Striatal Contribution to Cognition: Working Memory and Executive Function in Parkinson's Disease before and after Unilateral Posteroventral Pallidotomy

M. Jahanshahi[1], J. Rowe[2], T. Saleem[1], R. G. Brown[3], P. Limousin-Dowsey[1], J. C. Rothwell[1], D. G. T. Thomas[1], and N. P. Quinn[1]

Abstract

■ The basal ganglia are intimately connected to the frontal cortex via five fronto-striatal circuits. While the role of the frontal cortex in cognition has been extensively studied, the contribution of the basal ganglia to cognition has remained less clear. In Parkinson's disease, posteroventral pallidotomy (PVP) involves surgical lesioning of the internal section of the globus pallidus (GPi, the final output pathway from the basal ganglia) to relieve the motor symptoms of the disorder. PVP in Parkinson's disease provides a unique opportunity to investigate the impact of disruption of striatal outflow to the frontal cortex on cognition. We assessed executive function and working memory after withdrawal of medication in 13 patients with Parkinson's disease before and 3 months after unilateral PVP compared to 12 age- and IQ-matched normals assessed twice with an interval of 3 months. The tests used were: Wisconsin Card Sorting (WCST), Self-Ordered Random Number Sequences, Missing Digit Test, Paced Visual Serial Addition Test (PVSAT), and Visual Conditional Associative Learning Test (VCALT). After PVP, the patients performed significantly better on the Self-Ordered Random Number Sequences and the WCST, an improvement that was also observed in the normals across the two assessment and is therefore likely to reflect practice effects. Relative to the normals, the patients showed significant differential change following PVP on the Missing Digit Test and PVSAT, on which they performed worse after compared to before surgery, while the controls performed better on the second assessment. For the patients, performance on the VCALT also indicated deterioration after PVP, but the changes approached significance. The side of PVP had no effect on the results. The pattern of change observed 3 months after PVP was maintained at 15-month follow-up. The results suggest that striatal outflow to the frontal cortex may be essential for those aspects of executive function that showed deterioration after PVP. ■

INTRODUCTION

The frontal cortex and the basal ganglia are connected by five circuits: the ''motor'' circuit between the supplementary motor area (SMA) and the putamen, the ''associative'' circuit between the dorsolateral prefrontal cortex (DLPFC) and the dorsolateral caudate, the ''limbic'' circuit between the anterior cingulate and the ventral striatum, the ''lateral orbito-frontal'' circuit between the frontal areas and the ventromedial caudate, and finally the ''oculomotor'' circuit between the frontal eye fields and the body of the caudate (Alexander, de Long, & Strick, 1986). Each circuit originates from a discrete frontal area, passes through specific input and output portions of the basal ganglia, and projects back to the original frontal site via distinct thalamic nuclei. The five circuits are considered to operate in parallel and segregated fashion (Alexander et al., 1986). While the role of the frontal cortex in cognition has been extensively studied, the contribution of the basal ganglia to cognition has remained less clear. Treatment of Parkinson's disease, a basal ganglia disorder, with pallidotomy involving surgical lesioning of the output pathway from the striatum provides a unique opportunity to investigate the impact of disruption of striatal outflow to the frontal cortex on cognition.

According to current pathophysiological models of Parkinson's disease, the degeneration of dopamine cells in the substantia nigra and the resultant dopamine deficiency in the putamen lead to overactivity of the internal segment of the globus pallidus (GPi), the final output pathway from the basal ganglia to the frontal cortex. This excessive inhibitory outflow from the GPi, in turn, inhibits its thalamo-cortical targets (Wichman & de Long, 1996; de Long, 1990). In humans, some support for this model of Parkinson's disease has been provided by PET activation studies that have shown underactivation of the SMA, anterior cingulate, and the

[1]Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, UK, [2]Homerton Hospital, London, UK, [3]Institute of Psychiatry, London, UK

DLPFC in Parkinson's disease patients during performance of self-selected (Playford, Jenkins, Passingham, et al., 1991) or self-initiated movements (Jahanshahi, Jenkins, Brown, et al., 1995) relative to matched healthy individuals. According to this model, lesioning of the GPi should reduce the excessive inhibitory outflow from this area and ''release the brake'' on cortical activity and improve symptoms of Parkinson's disease such as bradykinesia and akinesia, considered a consequence of cortical underactivation. In fact, such surgical lesioning of the globus pallidus has a relatively long history as a treatment of Parkinson's disease, dating back to the 1950s. With the advent of levodopa therapy, such surgical treatments were largely abandoned except in severe cases of tremor. However, long-term experience with levodopa therapy has revealed the complications that can ensue, and since 1992 surgical lesioning of the GPi has been resurrected as a treatment for Parkinson's disease. The revised surgical procedure now targets the posteroventral section of the internal pallidum and has been shown to result in clinically significant improvement in severely disabled patients (Samuel, Caputo, Brooks, et al., 1998; Scott, Gregory, Hines, et al., 1998; Lang et al., 1997; Baron, Vitek, Bakay, et al., 1996; Dogali et al., 1995). This so-called posteroventral pallidotomy (PVP) results in dramatic reduction of drug-induced dyskinesias and some improvement of akinesia, bradykinesia, rigidity, and tremor, but less change in the impairment of gait or postural instability.

PET activation studies have demonstrated that compared to presurgical levels, PVP leads to decreased activation of the pallidum and increased activation of the SMA and the DLPFC during performance of random joystick movements (Samuel, Ceballos-Baumann, Blin, et al., 1997; Samuel, Ceballos-Baumann, Turjanski, et al., 1997) or the SMA and the lateral premotor cortex during visually cued reaching and grasping movements (Grafton, Waters, Sutton, et al., 1995). Using 18-fluorodeoxyglucose PET, Eidelberg, Moeller, Ishikawa, et al. (1996) reported that following unilateral PVP significant decreases in the lentiform nucleus and thalamic resting metabolism were coupled with significant increases in resting metabolism in the ipsilateral DLPFC, lateral premotor cortex, and the primary motor cortex. Overall, these functional imaging results support the view that PVP alters the functioning of the basal ganglia–thalamo-cortical circuits and more specifically the motor and the associative circuits. The changes observed in prefrontal cortex are difficult to explain given that the target of PVP is the posteroventrolateral part of the GPi, that is the sensorimotor section that is part of the motor circuit. It is possible that localization of the lesion in some cases is not limited to the posteroventrolateral section of the GPi but also extends to the anterodorsal GPi.

