A WAITLIST CONTROL GROUP STUDY OF NEUROBEHAVIOURAL OUTCOME FROM UNILATERAL POSTEROVENTRAL PALLIDOTOMY IN ADVANCED PARKINSON'S DISEASE

by

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ABSTRACT

There is evidence to suggest unilateral posteroventral pallidotomy (PVP) effectively treats aspects of the motor disabilities associated with advanced Parkinson's disease. However, neurobehavioural outcome from PVP is less well understood. In particular, the possibility of uncontrolled practice effects has prevented a full accounting of the cognitive sequelae of PVP, and little research has examined the widely held belief that dementia is associated with poorer surgical outcome. To address these issues, this research investigated neurobehavioural outcome from PVP in a manner that controlled for test practice, and examined the relationship between pre-operative level of cognitive functioning and surgical outcome.

Participants underwent baseline and two-month follow-up assessments. The surgery group underwent PVP (15 left, 7 right) after baseline assessment, while the waitlist group (n = 14) underwent PVP after follow-up. At follow-up, the waitlist and right PVP groups performed better than the left PVP group on verbal measures of list learning, fluency, working memory, and speeded color naming. The incidence of individual decline on these measures after left PVP was high. On retesting, the waitlist group demonstrated a mixed profile of improvement and decline on the cognitive measures, and changes were one quarter of a standard deviation or larger on one quarter of the measures. Pre-surgical level of cognitive functioning was not related to cognitive outcome.

At follow-up, members of the surgery group reported lower bodily pain and better social functioning than waitlisted participants. The incidence of significant individual improvement was high for bodily pain but not social functioning. Higher pre-operative level of cognitive functioning was associated with greater improvement in social functioning, vitality and fatigue/inertia, depression/dejection, and anger/hostility.

In conclusion, patients who undergo left PVP exhibit decline in circumscribed verbal

abilities. Controlling for practice effects did not increase the breadth of cognitive decline evident after PVP beyond that typically reported in the literature. Lower pre-operative cognitive functioning may be associated with smaller post-surgical improvements in quality of life and mood. In future research it will be important to focus attention on outcome amongst individuals who underwent right PVP, and individuals functioning at a lower cognitive level pre-operatively.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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OVERVIEW

Levodopa is an effective symptomatic treatment early in the course of idiopathic Parkinson's disease (PD). However, a growing number of individuals with advanced PD experience disabling medically-refractory motor symptoms, and side effects of levodopa including excessive, typically choreic, involuntary movements (levodopa-induced dyskinesia), and severe "on-off" fluctuations, when the effectiveness of levodopa suddenly declines leaving patients with reduced functioning. This has led to resurgence in the use of neurosurgical interventions for PD. In the technique examined in this thesis, unilateral posteroventral pallidotomy (PVP), a stereotactic thermolytic lesion is placed in the sensori-motor region of the internal segment of the pallidum (GPi). Accumulating evidence suggests PVP is an effective treatment for the cardinal motor signs of PD, on-off fluctuations, and especially levodopa-induced dyskinesia. However, neurobehavioural outcome from PVP in advanced PD is less well understood.[1]

The possibility of uncontrolled practice effects in much of the existing neuropsychological literature has prevented a full accounting of the cognitive effects of PVP. In particular, practice effects may have attenuated or hidden post-operative cognitive declines, and practice effects may also account for the reports of post-surgical improvement in test performance. To examine these possibilities, I studied neurobehavioural outcome from PVP in a manner that controlled for the effect of test practice and other retesting effects, and then compared the observed post-operative changes in cognition with the changes typically reported by previous studies that did not fully control for retesting effects.

Recently, attention has been directed at identifying factors predictive of neurobehavioural

[1] In this thesis I use the term neurobehavioural outcome as shorthand to refer to cognitive, quality of life, mood, and motor outcome from PVP, as reflected in participants' performance on tests of cognitive and motor functioning and self-report measures of health-related quality of life and mood.

outcome from PVP. Some researchers have advocated that dementia should be a contraindication for PVP, as patients functioning pre-operatively at a low cognitive level have a poorer outcome from surgery. This position appears to be based largely on clinical observations of significant post-operative cognitive decline in a few patients noted to be overtly demented before surgery. Recent attempts to address this question more systematically have not detected a relationship between pre-operative level of cognitive functioning and post-PVP change in cognitive or motor functioning. A second principal focus of this research was to examine the relationship between preoperative level of cognitive functioning and neurobehavioural outcome from PVP.

This dissertation begins with an overview of PD and PVP, including discussion of cognition, mood, and quality of life in PD, the pathophysiology of PD and the rationale for PVP, and the previous reports of neurobehavioural outcome from PVP. I then outline the five specific questions addressed by this research, delineate the methodological and statistical approaches used to address these five questions, and describe and discuss the results.

PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disease that occurs throughout the world and in all races (Ondo & Jankovic, 1998). The age of onset of PD is usually between 50 and 60, and the duration of illness can be up to 40 years (Hoehn & Yahr, 1967). The incidence of PD is 10-20/100,000 per year, and prevalence estimates have ranged from 200/100,000 to 300/100,000 (Barbosa, Limongi, & Cummings, 1997; Ondo & Jankovic, 1998; Rajput, 1992). PD is one of the most common neurological disorders of the elderly, and in geriatric samples prevalence rates of 1% are typical (Rajput, 1992).

The cardinal motor signs of PD include a tremor at rest, difficulty initiating movements, muscular rigidity, and diminished postural reflexes (Barbosa et al., 1997; Ondo & Jankovic, 1998). A 4-8 Hz. tremor at rest is often the first symptom evident. Tremor onset is frequently unilateral, and usually begins in the thumb producing a "pill-rolling" tremor. As the disease progresses tremor is evident in the fingers, then the wrist, and is eventually present in both arms and legs and in the perioral region. Most individuals with PD experience akinesia, and individuals with advanced PD may need to make multiple attempts to move, or they may be unable to move, feeling frozen to the floor. Slowness in the execution of movements, and reduced movement amplitude are also typically present. These motor impairments result in small handwriting (micrographia), and diminution of facial expressions, speech volume, and hand gestures. On passive limb movement, individuals with PD typically exhibit a resistance that releases in a rhythmic manner (cogwheel rigidity). Postural abnormalities usually occur relatively late in the course of PD. Typically the neck and trunk are bent forward and the arms are flexed at the elbows. While walking, individuals with advanced PD typically take progressively smaller shuffling steps and appear to be falling forward.

Individuals with PD have been found to be impaired on many neuropsychological

measures including those assessing attentional set shifting (Brown & Marsden, 1990), maintenance of attention (Filoteo et al., 1994), working memory and psychomotor speed (Gabrieli, Singh, Stebbins, & Goetz, 1996), recall of verbal information (Breen, 1993; Taylor, Saint-Cyr, & Lang, 1990; Tierney et al., 1994), procedural learning (Saint-Cyr, Taylor, & Lang, 1988), verbal fluency (Auriacombe et al., 1993; Zec et al., 1999), visual-spatial functioning (Bondi, Kaszniak, Bayles, & Vance, 1993; Cronin-Golomb & Braun, 1997), and problem solving (Gotham, Brown, & Marsden, 1988; Taylor, Saint-Cyr, & Lang, 1986). These cognitive deficits likely reflect the pathophysiology of PD, as they are not solely attributable to depression, motor impairment, or dopaminergic medication (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Levin, Labre, & Weiner, 1989; Raskin, Borod, & Tweedy, 1990).

Many authors have argued that individuals with PD have largely intact instrumental cognitive functions such as language, memory, and visual-spatial skills, but they have difficulty efficiently implementing these abilities to solve novel problems (e.g., Brown & Marsden, 1990; Buytenhuijs et al., 1994; Dubois & Pillon, 1997; Raskin et al., 1990; Taylor & Saint-Cyr, 1995). For example, Buytenhuijs et al. (1994) found individuals with PD failed to spontaneously use a semantic clustering strategy while learning a list of 16 words drawn from four semantic categories (spices, tools, fruits, clothing). Instead, they tended to use the less efficient strategy of recalling the words in the order in which they were read. As a result, the individuals with PD displayed poorer recall performance relative to controls. However, after the use of a semantic clustering strategy was made explicit by telling the participants the four categories within the list, the individuals with PD adopted the clustering strategy and their recall performance improved. These results suggest that verbal learning and memory per se are not impaired in PD, but rather individuals with PD appear to have difficulty generating strategies to guide their learning and memory, and as a result their mnemonic abilities may be employed in a sub-optimal manner. Findings such as these led to the suggestion that executive dysfunction is principally responsible

for many of the cognitive deficits displayed by individuals with PD (Bondi et al., 1993; Dubois & Pillon, 1997; Savage, 1997; Taylor & Saint-Cyr, 1995).

Psychiatric symptoms are common in samples of individuals with PD (Aarsland et al., 1999; Brown & MacCarthy, 1990). Mood difficulties have received the most extensive research attention, and it appears that mood disturbance in PD can range from dysthymia to severe mood disorder, and these difficulties may be evident before the motor symptoms of PD (Cummings, 1992; Poewe & Luginger, 1999). Reports of the incidence of depression in PD range greatly, depending on the assessment method employed. After reviewing the literature, Cummings (1992) concluded that depression is likely present in approximately 40% of individuals diagnosed with PD. There appear to be two peaks in the incidence of depression, the first occurring early in the disease, and the second occurring later in the course of PD (reviewed by Poewe & Luginger, 1999). Interestingly, the nature of the depression symptoms associated with PD may differ from those associated with idiopathic depression. In particular, depression in PD is associated with higher rates of anxiety and less guilt or self-reproach than idiopathic depression (Brown, MacCarthy, Gotham, Der, & Marsden, 1988). This latter finding suggests that there may be a PD-specific depression syndrome, perhaps related to the pathophysiology of PD. This notion is discussed in greater detail below.

