thomas, D. G. T., Lees, A. J., Quinn, N. P. 1998. A study of medial pallidotomy for Parkinson's disease: Clinical outcome, MRI location and complications. *Brain*, **121**, 59–75.
- Scott, R., Gregory, R., Hines, N., Carroll, C., Hyman, N., Papanastasiou, V., Leather, C., Rowe, J., Silburn, P., & Aziz, T. 1998. Neuropsychological, neurological and functional outcome following pallidotomy for Parkinson's disease. A consecutive series of eight simultaneous bilateral and twelve unilateral procedures. *Brain*, **121**, 659–675.
- Shannon, K. M., Penn, R. D., Kroin, J. S., Adler, C. H., Janko, K. A., York, M., & Cox, S.

- J. 1998. Stereotactic pallidotomy for the treatment of Parkinson's disease. *Neurology*, **50**, 434–438.
- Simon and Schuster's illustrated young reader's dictionary*. 1984. New York: Wanderer Books.
- Singh, J., Gabrieli, J. D. E., & Goetz, C. G. 1992. Impairments of working memory in patients with Huntington's disease. *Neurology*, **42**(Suppl. 3), 280.
- Smith, A. 1968. The Symbol Digit Modalities Test: A neuropsychologic test for economic screening of learning and other cerebral disorders. *Learning Disabilities*, **3**, 83–91.
- Soukup, V. M., Ingram, F., Schiess, M. C., Bonnen, J. G., Nauta, H. J., W., & Calverley, J. R. 1997. Cognitive sequelae of unilateral posteroventral pallidotomy. *Archives of Neurology*, **54**, 947–950.
- Stebbins, G. T., Gabrieli, J. D. E., Burton, K., Rinaldi, J., Fleischeman, D., & Monti, L. 1994. Dissociation between processing speed and mnemonic components of working memory in patients with Parkinson's disease and patients with global amnesia. *Society for Neuroscience Abstracts*, **20**, 430.
- Stebbins, G. T., Gabrieli, J. D. E., Masciari, F., Monti, L., & Goetz, C. G. 1999. Delayed recognition in Parkinson's disease: A role for working memory? *Neuropsychologia*, **37**, 503–510.
- Stebbins, G. T., & Goetz, C. G. 1998. Factor structure of the Unified Parkinson's Disease Rating Scale: Motor Examination section. *Movement Disorders*, **13**, 633–636.
- Stebbins, G. T., Singh, J., Weiner, J., Goetz, C. G., & Gabrieli, J. D. E. 1995. Selective impairments of memory functioning in unmedicated adults with Gilles de la Tourette's Syndrome. *Neuropsychology*, **9**, 329–337.
- Stone, M., Gabrieli, J. D. E., Stebbins, G. T., & Sullivan, E. V. 1998. Working and strategic memory deficits in schizophrenia. *Neuropsychology*, **12**, 278–288.
- Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. 1986. Frontal lobe dysfunction in Parkinson's disease: The cortical focus of neostriatal outflow. *Brain*, **109**, 845–883.
- Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. 1987. Parkinson's disease: Cognitive changes in relation to treatment responses. *Brain*, **110**, 35–51.
- Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. 1990. Memory and learning in early Parkinson's disease: Evidence for a "frontal lobe syndrome." *Brain and Cognition*, **13**, 211–232.
- Uitti, R. J., Wharen, R. E., Turk, M. F., Lucas, J. A., Finton, M. J., Graff-Radford, N. R., Boylan, K. B., Goerss, S. J., Kall, B. A., Adler, C. H., Caviness, J. N., & Atkinson, E. J. 1997. Unilateral pallidotomy for Parkinson's disease: Comparison of outcome in younger versus elderly patients. *Neurology*, **49**, 1072–1077.
- Waters G. S., & Caplan D. 1996 . The measurement of verbal working memory capacity and its relation to reading comprehension. *The Quarterly Journal of Experimental Psychology*, **49**, 51–79.
- Wechsler, D. 1981. *WAIS-R manual*. New York, NY: Psychol. Corp.
- Wilson, F. A. W., O. Scalaidhe, S. P., & Goldman-Rakic, P. S. 1993. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science*, **260**, 1955–1957.