In humans, the cortical target of the associative circuit, that is, the DLPFC, has been shown to be involved in executive function and working memory, since performance on tasks involving these processes is impaired following damage to the DLPFC (e.g., Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Milner, 1963, 1964) and this area shows significant activation in functional imaging studies during working memory tasks such as generation of Self-Ordered Random Number Sequences or the Missing Digit Test (Petrides, Alivisatos, Evans, & Meyer, 1993). Therefore, the question arises whether alteration of the functioning of the associative circuit and increased activation of the DLPFC following PVP is associated with any changes in these specific aspects of cognitive functioning. The aim of our study was to address this question. As stated above, the study of the impact of PVP on executive function and working memory is also important because it may clarify the role of the basal ganglia in cognitive function and shed some light on the issue of the functional segregation versus convergence of information processing across the five fronto-striatal circuits.

The effect of PVP on cognitive function has been examined in a number of studies, the results of which have been critically reviewed from a conceptual and methodological perspective by York, Levin, Grossman, and Hamilton (1999). The impact of PVP on cognitive function is not consistent across these studies. The present study differs from these published studies in several respects. First, we focused on specific aspects of cognitive function, namely executive function and working memory, which have been previously shown to be impaired in Parkinson's disease (Owen, Iddon, Hodges, Summers, & Robbins, 1997; Cooper, Sagar, Doherty, et al., 1992; Gotham, Brown, & Marsden, 1988; Taylor, Saint-Cyr, & Lang, 1986). Also, this focus was partly based on the results of the functional imaging studies that have demonstrated a significant increase in activation of the DLPFC following PVP in Parkinson's disease (Samuel et al., 1998), an area that is known to play a part in executive function and working memory. In fact, as noted by York et al. (1999), given that PVP interrupts fronto-striatal function, it is surprising that very few thorough investigations of executive function have been carried out. We also included some tests of executive function and working memory that had not been used in previous studies, but that were demonstrated to activate the DLPFC in functional imaging studies and to be impaired after focal lesions of this area. Second, unlike all previous studies that examined cognitive function when patients were on medication, we assessed our patients off medication both before and after PVP. This is important because PVP may result in the alteration of dose of medication in a proportion of patients postsurgically. This may, in turn, affect performance on tests of cognitive function, which have been previously shown to be sensitive to dopaminergic medication in Parkinson's disease (Cooper et al., 1992; Lange, Robbins, Marsden, et al., 1992; Gotham et al., 1988). Third, with repeated

assessment of cognitive function at short intervals of 3 months, which is commonly used for follow-up of patients following PVP, practice effects constitute possible confounding factors when assessing absolute change in cognitive function. Although use of alternate forms of tests (where available) aims to overcome this effect, nevertheless, it cannot circumvent the problem of ''learning to learn'' or the benefit that may accompany previous experience with the test. For this reason, we included a control group and assessed the performance of 12 healthy normal subjects matched with the patients in terms of age and estimates of ''premorbid IQ'' on the same tests on two occasions separated by an interval of 3 months. Finally, we also reassessed performance 12 months or longer after PVP in nine patients. Such long-term postsurgical follow-up is necessary as there is some evidence that cognitive deficits observed several months after PVP may not exist when reassessed after a longer period (Kumar et al., 1998).

RESULTS

For the patients, mean United Parkinson's Disease Rating Scale (UPDRS) Part III scores assessed off medication were significantly lower at 3 months follow-up than before PVP ($t = 2.5$, $df = 11$, $p = .03$), indicating significant improvement of motor symptoms after PVP. Improvement of dyskinesias with surgery was also evident from the significant change ($t = 3.83$, $df = 8$, $p = .005$) in the UPDRS Part IV scores, 3 months after PVP (mean = 6.8, $SD = 2.7$) compared to before (mean = 14.0, $SD = 4.1$). As a result of these symptomatic improvements with PVP, activities of daily living assessed on the UPDRS were also less affected 3 months after PVP (mean = 21.3, $SD = 8.4$) compared to before surgery (mean = 27.8, $SD = 10.1$), a change that was significant ($t = 3.4$, $df = 12$, $p = .005$).

Change in Executive Function in Parkinson's Disease 3 Months After PVP

The scores of the patients before and after PVP and the normal controls on the two assessment occasions are presented in Table 1.

The patients correctly sorted fewer categories than the controls on the Wisconsin Card Sorting Test (WCST) [main effect of Group: $F(1,23) = 6.1$, $p = .021$]. The main effect of Time was also significant [$F(1,23) = 4.9$, $MS = 14.7$, $p = .036$] with the number of categories correctly sorted being higher on the second occasion than the first across the two groups. The Group × Time interaction was not significant ($p > .05$). At the time of the first assessment, nine of the controls (75%) compared to four of the patients (30.8%) correctly sorted six categories. On the second assessment, this was achieved by 11 of the controls (91.7%) compared to seven of the patients (53.8%). The two groups also differed significantly in terms of mean perseverative errors [Group: $F(1,23) = 4.4$, $MS = 36.9$, $p = .046$], which were higher for the patients than the normals. The main effect of Time on perseverative errors approached significance [$F(1,23) = 2.8$, $p = .105$], indicating a trend for fewer perseverative errors on the second assessment occasion across the two groups. The Group × Time interaction effect was not significant. Nonperseverative errors on the WCST were significantly higher for the patients than controls [Group: $F(1,23) = 9.2$, $MS = 330.3$, $p = .006$] and were reduced across the two groups on the second assessment occasion as indicated by the significant main effect of Time [$F(1,23) = 6.1$, $MS = 179.4$, $p = .022$]. The Group × Time interaction effect on nonperseverative errors was not significant ($p > .05$). Nine of the controls (75%) and seven of the patients (53.8%) made fewer nonperseverative errors on the second assessment.