It is clear, however, that patients with PD suffer from a range of psychiatric difficulties. In an important contribution, Aarsland et al. (1999) described the range of psychiatric symptoms present in a large (n = 139) sample of patients drawn from an epidemiological study of PD in Rogaland County, Norway. An attempt was made to assess all individuals with PD within this region, and psychiatric symptoms were assessed using the Neuropsychiatric Inventory, a caregiver-based structured interview. Almost two-thirds of the sample exhibited one psychiatric symptom in the month preceding assessment, and nearly half of the participants had exhibited two or more psychiatric symptoms during this period. Depression was the most common

difficulty endorsed, followed by anxiety and hallucinations. Symptoms of apathy, anxiety, and depression were the most severe.

The magnitude of any cognitive deficits and psychiatric disturbance present varies across individuals with PD (Ross, Mahler, & Cummings, 1992). The cognitive and psychiatric changes in more compromised individuals appear qualitatively similar to those displayed by less impaired individuals, and they typically include prominent executive dysfunction, apathy, and depression (Dubois & Pillon, 1997; Kaufer & Cummings, 1997; Savage, 1997; but see McFadden, Mohr, Sampson, Mendis, & Grimes, 1996). In severe forms, this constellation of cognitive and mood/motivational deficits represent a form of subcortical dementia (Cummings & Benson, 1990; Freedman, 1990; Savage, 1997).

As PD progresses, the motor, cognitive, and psychiatric symptoms worsen (Aarsland et al., 1999; Hoehn & Yahr, 1967; Koplas et al., 1999), decreasing individuals' ability to independently conduct their daily activities (Cutson, Lamb, & Schenkman, 1995). The cognitive and motor deficits associated with advanced PD produce impairment in different types of activities of daily living. Cahn, Sullivan, Shear, Pfefferbaum, et al. (1998) found degree of impairment in upper extremity motor functioning was predictive of difficulties with activities such as eating and carrying objects. In contrast, degree of cognitive impairment was predictive of difficulty performing more complex, multi-step activities, such as cooking a meal, shopping, and managing medications or finances. This finding has important clinical implications, as an intervention for PD that improves motor functioning but reduces cognitive functioning may ultimately fail to improve patients' overall level of functioning and perceived quality of life (Cahn, Sullivan, Shear, Pfefferbaum, et al., 1998; Koplas et al., 1999; Schrag, Jahanshahi, & Quinn, 2000; Trepanier, Saint-Cyr, Lozano, & Lang, 1998).

As might be predicted, self-reported quality of life is reduced in samples of individuals with PD (e.g., Karlsen, Larsen, Tandberg, & Maeland, 1999). Interestingly, the magnitude of the

motor symptoms present may not be the sole, or even the best, predictor of quality of life in PD. Karlsen and colleagues found depression symptoms, insomnia, degree of independence, severity of PD symptoms, and medication dosage each had a significant and independent ability to predict perceived quality of life in a sample of individuals with PD. Additionally, Koplas et al. (1999) found that of physical disability, depression, and mastery and control beliefs, only mastery, or an individual's belief he or she can influence the outcome of personal life events, was predictive of self-reported quality of life. These findings underscore the notion that when evaluating the effectiveness of interventions for PD it is not enough to only employ clinician-based measures of motor symptoms. To comprehensively assess an intervention, we must also assess the impact of the intervention on patients' perceived quality of life (Straits-Troster et al., 2000).

CORTICAL-BASAL GANGLIA CIRCUITS: A PRINCIPAL SUBSTRATE FOR THE MOTOR, COGNITIVE, AND MOOD/MOTIVATIONAL SYMPTOMS OF PARKINSON'S DISEASE

My intention in this section of the thesis is to familiarize the reader with the neural systems that have been implicated in PD in order to provide the context for subsequent sections that discuss the rational for PVP and the reasons why this intervention might be expected to alter neurobehavioural functioning.

The basal ganglia are a group of gray matter masses deep within the cerebral hemispheres. They include the striatum and ventral striatum, internal pallidum (GPi), external pallidum (GPe), ventral pallidum, subthalamic nucleus (STN), substantia nigra pars compacta (SNpc), and substantia nigra pars reticulata (SNpr) (Cote & Crutcher, 1991; Nauta & Feirtag, 1986). Descending cortical fibers enter the basal ganglia via the striatum, which is comprised of the caudate, putamen, and ventral striatum (Chow & Cummings, 1999; Selemon & Goldman-Rakic, 1985). Neurons within the GPi and SNpr provide the principal outputs of the basal ganglia, sending inhibitory projections to brainstem nuclei and to thalamic nuclei, the latter of which in turn send extensive excitatory projections to precentral cortical regions (Figure 1).

There are two principal pathways through the basal ganglia (reviewed by Feifel, 1999). The monosynaptic direct pathway projects from the striatum to the GPi/SNpr. The polysynaptic indirect pathway synapses on neurons of the GPe, which in turn project to the GPi/SNpr. The direct and indirect pathways are envisioned to work in an antagonistic, gain control manner, producing areas of elevated activity in discrete anatomical regions within the GPi/SNpr, thalamus, and frontal cortex, a process thought to selectively boost the signal and dampen the noise in the cortical-basal ganglia circuit (Chow & Cummings, 1999; Feifel, 1999; Robertson &

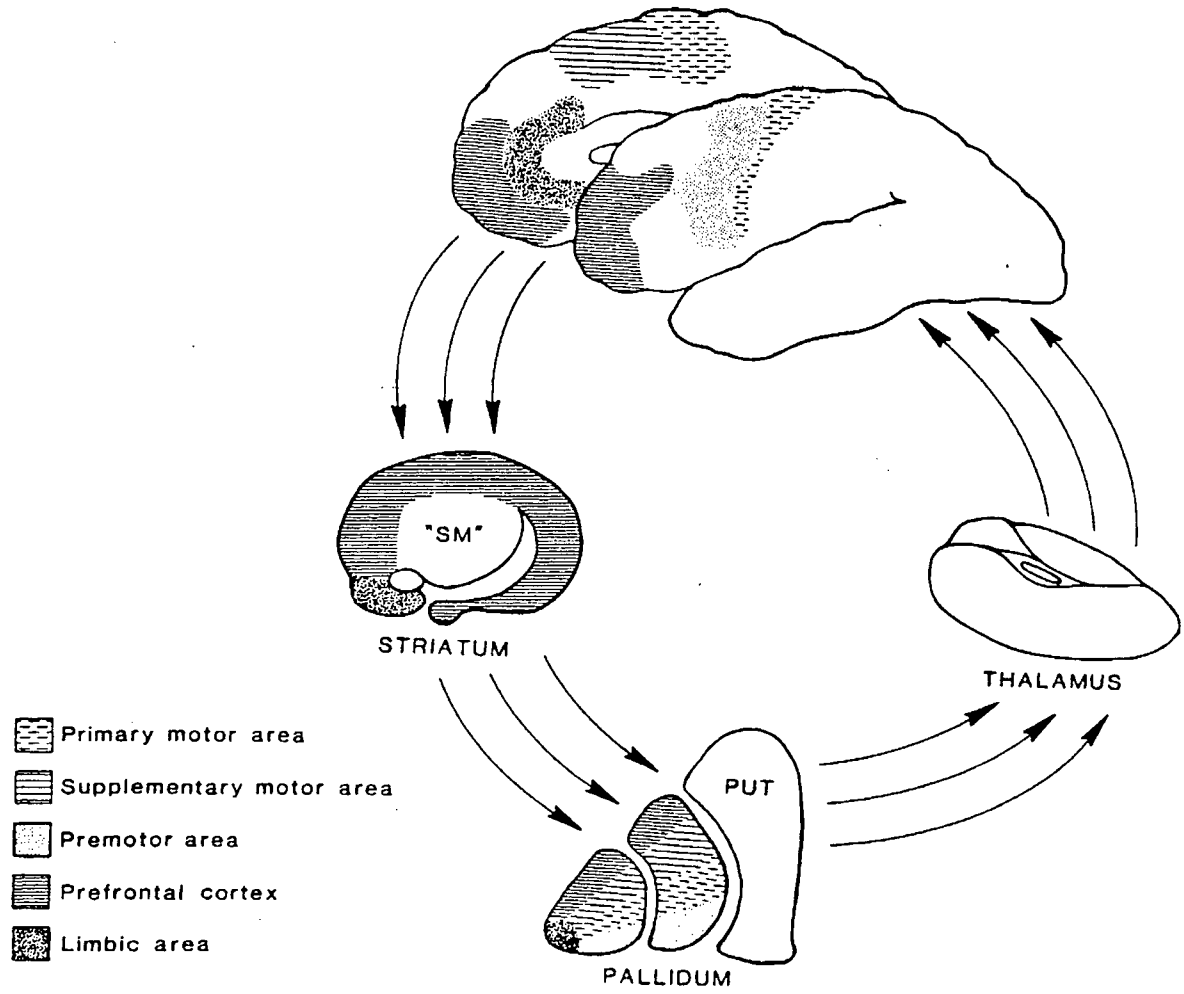

Figure 1. The segregated motor, cognitive (labeled prefrontal), and limbic circuits that pass through the basal ganglia. The motor circuit has been decomposed into premotor, motor, and supplementary motor subcircuits. PUT = Putamen; SM = sensori-motor circuits passing through the putamen. The internal and external segments of the pallidum are depicted on the left and right respectively. Adapted from Lombardi et al. (2000).

Flowers, 1990; Taylor & Saint-Cyr, 1995).

The current evidence suggests there are multiple cortical-basal ganglia circuits that are organized in a parallel, largely segregated manner, both structurally and functionally (Alexander, DeLong, & Strick, 1986; Alexander, Crutcher, & DeLong, 1990). Motor, oculomotor, dorsolateral, lateral orbitofrontal, and anterior cingulate/ventromedial orbitofrontal circuits have been identified (see Figure 1 and Alexander et al., 1986; 1990; Chow & Cummings, 1999; Masterman & Cummings, 1997). Each circuit can be thought of as comprising a closed loop, beginning and ending in a particular region of the prefrontal cortex. Additionally, each circuit contains open afferents and efferents that allow for communication with other brain regions (not depicted in Figure 1). The pre- and post-central cortical regions incorporated within each cortical-basal ganglia circuit typically have heavy direct connections with each other and are functionally related, suggesting each circuit is specialized to process a particular type of information (Alexander et al., 1986; 1990; Chow & Cummings, 1999; Cummings & Benson, 1990; Wichmann & DeLong, 1996).