Relative to the normals, on the test of Self-Ordered Random Sequences, the percent of sequences generated correctly was lower for the patients, a difference that approached significance [$F(1,223) = 3.2$, $MS = 106.2$, $p = .085$]. The patients missed out significantly more of the 10 items in the sequence [$F(1,23) = 4.8$, $MS = 1.50$, $p = .039$] and erroneously repeated the same item more frequently, a difference that also approached significance [$F(1,23) = 3.6$, $MS = .41$, $= .07$]. The main effect of Time was significant for the average number of items missing [$F(1,23) = 4.4$, $MS = .44$, $p = .046$], which was significantly lower on the second assessment occasion compared to the first across the two groups. Of the controls, 58.7%, and of the patients, 76.9% missed out fewer items from the sequence at the time of the second assessment compared to the first, a change that was significant in each of the two groups ($p < .05$). The main effect of Time was not significant for the percent correct or average number of repeated items. The Group × Time interaction was not significant for any of the measures obtained on this test ($p > .05$).

On the Missing Digit Test, the percent of items correct was lower for the patients than the controls across both assessment occasions, but the main effect of Group failed to achieve significance at the 5% level [$F(1,23) = 2.7$, $MS = 1646.2$, $p = .11$]. The main effect of Time was not significant [$F(1,23) = 1.3$, $MS = 60.6$, $p = .270$], but the Group × Time interaction was significant [$F(1,23) = 23.4$, $MS = 1192.6$, $p = .001$]. Post hoc tests revealed that the significant interaction resulted from the fact that while the patients performed significantly worse after PVP than before surgery ($t = 3.4$, $df = 13$, $p = .004$), the performance of the controls was significantly improved from the first assessment to the second ($t = 2.6$, $df = 11$, $p = .026$). Compared to the first assessment, performance on the Missing Digit Test was improved in 91.7% of the controls, but worse in 84.6% of the patients, when assessed on a parallel form of the test 3 months later.

Table 1. Mean and Standard Deviation (in Parentheses) Scores on Measures of Executive Function and Working Memory Before and 3 Months After PVP for the Patients and on Two Occasions Separated by Three Months for the Normal Controls

	Patients With Parkinson's Disease		*Matched Controls*	
	Pre-PVP	*Post-PVP*	*Time 1*	*Time 2*
WCST				
Number categories sorted	3.9 (2.1)	5.1 (1.5)	5.3 (1.5)	5.9 (0.29)[a]
Nonperseverative errors	10.8 (7.1)	6.8 (6.1)	5.4 (6.1)	1.8 (2.1)[a]
Perseverative errors	3.6 (3.8)	2.1 (2.7)	1.6 (2.6)	0.67 (0.89)
Perseverative errors (%)	20.4 (14.8)	17.9 (17.4)	13.2 (17.9)	16.6 (23.4)
Self-Ordered Random Sequences				
Percent correct	25.8 (19.5)	34.2 (24.2)	45.0 (25.7)	44.2 (20.7)
Average missing	1.1 (0.52)	0.83 (0.42)	0.67 (0.49)	0.56 (0.37)[a]
Average repetition	0.37 (0.23)	0.52 (0.39)	0.25 (0.19)	0.27 (0.21)
Missing Digit Test				
Percent correct	60.5 (15.9)	48.5 (16.7)	62.2 (21.9)	69.7 (17.6)[b]
PVSAT[b]				
Errors—slow rate	4.0 (4.0)	6.2 (6.8)	1.8 (1.7)	1.3 (2.5)
Errors—fast rate	10.2 (6.1)	11.1 (7.4)	6.2 (6.7)	4.1 (5.4)
VCALT				
Total trials to criterion	53.6 (22.5)	64.5 (21.2)	42.7 (17.4)	46.8 (29.3)
Total errors	25.0 (15.5)	31.7 (16.6)	15.7 (9.5)	22.6 (19.8)

[a]Significant main effect of time across the two groups.

[b]Significant Group × Time interaction.

On the Paced Visual Serial Addition Test (PVSAT), the main effect of Group [$F(1,23) = 6.6$, $MS = 526.2$, $p = .017$] was significant, indicating that mean errors were significantly higher for patients than controls across the two occasions and rate of presentation. The main effect of rates of presentation [$F(1,23) = 25.0$, $MS = 528.4$, $p = .001$] was also significant, with more errors at the faster rate of presentation across the two groups and the two assessment occasions. The significant Group × Time interaction [$F(1,23) = 5.5$, $MS = 51.4$, $p = .028$] resulted from the fact that the number of errors was significantly reduced from the first assessment the second for the normals ($t = 2.4$, $df = 11$, $p = .033$), whereas the patients tended to make more errors after PVP than before surgery, a difference that was not significant at the 5% level, however ($t = 1.5$, $df = 12$, $p = .164$). The other main or interaction effects were not significant ($p > .05$).

The total number of trials to criterion and the total number of errors on the Visual Conditional Associative Learning Test (VCALT) were higher for the patients than the controls, but the differences failed to achieve significance at the 5% level [total trials to criterion: $F(1,23) = 3.7$, $MS = 2547.9$, $p = .06$; total errors: $F(1,23) = 3.6$, $MS = 1061.2$, $p = .07$]. Neither the main effect of Time nor the Group × Time interaction were significant ($p > .05$). Before surgery, 8 of the 13 patients (61.5%) who completed the test reached criterion on the VCALT, compared to 4 (30.8%) after surgery, a decrease that approached significance ($\chi^2 = 3.6$, $df = 1$, $p = .057$). In contrast, in the control group, 7 (58.3%) and 8 (66.7%) of the 12 subjects reached criterion, respectively, on the first and second assessment occasions, an increase that also approached significance ($\chi^2 = 2.7$, $df = 1$, $p = .098$). The differences between the two groups in the proportion of subjects reaching criterion were not significant at the time of the first assessment ($\chi^2 = 0.27$, $df = 1$, $p > .05$), but approached significance at the second assessment ($\chi^2 = 3.2$, $df = 2$, $p = .07$), due to fewer patients than controls achieving criterion after PVP.

We repeated all the above analyses using the Spot-the-Word measure that was significantly higher in the normals than the patients as a covariate. The pattern of results was unchanged. All the ANOVAs were also repeated to assess the effects of side of surgery. The side of the unilateral PVP (four right, nine left) produced no significant main or interaction effects on any of the measures of executive function ($p > .05$). In light of the sex imbalance between the patient and control groups, the above analyses were repeated using sex as an independent variable. Sex did not produce any significant main or interaction effects with ''time of assessment'' in either the patient or control groups for any of the measures of executive function used, and did not interact with the ''time of assessment'' when the groups were combined.

Change in Executive Function in Parkinson's Disease 15 Months After PVP

The average duration of long-term follow-up for the nine patients was 14.9 months ($SD = 3.8$). The nine patients who participated in the long-term follow-up did not differ from the remaining four in terms of demographic or clinical features or on any of the cognitive measures before surgery or at 3 months follow-up ($p > .05$). Table 2 shows the scores of the nine patients, 3 and 12 months after the PVP. A series of paired t tests were used to assess long-term change in cognitive function after PVP. Significant change was found only on the test of Self-Ordered Random Number Sequences, on which the percent items correct was significantly higher ($t = 2.8$, $df = 7$, $p = .026$), while the average number of repetitions ($t = 2.9$, $df = 7$, $p = .022$) and the average number of items missing ($t = 3.6$, $df = 7$, $p = .009$) were significantly lower at long-term follow-up compared to 3 months after PVP.

Table 2. Scores on Measures of Executive Function and Working Memory 3 and 12 Months After PVP for the Nine Patients Who Took Part in the Long-Term Follow-Up

	3 Months	*15 Months*
WCST		
Number categories sorted	5.2 (0.97)	4.9 (1.5)
Nonperseverative errors	6.3 (5.3)	9.0 (6.9)
Perseverative errors	1.7 (1.9)	2.7 (2.1)
Perseverative errors (%)	13.6 (15.1)	24.3 (8.5)
Self-Ordered Random Sequences		
Percent correct	36.3 (29.1)	43.8 (31.0)*
Average missing	0.89 (0.52)	0.76 (0.54)*
Average repetition	0.44 (0.33)	0.27 (0.26)*
Missing Digit Test		
Percent correct	50.7 (19.1)	49.3 (16.9)
PVSAT		
Errors—slow rate	6.6 (7.6)	4.1 (3.2)
Errors—fast rate	12.6 (6.9)	10.0 (4.5)
VCALT		
Total trials to criterion	61.3 (9.0)	56.0 (9.0)
Total errors	30.0 (15.8)	23.3 (6.8)

*Significant change with $p < .05$.

DISCUSSION

The patients had significantly lower UPDRS motor and dyskinesia scores after PVP, indicating improvement of the motor symptoms of the disease and dyskinesias after surgery. The changes in working memory and executive function discussed below should be considered in the context of such symptomatic improvement.

Our 13 patients were in the average range in terms of intellectual ability and none were intellectually impaired. The patients were matched with the normal controls in terms of age and estimates of premorbid verbal IQ (VIQ). Across the two assessments, the patients performed worse than these matched normals on the tests of executive function and working memory, confirming previous studies that have shown such deficits in tests of executive function and working memory (Owen et al., 1997; Cooper et al., 1992; Gotham et al., 1988; Taylor et al., 1986) and conditional associative learning (Vriezen & Moscovitch, 1990; Gotham et al., 1988) in Parkinson's disease.

One possible confound in interpreting the results is the imbalance in the sex ratio in the patient and control group. The results confirmed that sex produced no significant main or interaction effects on any of the measures of executive function in either the patient or control groups. Parkinson's disease is not a sex-linked disorder, with the age-adjusted prevalence being the same in both sexes. We should not, therefore, expect any interaction between sex and cognitive change related to the disease process. The primary potential impact of such a sex imbalance is in the overall group effects. However, evidence from the literature for such an effect is sparse. Sex effects on tests of executive function are not commonly reported. On the WCST, most of the normative data suggests an absence of any significant sex difference across the age range (Paniak, Miller, Murphy, Patterson, & Keizer, 1996; Heaton, Chelune, Talley, Kay, & Curtis, 1993; Rosselli & Ardila, 1993) with only one study by Boone, Ghaffarian, Lesser, et al. (1993) indicating a female advantage. For the

specific version of the WCST used in the present study, no sex effect has been found in older adults (Lineweaver, Bond, Thomas, & Salmon, 1999). On the Paced Auditory Serial Addition Test (PASAT), sex has been shown to either have no effect (Roman, Edwall, Buchanan, & Patton, 1991) or only a minimal (and insignificant) effect with a slight male advantage (Brittain, La Marche, Reeder, et al., 1991; Stuss, Stethem, & Poirer, 1987). Finally, on a subject-ordered task analogous to our self-ordered generation task, no sex differences have been found (Daigneault & Braun, 1993). No normative data are available on sex effects in the remaining tests (VCALT and Missing Digit Test), and we can only assume that they show a similar insensitivity to sex. Even if an effect is present, we anticipate that it would be small compared to the main effect of group. A separate issue is the impact of sex on test–retest effects on the various tasks. To our knowledge, there is no evidence to suggest that men and women differ in their ability to benefit from practice on executive tasks, independently of any gender difference in overall performance. In the absence of such evidence, we have made the assumption that sex differences had no contribution to the Group × Time interactions reported.

Heterogeneous Effect of PVP on Cognitive Executive Function

In terms of the impact of PVP on executive function and working memory in Parkinson's disease, the tests can be divided into two groups. First, those on which performance was significantly improved on the second assessment compared to the first for both the patients and controls (WCST, Self-Ordered Random Sequences), which is likely to reflect practice effects. Second, tests on which the patients and controls showed differential patterns of change across the two assessments either significantly (Missing Digit Test, PVSAT) or nonsignificantly (VCALT); with the patients performing worse after PVP whereas the performance of the controls was better on the second compared to the first assessment. These results of PVP are reminiscent of the impact of dopaminergic medication on cognitive function in Parkinson's disease, which is also variable. While some aspects of executive function and working memory are improved following dopaminergic medication (Cooper et al., 1992; Lange et al., 1992; Gotham et al., 1988; Girotti, Carella, Grassi et al., 1986), others remain unchanged (Lange et al., 1992; Girotti et al., 1986) or even become impaired (Gotham et al., 1988). In the present study, PVP had a similarly heterogeneous effect on the measures of executive function and working memory.