Independence of the cortical-basal ganglia circuits appears to be maintained both anatomically and physiologically. Each circuit passes through largely segregated, non-overlapping anatomical regions within the nuclei of the basal ganglia and thalamus (Alexander et al., 1986; 1990; but see Percheron & Filion, 1991 for anatomical evidence for some degree of communication between the circuits), and striatal dopamine appears to restrict the development of correlated neuronal activity within adjacent regions of the basal ganglia (Bergman et al., 1998).

Each of these five cortical-basal ganglia circuits can in turn be divided into several more subcircuits, each concerned with different aspects of the functional domain processed by the circuit as a whole. For example, the motor circuit can be fractionated into motor, premotor, and supplementary motor subcircuits (see Figure 1), each of which contain non-overlapping arm, leg,

and oralfacial channels (Hoover & Strick, 1993; Middleton & Strick, 1994).

The motor circuit is perhaps the best understood of the cortical-basal ganglia circuits. It is thought to be principally involved in the control of voluntary movements of the distal and oralfacial musculature (Alexander et al., 1986; 1990). The motor circuit originates in the primary motor cortex, arcuate premotor area, supplementary motor area, and primary and association somatosensory cortex (Kunzle, 1975). These motor and sensory cortical regions send somatotopically-organized projections to the putamen (Crutcher & DeLong, 1984). The motor circuit then passes through the basal ganglia, projecting from the GPi/SNpr to nuclei of the thalamus, and then on to motor, premotor, and supplementary motor regions (Alexander et al., 1986; 1990). These precentral cortical regions are thought to play important roles in the planning and execution of movements of the limbs and face via the corticospinal, corticobulbar, and corticopontine systems (Cote & Crutcher, 1991; Ghez, 1991). There are also projections from the GPi to the pedunculopontine nucleus (Alexander et al., 1990), which in turn projects to the medullary reticular formation, suggesting the basal ganglia have the ability to influence the descending reticulospinal system.

The occulomotor cortical-basal ganglia circuit is thought to be principally involved in the control of saccadic eye movements (Alexander al., 1986; 1990). This circuit receives input from the frontal and supplemental eye fields, dorsolateral prefrontal cortex, and posterior parietal cortex. Projections from these cortical regions enter the basal ganglia via the caudate. This circuit then passes through the basal ganglia, projecting from the GPi/SNpr to the superior colliculus and thalamic nuclei, the later of which close the circuit with projections to the frontal and supplemental eye fields (Alexander al., 1986; 1990).

Three cortical-basal ganglia circuits incorporate regions of pre- and post-central cortex that have been associated with psychological functions. Consequently, these circuits have been referred to as complex or association circuits (Alexander et al., 1986; 1990). As the functions of

the association circuits are presently uncertain, they are named on the basis of their primary projection zone(s) within the prefrontal cortex. Accumulating clinical and experimental evidence is, however, beginning to identify the functions subserved by these circuits (Alexander et al., 1986; 1990; Chow & Cummings, 1999; Fuster, 1999; Litvan, 1999).

The dorsolateral circuit originates in the dorsolateral region of the prefrontal cortex and in the posterior parietal cortex. Axons from these cortical regions project principally to the head of the caudate (Selemon & Goldman-Rakic, 1985). The circuit passes through the basal ganglia to the GPi/SNpr, and then on to thalamic nuclei (Middleton & Strick, 1994). The circuit is then closed by projections from these thalamic nuclei to dorsolateral prefrontal cortex (Jacobson, Butters, & Tovsky, 1978).

The dorsolateral circuit is thought to participate in executive functions (Chow & Cummings, 1999; Fuster, 1999; Litvan, 1999). Clinically, dysfunction at various points within this circuit is associated with a dysexecutive syndrome that includes deficits such as concrete thought, decreased fluency, poor recall but intact recognition of information, perseveration, and stimulus-bound behaviour (Chow & Cummings, 1999; Litvan, 1999).

The lateral orbitofrontal circuit originates in lateral orbitofrontal cortex, and in visual and auditory association areas within the inferior and superior temporal gyri. These cortical areas project to the caudate (Selemon & Goldman-Rakic, 1985). The circuit projects from the caudate through the basal ganglia to the GPi/SNpr, which in turn sends projections to thalamic nuclei. Neurons from these thalamic nuclei then project to lateral orbitofrontal cortex, completing the closed loop portion of this circuit (Ilinsky, Jouandel, & Goldman-Rakic, 1985).

The lateral orbitofrontal circuit is thought to participate in the inhibitory control of behaviour and information processing (Litvan, 1999), and in experimental animals lesions of the lateral orbitofrontal cortex, or the region of the caudate through which this circuit passes, are associated with impairment in delayed alternation performance due to a perseverative tendency

to return to the previously rewarded location (Divac, Rosvold, & Szwarcbart, 1967). Hypermetabolism in the thalamus, caudate, and right orbital gyrus has been associated with obsessive-compulsive disorder (Baxter et al., 1987; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996), and lesions within this circuit are associated with personality changes including irritability, lability, and socially inappropriate behaviour (Chow & Cummings, 1999).

The anterior cingulate/ventromedial orbitofrontal, or "limbic" circuit originates in the anterior cingulate and ventromedial orbitofrontal cortex, the temporal pole and superior and inferior temporal gyri, basolateral nucleus of the amygdala, hippocampus, and the entorhinal and perirhinal cortices (Selemon & Goldman-Rakic, 1985). Neurons from these regions project to the ventral striatum. In turn, neurons project to the ventral pallidum and the SNpr (Alexander et al., 1986; 1990). From these nuclei, axons project to the thalamus, hypothalamus, lateral habenula, and ventromedial tegmental area (Alexander et al., 1986; 1990; Chow & Cummings, 1999; Haber, Groenewegen, Grove, & Nauta, 1985). The circuit is then closed by a projection from the thalamus to the anterior cingulate and ventromedial orbitofrontal cortices (Alexander et al., 1986; 1990; Chow & Cummings, 1999).

The limbic circuit is thought to subserve motivated behaviour, and dysfunction within this circuit is associated with amotivational or apathetic syndromes (Chow & Cummings, 1999; Litvan, 1999). Bilateral damage to the anterior cingulate is associated with profound indifference to the environment or bodily needs (Fesenmeier, Kuzniecky, & Garcia, 1990).

Death of dopaminergic cells within the nigrostriatal pathway, and consequent altered physiology within cortical-basal ganglia circuitry, is thought to be one cause of the motor and psychological signs and symptoms of PD. The causes of this cell death are currently poorly understood (Barbosa et al., 1997; Ondo & Jankovic, 1998; Stoessl, 1999). Cell death is greatest in the region of the SNpc which projects to the putamen. As a result, striatal dopamine depletion is greatest in the putamen (Graybiel, Hirsch, & Agid, 1990; Kish, Shannak, & Hornykiewicz,

1998). As the motor circuit enters the basal ganglia via the putamen, dysfunction is likely maximal in this cortical-basal ganglia circuit in PD (Litvan, 1999).

In the non-human primate model of PD, striatal dopamine depletion is associated with increased activity in the inhibitory projection from the GPi/SNpr to thalamic nuclei (e.g., Filion & Tremblay, 1991), and the development of temporally correlated activity in populations of adjacent neurons within the pallidum (e.g., Bergman et al., 1998). The resulting reduced excitation and degraded signal clarity within the excitatory thalamocortical projection of the motor circuit may account for many of the motor deficits associated with PD (Mandir & Lenz, 1998; Marsden & Obeso, 1994).

In PD, dopamine depletion also occurs in the caudate (Graybiel et al., 1990; Kish et al., 1998). Therefore, dysfunction might also be expected in the association cortical-basal ganglia circuits. Dopamine depletion is greatest in the head of the caudate (Kish et al., 1988), the region through which the dorsolateral cortical-basal ganglia circuit passes. Taylor and co-authors (1986) suggest that dopamine depletion in the head of the caudate in PD reduces excitation within the thalamocortical projection within the dorsolateral cortical-basal ganglia circuit, functionally deafferentating the basal ganglia from the dorsolateral prefrontal cortex. They also suggest this deafferentation effect is compounded by the dopamine depletion within the dorsolateral prefrontal cortex known to occur in PD (Scatton, Rouquier, Jovay-Agid, & Agid, 1982). This anatomical and physiological evidence for cortical and subcortical sources of disruption within the dorsolateral cortical-basal ganglia circuit is concordant with the neuropsychological evidence reviewed above which suggests the cognitive changes associated with PD primarily reflect executive dysfunction.

The motor and cognitive deficits and consequent impairments in activities of daily living associated with advanced PD likely contribute to the high incidence of depression and apathy in this population (Karlsen et al., 1999; Koplas et al., 1999). However, dysfunction within cortical-

basal ganglia circuits may also play a role in these neuropsychiatric signs and symptoms (Chow & Cummings, 1999; Litvan, 1999). This notion is supported by evidence that compared to normal controls and non-depressed individuals with PD, depressed individuals with PD exhibit hypometabolism within the caudate and the medial orbitofrontal cortex (Barbosa et al., 1997; Mayberg et al., 1990; Ring et al., 1994), and by Cantello et al.'s (1989) discovery that depressed individuals with PD do not exhibit the normal euphoric response to methylphenidate.