Our results are consistent with previous studies in two main respects. First, previous studies have also shown that the impact of unilateral PVP on tests of executive function can range from improvement (Lacritz, Cullum, Frol, Dewwy, & Giller, 2000; Junque et al., 1999; Riordan, Flashman, & Roberts, 1998; Scott et al., 1998; Trepanier, Sain-Cyr, Lozano, & Lang, 1998; Soukup et al., 1997; Baron et al., 1996), which is probably due to practice effects; to deterioration on specific tests (Lacritz et al., 2000; Stebbins, Gabrieli, Shannon, et al., 2000; Junque et al., 1999; Yokoyama, Imamura, Sugiyama, et al., 1999; Cahn, Sullivan, Shear, et al., 1998; Crowe et al., 1998; Masterman, DeSalles, Baloh, et al., 1998; Riordan et al., 1998; Scott et al., 1998; Trepanier et al., 1998; Soukup et al., 1997; Uitti, Wharen, Turk, et al., 1997; Baron et al., 1996). A second pattern in common with previous studies is the existence of individual differences in terms of the observed effects. While on a number of the tests, the effects were consistent and either clearly reflects deterioration (Missing Digit Test) or improvement due to practice (fewer items missing from the Self-Ordered Random Sequences), on others (PVSAT) there were major individual differences among the patients, some performing worse, others better, and a subgroup no differently after PVP compared to before the surgery.

One reason for such individual differences in the impact of PVP on executive function and working memory may be variations in the precise location of the lesion during surgery. In 11 of their 26 patients, which included some of the present sample, Samuel et al. (1998) found that the degree of improvement in contralateral bradykinesia as assessed with the UPDRS was significantly associated with the ventrality of the lesion (the distance of the most ventral point of the lesion below the AC–PC plane as determined by MRI), whereas no such significant correlation was found between the volume of the lesion and improvement of either contralateral bradykinesia or dyskinesias after PVP. Junque et al. (1999) also reported that the volume of the lesion showed no significant corrections with change in cognitive function after PVP. Recently, Lombardi, Gross, Trepanier, et al. (2000) have provided evidence suggesting that anatomical differences in the precise location of the lesion in the GPi along an anteromedial-to-posterolateral axis was related to cognitive outcome following PVP. Category fluency, paced serial addition, and release from proactive interference were linearly related to the distance along this axis, with anteromedial and posterolateral lesions being, respectively, associated with impairment and improvement of performance on these aspects of cognition. Thus, differences in the precise location of lesions across centers, together with variations in important sample characteristics such as age, stage of illness, premorbid levels of functioning, and efficacy of medication before and after PVP could partly explain the inconsistent findings across studies.

An interesting aspect of the present results, which is also mirrored in previous studies, is that PVP did not produce uniform effects across a range of tests of executive function and working memory, only some of which showed significant deterioration following surgery. In previous studies, word fluency (Cahn et al.,

1998; Junque et al., 1999; Yokoyama et al., 1999; Masterman et al., 1998; Riordan et al., 1998; Scott et al., 1998; Trepanier et al., 1998; Soukup et al., 1997; Soukup et al., 1997), digit span backwards (Trepanier et al., 1998), digit ordering and listening span (Stebbins et al., 2000), and the Wisconsin (Lacritz et al., 2000) were the tests of executive function that were significantly and selectively impaired in Parkinson's disease following PVP. In the present study, the patients and controls showed significant differential patterns of change between the two assessments on two tests: the Missing Digit Test and the PVSAT that were worse after PVP in the patients but improved on the second assessment for the controls. In contrast, the WCST and the Self-Ordered Random Number Sequences were improved possibly as a result of practice in both groups from the first to the second assessment. Why was it that only some of the tests of executive function were affected by PVP in Parkinson's disease and not others? The common feature of Missing Digit Test and PVSAT is that they are both externally and visually paced tasks that require holding one (PVSAT) or more (Missing Digit Test) items of information ''on line'' across an interval of several seconds in visual working memory. The visual and external nature of the pacing of performance for these two tests poses an additional processing demand, since on each trial a failure to process and manipulate the visually presented stimulus appearing on the VDU screen at a preset and relatively fast rate can affect performance by producing an error. While the Self-Ordered Random Number Sequences were also visually and externally paced, the pacing was less crucial to the accuracy of performance on this test, since the pacing stimulus did not carry any information to be processed and it simply operated to control the rate of generation of the sequence of numbers.

It may also be relevant that imaging studies have demonstrated that the Missing Digit Test and the Serial Addition Test activate the lateral premotor cortex as well as the DLPFC or the SMA among other areas (de Jong, van Zomeren, et al., 1996; Petrides et al., 1993). Recent evidence from animal studies has shown that in the motor circuit, there are multiple and separate projections from GPi to the motor cortex, SMA, and lateral premotor cortex (Hoover & Strick, 1993). In Parkinson's disease, while the SMA is underactive, the lateral premotor cortex is overactive relative to normals during complex movement (Samuel, Ceballos-Baumann, Blin, et al., 1997; Samuel, Ceballos-Baumann, Turjanski, et al., 1997) and shows significant increases in resting metabolism (Eidelberg et al., 1996) and movement-related activity (Grafton et al., 1995) following PVP. Thus, the deterioration in performance on the Missing Digit Test and PVSAT following PVP may relate to changes in activation of the lateral premotor cortex (possibly further increases in overactivity), which is one of the cortical sites of projection of the outflow from the GPi in the motor circuit and overactive in Parkinson's disease relative to normals even prior to surgery. It is of interest that the conditional associative learning, the other test on which the patients did nonsignificantly worse after PVP is also sensitive to lesions of the lateral premotor cortex (Halsband & Passingham, 1982; Petrides, 1982) and activates the dorsal premotor cortex among other areas in imaging studies in man (Grafton, Fagg, & Arbib, 1998; Deiber et al., 1997; Mitz, Wise, & Zeffiro, 1993).

The improved performance on the WCST and the Self-Ordered Random Number Sequences across the two assessment occasions was observed in both groups and was considered to reflect practice effects. Such significant practice effects are likely to result from the development and use of task-specific strategies. Since performance on these tests was also better in Parkinson's disease following PVP compared to before surgery, this suggests that PVP does not adversely affect use of task-specific strategies.

Other possible reasons for the apparent inconsistency in the impact of PVP across tests of executive function and working memory may be the differential sensitivity of particular tests and that the aspects of ''frontal'' function tapped by the various tests were not homogenous. The frontal cortex, which constitutes a sizeable proportion of brain volume in humans, is not homogenous either anatomically or functionally (Passingham, 1993; Stuss & Benson, 1984). One indication of the functional heterogeneity of frontal function is the lack of significant correlation between various tests commonly considered to tap frontal function such as the WCST and word fluency (Burgess & Shallice, 1994).

The results of Trepanier et al. (1998) have both similarities with and differences from our results and those of the other published studies. For example, we found that a PVSAT and VCALT tended to deteriorate after PVP, whereas Trepanier et al. (1998) found that performance on these tests to be, respectively, improved or unchanged. One important reason for these discrepancies may be that we assessed our patients off medication both before and after PVP, whereas Trepanier et al. (1998) evaluated their sample on medication. Previous studies have demonstrated that in Parkinson's disease dopaminergic medication may either improve (Cooper et al., 1992; Lange et al., 1992) or impair (Gotham et al., 1988) different aspects of executive function. A second reason may be procedural differences between studies. In the present study, the Paced Serial Addition Test was visually presented, whereas Trepanier et al. (1998) used an auditory version. On the PVSAT we used faster rates of presentation of items (one item every 2 or 4 sec compared to 3 or 5 sec in Trepanier et al.'s study) and on the VCALT a greater number of associations (six pairs compared to four in Trepanier et al.'s study), which make these tasks more demanding and may account for the deterioration observed by us.

Improvement of performance on specific tests of cognitive function has been reported in Parkinson's disease following PVP in some previous studies (Lacritz et al., 2000; Junque et al., 1999; Riordan et al., 1998; Scott et al., 1998; Trepanier et al., 1998; Soukup et al., 1997; Baron et al., 1996). Baron et al. (1996) found a short-term improvement of backward digit span, a test that requires executive processing. A near-significant reduction of perseverative errors on the WCST was found by Soukup et al. (1997). Trepanier et al. (1998) found performance on a PASAT to be improved. Junque et al. (1999) reported a significant improvement of visuospatial function assessed on a test of line orientation and Riordan et al. (1998) found enhanced performance on a delayed facial memory test in the patients with right-sided PVP. Three of the 20 patients in the series of Scott et al. (1998) were noted to show ''marked overall improvement in cognition postoperatively.'' Improvements in verbal and nonverbal memory and figural fluency were reported by Lacritz et al. (2000). However, none of these studies included a control group and therefore failed to exclude practice effects as a possible alternative explanation of the observed change. The matched normal control group used in the present study permitted us to assess possible practice effects, and established that the improved performance on the WCST and the Self-Ordered Random Number Sequences obtained in both groups is likely to be due to practice. A better comparison group would have been a group of patients with Parkinson's disease matched for disease severity who would not have undergone PVP. This would have also controlled for any effects of disease progression on changes in cognitive function that remains an alternative explanation for the deterioration of certain aspects of cognitive function. However, one problem with using a disease control group is that with cases with a long duration of illness as in the present sample, progression is difficult to detect. Furthermore, poorer performance on the tests of cognitive function was present 3 months after PVP, a period that is not sufficiently long for major deterioration due to disease progression to have occurred, and no further worsening of performance on these tests was observed at long-term follow-up an average of 15 months after PVP that would be expected if this change was due to disease progression. Therefore, the conclusion that deterioration in performance on these tests was a direct effect of PVP appears to be valid.

Long-Term Impact of PVP and Effect of Side of Operation on Cognitive Function

At long-term follow-up an average of 15 months after surgery, the majority of the measures of executive function did not show any overall change relative to the assessment 3 months after surgery. The exception was a significant improvement of performance on the Self-Ordered Random Sequences task, with a higher percent of the sequences being correct and fewer items missing or repeated. Since performance on this task was also improved at 3 months follow-up relative to the presurgical or initial assessment to a similar extent for the patients and normals, these short- and long-term effects are likely to reflect practice effects. However, as the controls were not reassessed at 15 months this cannot be clearly established. Baron et al. (1996) found that once the two patients with postoperative complications consisting of frontal subdural hematomas were excluded from their sample, none of the changes in cognition at short- or long-term follow-up were significant. In Trepanier et al.'s (1998) study, patients did not show any further significant improvement or deterioration of cognitive function at long-term (12 months or longer) compared to short-term (3 or 6 months) follow-up. The stability of the long-term results of PVP on cognitive function are consistent with those of the present study and the findings of Stebbins et al. (2000) who assessed their patients 12 months after surgery.

Bearing in mind that in our study, the number of cases with right-sided ($n = 4$) compared to left-sided ($n = 9$) PVP was small, nevertheless, our results, similar to those of Scott et al. (1998) and Baron et al. (1996), showed that the side of pallidotomy produced no significant effect on any of the aspects of cognitive function assessed. In contrast, Trepanier et al. (1998) reported that while left-sided PVP significantly impaired performance on tests with a verbal component (word fluency, California Verbal Learning Test and Digit Span Backward), the only impairment found following right-sided PVP was on a nonverbal memory test, the Rey Complex Figure. Differential effects of right versus left PVP on some tests of cognitive function has also been documented by Lacritz et al. (2000). In their study, patients with right PVP were more perseverative on the Wisconsin but showed improved word fluency, whereas those with left PVP were less perseverative on the Wisconsin but had impaired word fluency after surgery. The impact of lesion laterality on cognitive function in Parkinson's disease has been considered by Green and Barnhart (2000) in their review of seven relevant studies. From this literature, they concluded that while left-sided PVP was associated with deficits in measures sensitive to frontal lobe function, no consistent pattern of impairment was evident following right-sided PVP. Such differences in the effects of side of operation between studies may partly relate to the larger sample size and relatively equal numbers of left- and right-sided lesions in the studies of Lacritz et al. (2000) and Trepanier et al. (1998) and the seven studies reviewed by Green and Barnhart (2000). As the results of Trepanier et al. (1998) suggest that the pallidum, possibly by the nature of its cortical projections, is subject to lateralization effects similar to that commonly

found for cortical structures, this is a topic worth investigating in future studies.