PALLIDOTOMY AS A TREATMENT FOR ADVANCED PARKINSON'S DISEASE

There have been several accounts of the history of unilateral posteroventral pallidotomy (PVP) as a treatment of PD symptoms (e.g., Baron et al., 1996; Koller, Pahwa, Lyons, & Albanese, 1999; Krauss & Grossman, 1998; Obeso, Guridi, Obeso, & DeLong, 1997). By these accounts, surgical treatments for movement disorders developed largely by trial and error over the first half of this century. Early surgical procedures targeted motor and sensory cortex and their efferents, principally the pyramidal system, which typically replaced movement disorder symptoms with paresis. By the 1940's, the role of subcortical structures in movement disorders became more widely appreciated, and surgeons began to target structures within the basal ganglia and thalamus. The use of stereotactic lesions of the internal segment of the globus pallidus (GPi) to treat the motor symptoms of PD was first reported in the early 1950's, and by the early 1960's PVP was widely embraced by neurosurgeons.[2]

Use of PVP decreased during the late 1960's. This has been attributed to levodopa's ability to dramatically reduce motor symptoms early in the course of PD. However, there are increasing numbers of patients with advanced PD for whom current medical therapies are less effective, especially for gait, balance, and speech difficulties (Jankovic, Lai, Ben-Arie, Krauss, & Grossman, 1999; Obeso et al., 1997). Additionally, long-term use of levodopa is associated with distressing side effects including severe on-off fluctuations, dyskinesia, and psychiatric complications including hallucinations and addiction to the drug (Giovannoni, O'Sullivan, Turner, Manson, & Lees, 2000; Jankovic et al., 1999; Saint-Cyr, Taylor, & Lang, 1993).

Recognizing this growing number of patients who are poorly managed with the best

[2] In stereotactic neurosurgery the patient's head is placed in a stereotactic apparatus before a head CT or MRI scan. As the relationship between the stereotactic frame and cerebral anatomical landmarks can be precisely determined, electrodes or cannulae can then be placed quite precisely within the brain.

available medical treatment, Laitinen, Bergenheim, and Hariz (1992) investigated PVP as a treatment for the symptoms associated with advanced PD. Their efforts were facilitated by innovations in neurosurgical and neuroradiological techniques, and guided by recent insights into the pathophysiology of PD. As described above, Parkinsonian monkeys exhibit a chronic increase in the inhibitory output from the GPi/SNpr to thalamic nuclei. Furthermore, lesions of the GPi reduced their PD symptoms (Filion & Trembly, 1991). Consequently, it has been suggested that lesioning the GPi in PD improves motor functioning by restoring thalamo-cortical excitation (Davis et al., 1997; Grafton, Waters, Sutton, Lew, & Couldwell, 1995; Mandir & Lenz, 1998; Obeso et al., 1997; Wichman & DeLong, 1996). This rationale for PVP is supported by the results of neuroimaging studies, which confirmed PVP is followed by an increase in movement-related metabolic activity in premotor and supplementary motor cortex (Grafton et al., 1995).[3]

Laitinen et al. (1992) found unilateral stereotactic thermolytic lesions of the posteroventral region of the GPi improved akinesia, rigidity, and tremor in patients with advanced PD. Pain, levodopa-induced dyskinesia, and gait difficulties were also significantly improved. These benefits were still evident 28 months after surgery. Since the publication of this work there have been many investigations of the effects of contemporary PVP on motor functioning in PD, and much evidence suggests PVP is an effective treatment for cardinal motor signs, motor fluctuations, and levodopa-induced dyskinesia in patients with advanced PD (for reviews see Ahmad, Mu, & Scott, 2001; Alkhani & Lozano, 2001; Bronstein, DeSalles, &

[3] However, as described below, reduction in medication-induced dyskinesia is perhaps the most robust and lasting effect of PVP. This finding sits uncomfortably with the model of the pathophysiology of PD described above, which posits the GPi/SNpr excessively inhibit the motor thalamus in PD. According to this model, lesions of the GPi would be expected to increase thalamocortical excitation, increasing activity in precentral motor areas and facilitating cortically initiated movement. This would be expected to decrease akinesia, but at the same time make unwanted movements such as dyskinesia worse, not better (Bronstein et al., 1999; Marsden & Obeso, 1994). This observation led to the suggestion that PVP actually works by disconnecting the disordered basal ganglia from precentral motor regions (Marsden & Obeso, 1994; Stebbins, Shannon, Penn, & Goetz, 2000). Clearly current models of the pathophysiology of PD are incomplete, and there is no shortage of suggested problems (e.g., Mandir

DeLong, 1999; Lang, 2000; Mendis, Suchowersky, Lang, & Gauthier, 1999; Zesiewicz & Hauser, 2001). Improvements are most striking and long lasting for contralateral dyskinesia, and at present PVP is one of the most widely available and reliable surgical treatments for this common complication of advanced PD (Lang, 2000).

In PVP, a stereotactic lesion is made in the posteroventral region of the GPi, the region of this structure that is thought to lie in the motor cortical-basal ganglia circuit (Figure 1). Consequently, a perfectly placed lesion that includes only this pallidal region might be expected to solely alter motor functioning. However, there are reasons to suspect PVP might alter psychological functioning. First, there is variability in the ultimate location of lesions in PVP (e.g., Gross et al., 1999; Junque et al., 1999; Lombardi et al., 2000; Tsao et al., 1998), and lesions that extend beyond the sensori-motor region of the GPi might be expected to alter psychological functioning (Green & Barnhart, 2000). Secondly, there is anatomical evidence that the cortical-basal ganglia circuits do not function in a completely segregated manner (e.g., Percheron & Filion, 1991), and as mentioned above, there is physiological evidence that Parkinsonism is associated with degradation of segregated processing within the basal ganglia (e.g., Bergman et al., 1998). Consequently, even on-target lesions perfectly centered on the sensori-motor region of the GPi may actually disrupt processing in adjacent regions of the GPi that subserve cognitive and affective functions. Consistent with these notions, functional imaging studies have demonstrated that PVP leads to increased resting metabolism in ipsilateral motor, premotor, and dorsolateral prefrontal cortex (e.g., Eidelberg et al., 1996), suggesting that PVP does indeed have the potential to alter functioning within motor and associative cortical-basal ganglia circuits.

It is not clear whether a lesion within the GPi would be predicted to increase or decrease psychological functioning in PD. It could be argued if the motor and association cortical-basal ganglia circuits are compromised in similar fashions in PD, a lesion that encroached on an

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& Lenz, 1998; Marsden & Obeso, 1994; Lang et al., 1998).

association circuit would increase psychological functioning through similar mechanisms as those envisioned to occur within the motor circuit (i.e., restoration of thalamocortical excitation via reduction of the excessive inhibitory output from the GPi to the thalamus). However, in PD there is relatively less dopamine depletion in the caudate (Graybiel et al., 1990; Kish et al., 1998), and as a result the association cortical-basal ganglia circuits may be less compromised than the motor circuit (Litvan, 1999). Consequently, a lesion placed within association circuitry might decrease psychological functioning by overcompensating for the pathophysiology actually present. It is also possible that PVP could indirectly improve cognitive functioning via reduction of motor or mood/motivational symptoms. For example, some authors have argued post-surgical reduction of dyskinesia may improve patients' ability to attend and concentrate (e.g., Obwegeser et al., 2000; Scott et al., 1998; Trepanier et al., 1998).

Interest in the psychological sequelae of PVP is high, and recently several groups have begun to describe the effects of PVP on cognitive functioning in advanced PD (Alegret et al., 2000; Baron et al., 1996; Cahn, Sullivan, Shear, Heit, et al., 1998; Demakis et al., 2002; Green et al., 2002; Jahanshahi et al., 2002; Junque et al., 1999; Kubu, Grace, & Parent, 2000; Lacritz Cullum, Frol, Dewey, & Giller, 2000; Masterman et al., 1998; Obwegeser et al., 2000; Perrine et al., 1998; Rettig et al., 2000; Riordan, Flashman, & Roberts, 1997; Schmand et al., 2000; Scott et al., 1998; Soukup et al., 1997; Stebbins et al., 2000; Trepanier et al., 1998; Uitti et al., 1997; Yokoyama et al., 1999). The principal results of these studies are summarized in Table 1. The findings are listed by cognitive domain, beginning with the domains most clearly affected by PVP.

Almost every study has reported decline in phonemic or semantic verbal fluency, and declines in working memory and verbal learning and memory were also common. Post-operative decline on measures of executive functions (such as problem solving, inhibition/mental control, and sequencing) was also common, but so too were improvements in these skills. Post-surgical

Table 1. Principal Results of the Previous Investigations of Neuropsychological Outcome from Posteroventral Pallidotomy for Advanced Parkinson's Disease

Cognitive domain	Studies reporting improvement	Studies reporting decline
Phonemic fluency		• Demakis et al. (2002) (after left PVP) • Schmand et al. (2000) (after left PVP, still present at one year) • Kubu et al. (2000) (after left PVP, decline larger the older the participant at PD onset) • Obwegeser et al. (2000) (after left PVP) • Rettig et al. (2000) (did not improve by 12 months) • Alegret et al. (2000) (no hemisphere analysis) • Cahn et al. (1998) (after left PVP) • Trepanier et al. (1998) (after left PVP, still present at 12 months) • Riordan et al. (1997) (after left PVP) • Uitti et al. (1997) (all left PVP) • Junque et al. (1999) (left PVP had greater decline) • Green et al. (2002) (left PVP group below right PVP and medical management groups at three, but not six months)
Semantic fluency	• Lacritz et al. (2000) (right PVP)	• Schmand et al. (2000) (after left PVP) • Obwegeser et al. (2000) (after left PVP, still present at 12

Cognitive domain	Studies reporting improvement	Studies reporting decline
		months) • Lacritz et al. (2000) (after left PVP) • Trepanier et al. (1998) (after left and right PVP, still present at 12 months) • Scott et al. (1998) (no hemisphere effect) • Riordan et al. (1997) (after left PVP) • Uitti et al. (1997) (all left PVP) • Yokoyama et al. (1999) (after left PVP, resolved by 3 months) • Masterman et al. (1998) (no hemisphere effect) • Green et al. (2002) (left PVP group below right PVP and medical management groups at 3 but not 6 mths)
Working memory	• Baron et al. (1996) (no hemisphere effect, transient)	• Stebbins et al. (2000) (no hemisphere analysis, effect present on Digit Reordering and Listening Span) • Yokoyama et al. (1999) (after left PVP, resolved by 3 months) • Trepanier et al. (1998) (Digit Span backwards declined after left PVP) • Jahanshahi et al. (2002) (no hemisphere effect, decline evident on the Missing Digit Test and the Paced Visual Serial Addition Test) • Green et al. (2002) (WAIS-R Digit Span backwards, left PVP group below right PVP group at 3 but not 6 months,