Theoretical and Clinical Implications

Following PVP, the improvement of bradykinesia (Samuel et al., 1998; Dogali et al., 1995), the increased activation of premotor and prefrontal cortices during motor tasks (Samuel, Ceballos-Baumann, Blin, et al., 1997; Samuel, Ceballos-Baumann, Turjanski, et al., 1997; Grafton et al., 1995), and the reduction of resting metabolism in the lentiform nucleus and thalamus coupled with increased metabolism in the primary motor, premotor, and dorsolateral prefrontal cortices (Eidelberg et al., 1996) all support current models of fronto-striatal connectivity (Alexander et al., 1986) and its impairment in Parkinson's disease (Wichman & de Long, 1996; de Long, 1990). However, in current models, the posteroventral section of the GPi is considered to be purely sensorimotor with no projections that would implicate it in cognitive function. However, activation of the DLPFC, the cortical target of the associative circuit is increased following PVP (Samuel, Ceballos-Baumann, Blin, et al., 1997; Samuel, Ceballos-Baumann, Turjanski, et al., 1997; Grafton et al., 1995) and the present and other studies have demonstrated significant change in executive function following PVP in Parkinson's disease. How can these findings be explained? One possibility is that the localization of the lesions is not correct or not limited to the posteroventral or sensorimotor region of the GPi but impinging on the lateral dorsomedial pallidal outflow to the ''associative'' circuit. Although possible, this is unlikely to be the sole explanation, as in the majority of studies, including the present one, deterioration in executive functioning is observed despite significant improvement of the motor symptoms of the disorder that suggests correct localization of the lesion in the sensorimotor section of the GPi. The latter is also confirmed by postsurgical MRIs in a number of studies of the impact of PVP on cognitive function (e.g., Scott et al., 1998; Trepanier et al., 1998). A second possibility is that the five fronto-striatal circuits do not operate in a fully segregated fashion, but that some degree of interaction and exchange of information between the circuits occurs. In fact, more recent anatomical evidence suggests that due to dendritic arborization some degree of functional integration does occur between the circuits (Percheron & Filion, 1991). It has also been proposed that the ''motor,'' ''associative,'' and ''limbic'' fronto-striatal circuits operate as ''split circuits,'' with both closed- and open-loop elements with the latter allowing interaction between circuits (Joel & Weiner, 1994). It is also possible that the deterioration in specific aspects of cognitive executive function observed following PVP are mediated by changes in the activity of the motor circuit between the GPi and the lateral premotor cortex rather than the GPi and the SMA.

The most important aspect of the present results both from a clinical and a theoretical perspective is the finding that the patients' performance deteriorated following surgery (or failed to show the normal benefit from repeated testing) on some tasks engaging working memory and executive processes, namely Missing Digit Test, PVSAT, and VCALT. These changes were maintained 15 months after the surgery. From a clinical perspective, such deterioration of specific aspects of cognitive function found in this and other studies (Lacritz et al., 2000; Stebbins et al., 2000; Junque et al., 1999; Yokoyama et al., 1999; Cahn et al., 1998; Crowe et al., 1998; Masterman et al., 1998; Riordan et al., 1998; Scott et al., 1998; Trepanier et al., 1998; Soukup et al., 1997; Uitti et al., 1997; Baron et al., 1996) introduces a note of caution when considering the value of PVP in the treatment of Parkinson's disease. On the other hand, it should also be noted that despite statistical significance of the change in cognitive function found in this and previous studies, the clinical significance of such change remains uncertain. No changes in concentration, attention, or memory were reported by any of the patients either spontaneously or on direct questioning. It is therefore difficult to determine whether the observed deteriorations of cognitive function following PVP demonstrated on formal cognitive assessment have any discernable effects on daily functioning, unlike the improvements of motor function that were associated with a significant improvement in activities of daily living.

From a theoretical perspective, it is possible to suggest that any cognitive processes that may improve following PVP that are not attributable to mere practice effects, are not directly dependent on striatal function, but are simply facilitated by enhanced prefrontal activation following lesioning of the GPi during PVP that reduces the excessive inhibitory outflow flow from this structure. In contrast, it can be proposed that striatal input to the frontal cortex may play a more central role or is essential for those aspects of working memory and executive function that showed significant deterioration after PVP. What is unclear is whether the impairments are due to loss of striatal function per se or simply due to loss of output to cortical sites. The question of the contribution of the basal ganglia to cognitive function is important and requires further investigation.

METHODS

Participants

Thirteen patients (10 men, 3 women) with a clinical diagnosis of idiopathic Parkinson's disease based on presence of two of three cardinal symptoms—bradykinesia (obligatory), tremor and rigidity, and responsiveness to levodopa, were assessed. All had marked ''on''

state dyskinesias and on–off fluctuations. Prior to surgery, all patients had moderate to severe Parkinson's disease. When assessed off medication before surgery, their mean Hoehn and Yahr (1967) rating was 2.9 (*SD* = .52) (Table 3). All patients were also rated on the UPDRS (Fahn, Elton, & the members of the UPDRS Development Committee, 1987) both before and after surgery (Table 3). The mean age of the sample was 57.0 years (*SD* = 7.1), and the mean disease duration of 14.5 years (*SD* = 6.5, range 5–25 years). All patients were taking levodopa and were assessed after overnight withdrawal of medication on both occasions. The PVP performed as described previously (Samuel et al., 1998) was on the left in 9 patients and on the right in 4 patients.

The patients were compared to 12 normal healthy controls (3 men, 9 women) with no previous history of neurological or psychiatric illness or head injury. Their mean age was 55.1 years (*SD* = 13.7). All patients and controls were right-handed. All participants gave informed consent following guidelines set out by our local Ethics Committee prior to participation in the study.

For the patients, the average time since the last dose was 10.9 hr (*SD* = 2.7) when assessed prior to surgery and 11.6 hr (*SD* = 2.5) at the time of the postsurgical assessment. These were not significantly different (t = 1.3, df = 10, $p > .05$). The patients and the normal controls did not differ in terms of age (t = .43, df = 23, $p > .05$) or National Adult Reading Test (NART)-obtained estimates of premorbid VIQ (t = 1.8, df = 21, $p > .05$). For the patients, the mean current VIQ on the Wechsler Adult Intelligence Scale—Revised (WAIS-R) was 106.5 (*SD* = 10.6, range 93–123), which was not significantly different from NART-obtained estimates of premorbid VIQ (t = 1.9, df = 9, $p > .05$).