Cognitive domain	Studies reporting improvement	Studies reporting decline
		left PVP group below control group at 6 months)
Verbal learning and memory	• Trepanier et al. (1998) (after right PVP) • Lacritz et al. (2000) (no hemisphere effect, on CVLT)	• Trepanier et al. (1998) (after left PVP, still present at one year) • Rettig et al. (2000) (no hemisphere effect, deficit resolved by 12 months) • Riordan et al. (1997) (left PVP group, right PVP group exhibited a smaller effect) • Green et al. (2002) (CVLT total trials 1-5, left PVP group below right PVP group at 3 but not 6 months; CVLT long delay free recall, left PVP group below right PVP and medical management groups at 3 but not 6 months; % retained, left PVP group below medical management group at 3 months, left PVP group above right PVP group at 6 months)
Executive functioning	• Lacritz et al. (2000) (Design Fluency, no hemisphere effect) • Rettig et al. (2000) (WCST errors and Stroop colour-words, no hemisphere effect) • Lacritz et al. (2000) (left PVP followed by decreased perseveration on the WCST)	• Obwegeser et al. (2000) (after left PVP decrease in number of WCST categories completed) • Stebbins et al. (2000) (no hemisphere analysis, Raven's Progressive Matrices) • Lacritz et al. (2000) (WCST categories, no hemisphere effect; WCST perseveration increased after right PVP)

Cognitive domain	Studies reporting improvement	Studies reporting decline
	• Alegret et al. (2000) (Stroop colour-words, no hemisphere effect) • Junque et al. (1999) (Trials B time – Trials A time, no hemisphere effect)	• Riordan et al. (1997) (Trials B, no hemisphere effect) • Green et al. (2002) (left PVP group obtained fewer categories on the WCST than the right PVP and medical management groups at 3 and 6 months)
Visual memory	• Obwegeser et al. (2000) (after right PVP, still present at 1 year) • Lacritz et al. (2000) (Rey Complex Figure, no hemisphere effect) • Riordan et al. (1997) (delayed facial recognition, effect present in entire sample and right PVP group)	• Jahanshahi et al. (2002) (trend for decrease on Visual Conditional Associative Learning Test)
Attention	• Trepanier et al. (1998) (no hemisphere effect, improvement on the PASAT)	
Psychomotor speed	• Cahn et al. (1998) (no hemisphere effect, WAIS-R Digit Symbol) • Uitti et al. (1997) (no hemisphere effect, trend on the Digit Symbol Test)	• Stebbins et al. (2000) (all left PVP, Symbol Digit Modalities Test)
Visual-spatial functioning	• Rettig et al. (2000) (no hemisphere effect, Hooper Visual Organization Test	• Trepanier et al. (1998) (decline in copy of Rey Complex Figure after right

Cognitive domain	Studies reporting improvement	Studies reporting decline
	performance improved over three assessments) • Junque et al. (1999) (no hemisphere effect, Judgment of Line Orientation)	PVP, deficit absent at 6 months) • Riordan et al. (1997) (after right PVP decline in WAIS-R Block Design)
Expressive vocabulary		
		• Obwegeser et al. (2000) (decline after left PVP)
Naming		
	• Rettig et al. (2000) (no hemisphere effect, naming improved over repeated assessments over one year) • Lacritz et al. (2000) (no hemisphere effect)	• Kubu et al. (2000) (no hemisphere effect)
Orientation		
		• Yokoyama et al. (1999) (after right PVP, resolved by 3 months)

Note. CVLT = California Verbal Learning Test; WCST = Wisconsin Card Sorting Test; PASAT = Paced Serial Addition Test; WAIS-R = Wechsler Adult Intelligence Scale- Revised.

declines in visual memory, attention, psychomotor speed, visual-spatial functioning, expressive vocabulary, naming, and orientation were infrequently reported. However, there are also reports of improvements after PVP in visual-memory, psychomotor speed, visual-spatial skill, and naming.

There is evidence that individuals with lateralized Parkinsonian symptoms also exhibit lateralized cognitive deficits. Patients with principally right hemiparkinsonism (and presumably greater dysfunction in fronto-subcortical circuits in the left hemisphere) exhibit relatively greater verbal deficits, while patients with left hemiparkinsonism demonstrate greater weakness in visual-spatial skill (Starkstein, Leiguarda, Gershanik, & Berthier, 1987; Taylor et al., 1986). Given these findings, right and left PVP might be expected to have different cognitive sequelae, and indeed there is evidence for differences in the cognitive effects of right and left PVP. In particular, left PVP is generally associated with greater cognitive decline, particularly in verbal fluency and learning and memory (see Table 1; reviewed by Green & Barnhart, 2000 and York, Levin, Grossman, & Hamilton, 1999), and two studies (Riordan et al., 1997; Trepanier et al., 1998) have described visual-spatial declines after right PVP. However, the effect of lesion laterality on cognitive outcome from PVP has not been consistently studied, usually because small sample sizes have precluded hemisphere analyses. Consequently, with the exception of the commonly observed post-surgical declines in verbal fluency, working memory, and verbal learning and memory after left PVP, cognitive outcome from left and right PVP remains unclear.

Cognitive outcome from PVP has typically been studied by comparing the performance of a single group of participants before and after surgery (e.g., Alegret et al., 2000; Baron et al., 1996; Cahn, Sullivan, Shear, Heit, et al., 1998; Demakis et al., 2002; Jahanshahi et al., 2002; Junque et al., 1999; Kubu et al., 2000; Lacritz et al., 2000; Masterman et al., 1998; Obwegeser et al., 2000; Rettig et al., 2000; Riordan et al., 1997; Scott et al., 1998; Stebbins et al., 2000; Soukup et al., 1999; Trepanier et al., 1998; Uitti et al., 1997; Yokoyama et al., 1999). Implicit in

this approach is the assumption that if PVP has no effect on a given ability, participants should perform at about the same level post-PVP as they did pre-operatively. However, performance on many cognitive tests is known to improve simply with test re-administration. This improvement is thought to reflect the net effect of factors such as such as test practice, measurement error, and regression to the mean (e.g., Basso, Bornstein, & Lang, 1999; Dikmen, Heaton, Grant, & Temkin, 1999; McCaffrey & Westervelt, 1995; Mitrushina & Satz, 1991). Most studies in the PVP literature have used alternate forms of test stimuli on retesting in an attempt to reduce practice effects. While this maneuver is helpful, the use of parallel test materials does not adequately control for practice effects, as on retesting participants are still able to refine the strategy they use when performing each test (Anastasi, 1988; Basso et al., 1999; Dikmen et al., 1999; McCaffrey & Westervelt, 1995; Soukup et al., 1997; York et al., 1999).

The magnitude of retesting effects on a given neuropsychological measure is thought to depend on many factors including the nature of the test and the subject's age, level of cognitive functioning, and initial performance level (Lezak, 1995; McCaffrey & Westerveld, 1995; Temkin, Heaton, Grant, & Dikmen, 1999). In general, practice effects are larger on tests that require the formulation of a strategy or problem solving, have a large speeded component, require an unfamiliar response, or have a single easily conceptualized solution (Basso et al., 1999; Lezak, 1995; McCaffrey & Westervelt, 1995). Several groups have reported that the magnitude of practice effects on some cognitive measures declines with age (e.g., Dikmen et al., 1999; Matarazzo, Carmondy, & Jacobs, 1980; Mitrushina & Shatz, 1991; Ryan, Paolo, & Brungardt, 1992; Shatz, 1981; Temkin et al., 1999), and there is also evidence that practice effects are attenuated or absent amongst individuals of below average intelligence and individuals with cerebral dysfunction (Basso et al., 1999; Dikmen et al., 1999; McCaffrey et al., 1995; Rapport, Brines, Axelrod, & Theisen, 1997; Shatz, 1981; Temkin et al., 1999).

The evidence suggesting that advanced age and cognitive impairment are associated with

diminution of practice effects might lead one to suspect patients undergoing PVP for advanced PD would exhibit relatively small practice effects on repeated neuropsychological assessment. However, Lezak (1995) has cautioned that the type of cognitive impairment present is important, as practice effects can be quite large with brain injured patients who "are slow to achieve a new set in an unfamiliar task..." (Lezak, 1995, p. 129), a characteristic typical of patients with advanced PD (e.g., Buytenhuijs et al., 1994; Taylor & Saint-Cyr, 1995). By this logic, individuals with advanced PD may have difficulty developing a strategy to solve novel neuropsychological tests during an initial assessment. However, on retesting they may refine the strategies they use to solve the tests, and consequently demonstrate sizable practice effects.

Little has been published regarding the practice effects displayed by individuals with advanced PD. However, there is some evidence that individuals with advanced PD do display practice effects when tested with the clinical measures and test-retest intervals typically used to evaluate the effects of PVP on cognition. Perrine et al. (1998) reported test-retest data over a 3-12 month interval for 10 patients with advanced PD. The effect sizes of the changes observed on retesting ranged from -.17 to +.81 standard deviations (*SD*), and the improvement on 4/12 tests was greater than +.25 *SD*.[4]

Many contributors to this literature (e.g., Cahn, Sullivan, Shear, Heit, et al., 1998; Green et al., 2002; Jahanshahi et al., 2002; Kubu et al., 2000; Lacritz et al., 2000; Obwegeser et al., 2000; Rettig et al., 2000; Riordan et al., 1997; Schmand et al., 2000; Scott et al., 1998; Soukup et al., 1997; Wilkinson & Troster, 1998; York et al., 1999), have cautioned that failure to account for the improvement in test scores that would be expected on retesting may have resulted in the under-reporting of cognitive decline following PVP. Similarly, the reports of improvement in

[4] I computed these values using the formula effect size = (score at retest - score at baseline)/pooled *SD* at baseline, based on the data in Perrine et al. (1998) Table 1. Computation of the pooled *SD* for each measure was based on the baseline data provided for their waitlist (n = 10) and surgery (n = 28) groups using the procedure described by Howell (1987, p. 170-171). The order of score subtraction was reversed for negatively keyed tests, so for all

cognitive test performance following PVP may in fact represent practice effects, and not surgically produced improvements in cognitive functioning (Demakis et al., 2002).

The importance of controlling for retesting effects on cognitive measures can be seen in the literature examining cognitive outcome from other surgical interventions. For example, accounting for the effects of test practice increased the breadth of cognitive decline evident after temporal lobectomy for epilepsy (e.g., Chelune, Naugle, Luders, Sedlak, & Awad, 1993) and cardiopulmonary bypass surgery (e.g., Keith et al., 2002). Consequently, there is a need for investigations of the cognitive effects of PVP that adequately control for retesting effects.

Accumulating evidence suggests that PVP is followed by improvements in reported quality of life. Benefit has been reported in bodily pain and discomfort (Martinez-Martin et al., 2000; Scott et al., 1998), physical (Baron et al., 1996; Cahn, Sullivan, Shear, Heit, et al., 1998; Gray et al., 2001; Martinez-Martin et al., 2000; Scott et al., 1998; Straits-Troster et al., 2000), and social/emotional functioning (Baron et al., 1996; Martinez-Martin et al., 2000; Scott et al., 1998; Straits-Troster et al., 2000). To date, few studies have compared quality of life outcome from right and left PVP. However, there is some evidence the hemisphere operated on may be an important determinant of functional outcome from PVP, as Cahn, Sullivan, Shear, Heit, et al. (1998) found caregiver reports of patients' ability to perform activities of daily living improved significantly after left but not right PVP.

It is conceivable PVP could improve or worsen mood functioning. Reduced motor symptoms and disability after PVP might be expected to improve mood functioning. However, stereotactic lesions that extend into the more medial limbic region of the GPi (see Figure 1) might disrupt mood or motivation (Higginson, Fields, & Troster, 2001). There are reports of post-surgical decreases in symptoms of anxiety (Green et al., 2002; Higginson et al., 2001; Junque et al., 1999; Martinez-Martin et al., 2000; Riordan et al., 1997; Scott et al., 1998; Straits-

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measures a positive effect size represents an improvement in performance on retesting.

Troster et al., 2000) and depression (Green et al., 2002; Martinez-Martin et al., 2000; Masterman et al., 1998; Rettig et al., 2000; Riordan et al., 1997; Scott et al., 1998; Straits-Troster et al., 2000), and there is some evidence that symptom improvement may be greater after surgery in the left hemisphere (e.g., Green et al., 2002; Riordan et al., 1997). However, significant improvement in mood functioning is not always found (Baron et al., 1996; Junque et al., 1999; Kubu et al., 2000; Obwegeser et al., 2000; Perrine et al., 1998; Schmand et al., 2000; Uitti et al., 1997), and instances of serious psychiatric complications have been reported (e.g., Dogali et al., 1995; Sutton et al., 1995).

Some recent research publications and consensus statements have advocated that dementia should be a contraindication for PVP as patients functioning pre-operatively at a low cognitive level have a poorer outcome from surgery (e.g., Baron et al., 1996; Bronstein, DeSalles, & DeLong, 1999; Masterman et al., 1998; Mendis et al., 1999; Scott et al., 1998). This impression appears to be based largely on clinical observations of significant post-operative cognitive decline in a few patients noted to be overtly demented before surgery (e.g., Baron et al., 1996, Masterman et al., 1998). However, recent attempts to address this question more systematically have failed to find a relationship between pre-operative level of cognitive functioning and post-PVP change in cognitive (Rettig et al., 2000) or motor (Riordan et al., 1997) functioning. On the basis of this evidence, Rettig and co-authors argue that patients with mild to moderate dementia should not be denied PVP. However, they suggest patients with more severe dementia might not be good surgical candidates, as they may not have sufficient cognitive resources and retained activities to support improvement in their daily functioning and perceived quality of life after surgical reduction of their motor deficits.

Given the high incidence of cognitive impairment in samples of individuals with advanced PD, the relationship between pre-operative level of cognitive functioning and outcome from PVP needs to be better understood. If further research were to suggest that pre-operative

level of cognitive functioning is related to outcome, then efforts could be directed towards elucidating how the magnitude and nature of cognitive impairment present relate to surgical outcome. On the other hand, if no relationship is found between pre-operative level of cognitive functioning and outcome from PVP, the well-documented symptomatic benefits of this intervention could be made available to a greater number of individuals with advanced PD.

QUESTIONS ADDRESSED BY THE PRESENT RESEARCH

The present research examined neurobehavioural outcome from PVP using a waitlist control-group design. The chief goals of this research were to determine whether controlling for retesting effects increases the cognitive declines observed after left and right PVP beyond those typically reported in the literature, and to examine whether a lower preoperative level of cognitive functioning is associated with poorer neurobehavioural outcome from PVP.

This research also had three auxiliary goals designed to maximize the clinical usefulness of this work. First, clinicians are typically interested in how frequently individual patients exhibit effects that are present at the group level, as an effect that is statistically significant at the group level but infrequent at the individual patient level may have limited clinical significance. Accordingly, an auxiliary goal of this research was to measure the incidence of significant individual change on the variables found to be significantly affected by PVP at the group level.

Statistically reliable declines in cognitive test performance, even those shown to be present in the majority of participants, do not directly correspond to functional decline (Keith et al., 2002; Stebbins et al. 2000). To be sure, there is evidence that performance on many clinical neuropsychological measures is predictive of aspects of real-world functioning (reviewed by Sbordone, 1996). However, to understand fully the functional implications of changes in cognitive test performance observed after PVP, these changes in test performance need to be empirically related to changes in real-world functioning. Consequently, a second auxiliary goal of this research was to examine whether the magnitude of cognitive change observed post-PVP is related to the magnitude of post-operative change participants reported in their quality of life.

Finally, little research has examined the retesting effects demonstrated by individuals with advanced PD. With the hope of contributing to this literature, a third auxiliary goal of this research was to describe the direction and magnitude of the changes in cognitive, quality of life,

mood, and motor test performance demonstrated on retesting by individuals with advanced PD who were waitlisted for PVP.

To meet the chief and auxiliary goals described above, this research was designed to answer five specific questions:

Question 1: Group Analysis of Outcome from Pallidotomy

After accounting for the effects of test practice and other retesting effects, what are the cognitive, quality of life, mood, and motor effects of PVP at the group level? Additionally, after controlling for retesting effects, are the cognitive changes observed after left and right PVP greater than those typically reported by previous studies that did not fully control for retesting effects?

Question 2: Individual Participant Analysis of Outcome from Pallidotomy

What is the incidence of significant individual change on those measures found to be affected by PVP at the group level? In particular, do these significant effects of PVP at the group level reflect a high or low incidence of significant change at the individual participant level?

Question 3: Changes in Test Performance Displayed by Waitlisted Participants on Retesting

What is the direction and magnitude of the changes displayed by waitlisted participants retested with measures of cognition, quality of life, mood, and motor functioning, and how does accounting for these retesting effects alter the profile of cognitive, quality of life, mood, and motor changes observed after PVP?

Question 4: Relationship Between Pre-Operative Level of Cognitive Functioning and Outcome from Pallidotomy

Is there a relationship between participants' pre-operative level of cognitive functioning

and the changes they demonstrate in cognitive, quality of life, mood, and motor functioning after PVP?

Question 5: Relationship Between Cognitive and Quality of Life Outcomes from Pallidotomy

Is there evidence that magnitude of cognitive change observed post-PVP is related to magnitude of post-operative change in reported quality of life? In particular, do participants who exhibited relatively larger post-operative cognitive decline also report relatively smaller post-operative improvement in their quality of life?

STUDY DESIGN AND METHODS

Participants

Patients with advanced PD referred to the Surgical Center for Movement Disorders (SCMD) at the University of British Columbia were prospectively entered into the study between May 1997 and December 2000.[5] PVP candidates had a clinical diagnosis of PD and disabling levodopa-induced dyskinesia. Of 44 consecutive PVP candidates at the SCMD, five declined to participate in this study, and two were not asked to participate as they were judged to not have sufficient proficiency in English for valid neurobehavioural test administration, producing a study enrollment of 37 individuals. With one type of exception described in detail below, study participants were randomly assigned to either the surgery or waitlist group. Twenty-three participants were assigned to the surgery group. Fifteen underwent left PVP, seven underwent right PVP, and one participant declined PVP after undergoing baseline assessment, and he was dropped from the study. The baseline data from the participant in the surgery group who declined surgery were not included in any of the analyses reported below, and consequently the final sample size of the surgery group was 22. Fourteen participants were assigned to the waitlist group.

Dementia was not an exclusion factor for surgery. However, relatively few overtly demented individuals were referred for consideration for PVP. This likely reflects the belief held by referring physicians that dementia is a contraindication for PVP.

Participants underwent PVP in the hemisphere contralateral to the most affected side of their body. If a patient's symptoms were symmetrical, PVP was typically performed in the hemisphere contralateral to his or her dominant hand. One participant in the surgery group was

[5] Ethical approval was obtained for this study from the University of British Columbia Ethics Review (Approval

studied as he underwent a second right PVP. This patient exhibited little motor benefit from a prior PVP, and MRI results suggested the original lesion was not ideally placed.

To ensure changes in dopaminergic medications did not confound assessment of outcome from PVP, participants agreed to not alter their Parkinsonian medication(s) over the course of the study. Participants were reminded of this agreement during each assessment, and adherence was verified by chart review.

Surgical Procedure

Dr. Christopher Honey performed all the pallidotomies between July 23, 1997 and January 19, 2001. Honey and Nugent (2000) describe the surgical procedure for PVP at the SCMD in detail. Briefly, patients were admitted the day before surgery and their medications for PD were held at midnight. On the day of surgery, a stereotactic frame was affixed to their skull (Cosman-Roberts-Wells, Radionics Inc., Burlington, MA), and a localizing MRI and/or CT scan was performed. Pallidal targets were selected 4 to 6 mm below, 19 to 23 mm lateral and 2 mm anterior to the midpoint of the intercommissural line. Direct visualization of the internal segment of the pallidum (GPi) with MRI aided target selection. Intra-operative localization was finalized with macrostimulation. Radiofrequency lesions were made at 80°C for 60 seconds at the target and 3 mm and 6 mm above the target using a 1.8 mm diameter electrode with a 1.5 mm exposed tip (Radionics Inc.).