On the first assessment occasion, current verbal ability as measured by the Spot-the-Word Test, was significantly higher for the normals (mean = 12.8, *SD* = 2.9) than the patients with Parkinson's disease (t = 2.3, df = 23, p = .033). For the patients, mean scaled scores on the Spot-the-Word Test were not significantly different, before (mean = 10.2, *SD* = 2.9) and after (mean = 10.2, *SD* = 2.5) surgery (t = .11, df = 12, p = .913).

Table 3. The Characteristics of the Two Samples

	Parkinson's disease	*Normals*
Sample size	13	12
Age (years)	57.0 (7.1)	55.1 (13.7)
Sex (M:F)	10:3	3:9
NART VIQ estimate	111.1 (8.2)	116.7 (6.6)
Duration of illness (years)	14.5 (6.5)	
Hoehn and Yahr ratings		
Pre-PVP, off medication	2.9 (0.57)	
UPDRS Part III		
Pre-PVP		
On medication	14.4 (5.0)	
Off medication	42.1 (13.7)	
Post-PVP		
On medication	15.2 (4.7)	
Off medication	35.5 (10.7)	

Design

A mixed between-groups and within-subject repeated measures design was used. Each patient was assessed on all the tests on two occasions before and 3 months after PVP. To control for possible practice effects, the normal controls were also assessed on the same tests of cognitive function on two occasions separated by an interval of 3 months. Where appropriate and possible (Spot-the-Word Test, Missing Digit Test, PVSAT, Visual–Visual Conditional Learning Test), parallel forms of the tests were used for the second assessment. Nine of the 13 patients were also reassessed 12 months or longer after the surgery.

Procedure

Scores on Parts III (motor symptoms) and IV (dyskinesias) and Activities of Daily Living subscales of the UPDRS were obtained before and 3 months after surgery and used to assess the impact of PVP on the symptoms of Parkinson's disease and on functional capacity. The NART (Nelson, 1992) was used to obtain an estimate of premorbid VIQ. The Vocabulary, Similarities, Arithmetic, and Digit Span subscales of the WAIS-R (1981) were administered to obtain current VIQ for the patients. The Spot-the-Word Test (Baddeley, Emslie, & Nimmo-Smith, 1992) provides an estimate of current verbal capacity. It is a silent lexical decision task. The subject silently reads through a list of 60 pairs of letter strings, each pair containing a genuine word and a nonword, and ticks the real word. The following tests of executive function were administered on two occasions separated by 3 months, which were before and after PVP for the patients. For nine patients, the same tests were also completed 1 year or more after PVP.

Wisconsin Card Sorting Test (Nelson, 1976)

The Nelson version consists of a pack of 64 cards on which are printed colored geometrical figures that differ in one or more dimensions: shape, color, and number. The subject is asked to discover the rule and sort each card by matching it to one of the four stimulus cards, with the rule changing after a number of correct sorts. The score is the number of categories correctly sorted (maximum six), the number and per-

centage of perseverative errors (two successive sorts on an incorrect dimension), and the number of nonperseverative errors.

Self-Ordered Random Number Sequences

In this test, adapted from Petrides et al. (1993) and Wiegersma, van der Scheer, and Human (1990), the subject is required to produce random sequences of numbers between 1 and 10 with the additional requirement of always starting with 1 to indicate a ''new sequence and not missing out or repeating any numbers.'' In the present version, subjects were required to produce 20 such sequences. Subjects were asked to generate responses at the rate of one every 2 sec, synchronized with a visual pacing stimulus. The number of correct sequences (no missing items or repetitions) was noted and the percent correct score was calculated. In addition, the average number of the 10 items that were repeated or missing across the sequences was calculated.

Missing Digit Test

In this version modified from Petrides et al. (1993) subjects are presented with a random sequence of 9 of the 10 numbers between 1 and 10 and have to identify the missing digit. Numbers were presented on a VDU at the rate of one digit per 2 sec, followed by a response prompt. Subjects were provided with feedback after each response. Thirty such sequences were completed with a short break after a block of 10 sequences. The percent correct was calculated.

Paced Visual Serial Addition Test

This is a visual version of the PASAT (Gronwall & Wrightson, 1981). Subjects were presented with a series of 33 random single-digit numbers on the VDU. Each digit was presented for 1.5 sec. The subject's task was to add the most recent number to the preceding one and say aloud the sum. In two separate blocks of trials, digits were presented at two rates, fast (one digit every 2 sec) or slow (one digit every 4 sec). For each rate of presentation, the total number of errors (maximum 32) was noted.

Visual–Visual Conditional Associative Learning Test

Petrides (1985) modified this task for administration to human subjects and demonstrated its sensitivity to frontal pathology in man. The task requires subjects to learn arbitrary associations between pairs of visual stimuli by trial and error. The arbitrary nature of the pairings reduces contextual discrimination. The test material consisted of six cards, each bearing one of the six colors, and six cards bearing six abstract geometric designs arranged in a different random order. For each block of trials, the subject was presented with the six color stimuli, in turn, in a predetermined sequence. For each color stimulus, the subject had to indicate a design that they thought to be associated with that color. For each selection, the subject was told whether it was correct or not. If the selection was wrong, the subject continued to select other designs until the correct pairing was achieved. This procedure was repeated for a maximum of six blocks, with the color stimuli presented in a new random sequence and using the six cards each bearing the designs in different random positions. The test ended when the subject had learned the six-color pattern associations or after six blocks. The total number of trials, the total number of errors across blocks, and the number of blocks to reach criterion were recorded.

Statistical Analysis

A series of two-way repeated measures analysis of variance (ANOVA) was used, with Group (patients with Parkinson's disease vs. normals) as the between-groups factor and Time (Time 1 vs. Time 2 for normals and pre- vs. postsurgery for patients) as the repeated measures within-subject factor. For PVSAT where task difficulty was also a relevant within-subject factor, a three-way repeated measures ANOVA was used, with Group (patients with Parkinson's disease vs. normals) as the between-groups factor and assessment Occasion and Difficulty (one item every 2 or 4 sec) as the within-subject factors.

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Reprint requests should be sent to Dr. M. Jahanshahi, Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen Square, London WC1N 3BG, UK, or via e-mail: m.jahanshahi@ion.ucl.ac.uk.

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