Due to financial limitations, post-operative neuroimaging studies were not routinely conducted on participants to confirm that surgical lesions were placed within the posteroventral region of the GPi. This is unfortunate given the evidence that motor and cognitive outcome from

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PVP depends on the location of the lesion within the GPi (Gross et al., 1999; Lombardi et al., 1999). There is evidence that surgical lesions typically included the sensori-motor region of the GPi. First, clinical ratings of dyskinesia made by the neurosurgeon decreased significantly after surgery [paired $t(21) = 8.8, p < .001$; see the Appendix and Table 2 for additional information regarding the dyskinesia rating scale used], and this improvement was also evident at the individual participant level, as 18 of 21 (86%) members of the surgery group demonstrated some post-operative improvement in their dyskinesia rating. This data is potentially biased by the surgeon's expectations. However, converging support is provided by the results of neuroimaging studies performed on a subset of the participants in the surgical group. Subsequent to participating in this study, four members of the surgery group underwent an MRI of their head for clinical purposes. An MRI was obtained from one participant who sustained a right arm paresis after undergoing a left PVP (described in more detail below), two MRIs were obtained when participants were later investigated for neurological illness unrelated to surgery, and the fourth MRI was obtained prior to implantation of a deep brain stimulator contralateral to the PVP. In all four instances, an experimentally naive neuroradiologist reported a lesion within the GPi consistent with PVP. The evidence reviewed above suggests surgical lesions typically included the sensori-motor GPi. However, in the absence of post-operative neuroimaging data I cannot exclude the possibility that lesions extended beyond the sensori-motor region of the GPi.

Surgical Complications

As mentioned above, one member of the surgery group developed a right arm paresis after undergoing a left PVP. This likely reflected post-operative swelling, as an MRI scan of her head performed after surgery did not show hemorrhage or stroke near the surgery. The patient's

Table 2. Tests and Measures Used in the Present Study

Measures by domain	Dependent variable(s)
Premorbid Intellectual Level	
North American Adult Reading Test (NAART) [1]	Number of errors
Preoperative Overall Level of Cognitive Functioning	
Mattis Dementia Rating Scale (DRS) [1]	Total score
Attention and Working Memory	
WAIS-R Digit Span	Total score forwards and backwards
Corsi Blocks	Total score forwards and backwards
Visual-Spatial Processing and Synthesis	
Judgment of Line orientation [2]	Number of correct responses
Hooper Visual Organization Test	Number of correct responses
Verbal and Visual Learning and Memory	
Rey Auditory Verbal Learning Test (RAVLT)[2]	Total recall of List A on trials 1-5 (RAVLT total trials 1-5), immediate and delayed recall List A, true-positives minus false-positives on delayed recognition testing for List A
Benton Visual Retention Test (Admin. A)[2]	Number of errors
Clinical Measures of Executive Functions	
Controlled Oral Word Association (COWA)[2]	Number of correct words provided for three phonemic cues
Stroop Test	Number of correct utterances in 45 seconds in the word, colour, and colour-word conditions
Trail Making Test A & B (Trails A and B)	Time to complete Trails A and time to complete Trials B

Measures by domain	Dependent variable(s)
Experimental Neuropsychology Measures of Executive Functions	
Delayed Responding (DR)	Total errors summed across 0, 10, 30, & 60 second delay periods
Delayed Alternation (DA)	Total errors
Conditional Associative Learning (CALT)[2]	Total errors
Subject Ordered Pointing (SOP)[2]	Errors on SOP words, SOP designs, and SOP drawings
Tower of Toronto	Total number of moves, total time, and total errors summed across the three trials
Quality of Life	
Medical Outcomes Study Short Form (SF-36)	Physical functioning, social functioning, role-physical, role-emotional, bodily pain, general health, vitality, mental health, and health in transition subscales plus the SF-36 total score
Mood	
Profile of Mood States (POMS)	Tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment subscales plus the POMS total score
Motor Functioning	
Clinical rating of dyskinesia	Dyskinesia was assessed when participants were in a self-described "on" state using a clinical rating scale of increasing severity which ranged from 0 to 4
Grooved Pegboard	Time to complete the first two rows using only the dominant hand and then only the non-dominant hand
MNO	Micrographia = average difference in mm between the heights of the first and last "MNO" in two writing samples; perseveration = total number of repeated elements present in the two writing samples

Note. [1] = only administered during the baseline assessment; [2] = different test stimuli presented

across the assessments, and the order of presentation of the parallel forms was counterbalanced across the participants; WAIS-R = Wechsler Adult Intelligence Scale- Revised.

paresis recovered by 2 months after surgery, and the pattern of results obtained did not change when her data were excluded from the following analyses. This patient's data were included in the results described below.

Study Design

Members of the surgery group underwent baseline assessment in the week prior to surgery and follow-up assessment 2 months after surgery. A 2-month follow-up period was used in order to provide sufficient time for post-surgical edema to resolve, whilst minimizing the potential for cognitive decline due to disease progression. For some of the analyses reported below, the surgery group was subdivided into groups of participants who underwent left and right PVP. For other analysis, the surgery group was divided into groups of participants who underwent PVP ipsilateral (non-dominant PVP) and contralateral (dominant PVP) to their dominant hand.

Members of the waitlist group underwent baseline assessment 2 months before surgery and follow-up assessment in the week prior to surgery. All surgical candidates at the SCMD had to wait 2 to 3 months to undergo PVP. Consequently, it was possible to conduct baseline and follow-up assessments on members of the waitlist group during this period and not delay when they underwent PVP.

As mentioned above, one type of exception was made to the random assignment of participants to the study groups. Eight participants who lived a significant distance from the study center were unable to commit to randomization (and the chance they would participate in the waitlist group) due to the extra travel required.[6] Rather than forgo the opportunity to study

[6] All PVP candidates had a clinical follow-up appointment with the neurosurgeon 2 months after surgery. This coincided with the study follow-up assessment for members of the surgery group, but necessitated a third trip to the

these surgical candidates they were assigned to the surgery group. This resulted in the under representation of rural dwellers in the waitlist group. Despite this difference in the proportion of rural and urban dwellers in the study groups, the surgery and waitlist groups did not differ on demographic and clinical variables that might be expected to influence outcome from pallidotomy or practice effects on retesting (by *t*- or χ^2-test as appropriate; see Table 3).

Tests and Measures

The dependent variables employed in this study are listed in Table 2, and they are described in more detail in the Appendix. Raw scores were used for each variable. Cognitive tests were selected to obtain a survey of functioning in core cognitive domains (e.g., attention, verbal and visual skill, learning and memory). However, given the potential for PVP to alter functioning within pallidal-thalamic-prefrontal circuitry, a heavy emphasis was placed on clinical measures of executive functioning and tests from the experimental neuropsychology literature that have demonstrated sensitivity to dysfunction within prefrontal-basal ganglia circuits (Stuss & Levine, 2002). Most of the clinical measures of cognitive functioning used in the present study have been employed extensively in previous investigations of cognitive outcome from PVP. However, surprisingly few studies have examined the effect of PVP on the measures I included from the experimental neuropsychology literature (Jahanshahi et al., 2002; York et al., 1999). Whenever available, alternate versions of test stimuli were used across the assessments, and the order of presentation of these parallel forms was counterbalanced across the participants

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SCMD for members of the waitlist group.

Table 3. Comparison of the Surgery and Waitlist Groups on Demographic and Clinical Variables that Might be Expected to Influence Either Outcome from Pallidotomy or Performance on Retesting

Variable	Left PVP group (n = 15)	Right PVP group (n = 7)	Waitlist group (n = 14)
Gender	F = 7, M = 8	F = 3, M = 4	F = 7, M = 7
Residence *	R = 8,U = 7	R = 1,U = 6	R = 0,U = 14
Handedness	L = 2,R = 13	R = 7	L = 1,R = 13
Age	69.5 (2.0)	61.6 (5.2)	63.4 (3.6)
Years of education	11.1 (1.1)	12.3 (1.3)	12.0 (.6)
English as second language (%)	1 (7)	3 (43)	4 (29)
Psychiatric history (%)	3 (20)	2 (29)	7 (50)
Duration of PD in years	13.1 (1.1)	13.0 (1.8)	11.3 (1.5)
Age at PD onset	56.5 (2.2)	48.6 (4.9)	52.07 (3.0)
NAART errors	24.1 (4.0)	26.6 (4.0)	25.1 (3.5)
DRS total score	131.6 (2.2)	128.7 (7.0)	130.8 (3.1)
Number impaired on DRS (%)	2 (13)	2 (28)	2 (14)
Baseline POMS total score	42.4 (8.7)	45.0 (9.1)	45.8 (10.2)
Baseline SF-36 total score	423.1 (44.0)	387.9 (60.0)	397.8 (39.0)
Days between assessments	70.2 (8.9)	71.7 (5.5)	65.4 (4.0)

Note. Unless indicated otherwise, numbers in bracket refer to the standard error of the mean; * = $p < .05$ by χ^2; for gender F = female, M = male; for residence R = rural (pop. < 2,500), U = urban (pop > 2,500); for hemisphere of PVP and handedness L = left, R = right; NAART= North American Adult Reading Test; DRS = Dementia Rating Scale; impaired on DRS taken to be a total score < 123/144 (Mattis, 1988); POMS = Profile of Mood States; SF-36 = Medical Outcomes Study-Short Form. For additional information regarding the NAART, DRS, POMS, and SF-36 see Table 2 and the Appendix.

(see Table 2).

Self-reported health-related quality of life and mood functioning were assessed using generic rating scales that have documented sensitivity to change. The Medical Outcomes Study Short Form (SF-36) was used a measure of health-related quality of life (Ware, Snow, Kosinski, & Gandek, 1993). On the SF-36 respondents rated the extent to which illness (physical or mental) and pain interfered with their ability to perform specific daily activities such as lifting objects and performing household chores, medication management, and socialization. Responses were used to generate scores for physical functioning, social functioning, role-physical, role-emotional, bodily pain, general health, vitality, mental health, and health in transition subscales.

Some quality of life research with elderly, cognitively impaired groups has used information from third-party informants due to concerns about the ability of cognitively impaired individuals to provide valid self-report information (e.g., Albert, Del Castilo-Castaneda, & Sano, 1996). I elected to employ a self-report measure of quality of life in the present research for two reasons. First, it is widely held that appraisal of constructs such as one's quality of life is highly personal and subjective, and that patients should be the first source of such information (Mozley et al., 1999; Novella et al., 2001; Selai, Trimble, Rosser, & Harvey, 2001). Indeed there is evidence that proxies may underestimate other peoples' quality of life, particularly for more subjective aspects of functioning (Novella et al., 2001; Selai et al., 2001). Second, there is accumulating evidence that patients with mild to moderate dementia are capable of responding to self-report measures of quality of life in a reliable, internally consistent manner (Bureau-Chalot et al., 2002; Logsdon, Gibbons, McCurry, & Teri, 2002; Mozley et al., 1999; Novella et al., 2001; Ready, Ott, Grace, & Fernandez, 2002), and that their responses correlate with external objective criteria such as measures of day-to-day functioning and pleasant events frequency (e.g., Logsdon et al., 2002)

The Profile of Mood States (POMS) was used as a measure of self-reported mood state

(McNair, Lorr, & Droppleman, 1981). On the POMS, respondents indicated the extent to which each of 65 adjectives (e.g., happy, sad) applied to how they felt during the week preceding assessment. Responses were used to generate scores for tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment subscales.

Dyskinesia severity contralateral to PVP was rated by the neurosurgeon 2 months before and 2 months after surgery using the rating scale of Goetz et al., (1994). Motor functioning was also assessed using a measure of speeded dominant and non-dominant manual dexterity, and by the magnitude of micrographia and motor perseveration present in a handwriting sample (described in the Appendix).

All tests were administered when participants were in a self-described on period (i.e., when their Parkinsonian medications were providing symptom relief). The total testing time per assessment ranged from 2.5 to 5 hours, and rest/meal breaks were taken as needed.

Participant Retention and Missing Data

Participant retention

There was 100% retention of the waitlist group, with every participant providing baseline and follow-up assessment data. As mentioned above, one participant in the surgery group elected to not undergo PVP, and he was dropped from the study after the baseline assessment. His baseline data were not included in any of the analyses reported here. Retention of the surgery group was otherwise complete.

Missing data at baseline

While study drop out was very low, there were missing data as every participant was not able to complete all the measures during the baseline session. When a participant was unable to

complete a measure at baseline, the measure was typically not administered during his or her follow-up assessment. The number of participants in the left PVP, right PVP, and waitlist groups who completed each cognitive, quality of life, and mood measure during the baseline and follow-up sessions is detailed in Table 4A. The same information for the motor variables is presented in Table 4B, except here the surgery group was divided into participants who underwent PVP ipsilateral and contralateral to their dominant hand (referred to as non-dominant and dominant PVP respectively).

For most variables, all but one or two participants in each of the study groups provided data in the baseline session. This isolated missing baseline data reflected factors such as participant fatigue or limited availability for testing, error when completing self-report instruments, and occasionally experimental error. However, a small number of variables were missing baseline data from more than one or two participants per group. The different causes for this missing data are outlined below. The potential implications of this missing data are discussed in subsequent sections of the thesis.

Some participants were unable to complete the Benton Visual Retention Test (BVRT), Tower of Toronto, and handwriting tests due to limitations in their manual functioning, and deficient colour vision prevented some participants from completing the Stroop test.

Premature termination of test administration during the baseline assessment due to a participant's persisting inability to understand or follow test instructions decreased the sample size by three participants for the Trail Making Test Part B and by two participants for the Tower of Toronto. These participants tended to have a relatively low pre-operative overall level of cognitive functioning (all had a Dementia Rating Scale (DRS) total score ≤ 114, which is well below the cut-off score for impairment of 123/144 recommended by the test developer; Mattis, 1988). Consequently, some of the more cognitively impaired participants before surgery did not

Table 4A. The Number of Participants in the Left PVP, Right PVP, and Waitlist Groups who Completed each Cognitive, Quality of Life, and Mood Variable During the Baseline and Follow-Up Sessions

Measures by domain	Dependent variable	Left PVP (n = 15)		Right PVP (n = 7)		Waitlist (n = 14)	
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Premorbid Intellectual Level							
North American Adult Reading Test	Number of errors	14	n/a	7	n/a	13	n/a
Preoperative Overall Level of Cognitive Functioning							
Mattis Dementia Rating Scale	Total score	14	n/a	7	n/a	14	n/a
Attention and Working Memory							
WAIS-R Digit Span	Forwards score	7	7 (7)	4	4 (4)	7	7 (7)
	Backwards score	7	7 (7)	4	4 (4)	7	7 (7)
Corsi Blocks	Forwards score	15	15 (15)	7	7 (7)	13	14 (13)
	Backwards score	15	15 (15)	7	7 (7)	13	14 (13)

Measures by domain	Dependent variable	Left PVP (n = 15)		Right PVP (n = 7)		Waitlist (n = 14)	
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Visual-Spatial Processing and Synthesis							
Judgment of Line Orientation	Total correct	14	14 (14)	6	7 (6)	14	14 (14)
Hooper Visual Organization Test	Total correct	15	14 (14)	7	7 (7)	14	14 (14)
Verbal and Visual Learning and Memory							
RAVLT	Total recall trials 1-5	15	15 (15)	7	7 (7)	13	14 (13)
	Immediate recall List A	15	15 (15)	7	7 (7)	13	14 (13)
		15	14 (14)	7	7 (7)	12	14 (12)
	Delayed recall List A	15	14 (14)	7	7 (7)	13	14 (13)
	Delayed recog List A						
BVRT	Total errors	13	12 (12)	7	7 (7)	14	14 (14)
Clinical Measures of Executive Functions							
COWA	Number of words	15	15 (15)	7	7 (7)	14	14 (14)
Stroop	Number of words	14	14 (14)	5	5 (4)	13	14 (13)
	Number of colours	13	13 (13)	5	5 (4)	13	14 (13)
	Number of color-words	13	13 (13)	5	5 (4)	13	14 (13)
Trail Making Test A	Time	15	14 (14)	6	6 (6)	14	14 (14)
Trail Making Test B	Time	13	10 (10)	4	6 (4)	14	14 (14)

Measures by domain	Dependent variable	Left PVP (n = 15)		Right PVP (n = 7)		Waitlist (n = 14)	
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Tower of Toronto	Total moves	11	8 (8)	4	5 (3)	12	13 (12)
	Total time	11	8 (8)	3	5 (3)	12	13 (12)
	Total errors	11	8 (8)	4	5 (3)	12	13 (12)
Experimental Neuropsychology Measures of Executive Functions							
Delayed Responding	Total errors	13	11 (11)	5	5 (4)	11	11 (10)
Delayed Alternation	Total errors	12	10 (10)	5	5 (4)	12	12 (11)
Conditional Associative Learning Test	Total errors	14	13 (13)	6	5 (4)	12	14 (12)
Subject Ordered Pointing	Words errors	15	14 (14)	7	6 (6)	14	14 (14)
	Designs errors	15	14 (14)	7	6 (6)	14	14 (14)
	Drawings errors	15	14 (14)	7	6 (6)	14	14 (14)
Quality of Life							
SF-36	Physical functioning	13	14 (12)	7	7 (7)	13	14 (13)
	Social functioning	14	14 (14)	7	7 (7)	13	14 (13)
	Role-physical	14	14 (13)	7	7 (7)	13	14 (13)
	Role-emotional	14	14 (13)	7	7 (7)	13	14 (13)
	Bodily pain	14	14 (14)	7	7 (7)	13	14 (13)
	General health	14	14 (14)	7	7 (7)	13	14 (13)
	Vitality	14	13 (13)	7	7 (7)	13	14 (13)

Measures by domain	Dependent variable	Left PVP (n = 15)		Right PVP (n = 7)		Waitlist (n = 14)	
		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
	Mental health	14	14 (14)	7	7 (7)	13	14 (13)
	Health in transition	15	14 (14)	7	7 (7)	14	14 (14)
Mood							
POMS	Tension-anxiety	14	14 (14)	7	6 (6)	14	14 (14)
	Depression-dejection	14	14 (14)	7	6 (6)	14	14 (14)
	Anger-hostility	14	14 (14)	7	6 (6)	14	14 (14)
	Vigor-activity	14	14 (14)	7	6 (6)	14	14 (14)
	Fatigue-inertia	14	14 (14)	7	6 (6)	14	14 (14)
	Confusion-bewilderment	14	14 (14)	7	6 (6)	14	14 (14)

Note. The numbers within the brackets indicate the number of participants included in the statistical analyses for each variable. For some variables, the sample included in the statistical analysis was smaller than the smallest sample size during each of the assessments because different participants provided data in the baseline and follow up assessments. n/a = not applicable as the measure was only administered at baseline. SF-36 = Medical Outcomes Study Short Form; RAVLT = Rey Auditory Verbal Learning Test; POMS = Profile of Mood States; COWA = Controlled Oral Word Association; BVRT = Benton Visual Retention Test; WAIS-R = Wechsler Adult Intelligence Test – Revised.

Table 4B. The Number of Participants in the Dominant PVP, Non-dominant PVP, and Waitlist Groups who Completed each Motor Variable During the Baseline and Follow-Up Sessions

	Dependent variable	Dominant PVP (n = 13)		Non-dominant PVP (n = 9)		Waitlist (n = 14)	
Motor measure		Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Clinical rating of dyskinesia	Rating	12	12 (12)	9	9 (9)	n/a	n/a
Grooved Pegboard	Dominant time	12	11 (11)	8	8 (7)	12	13 (12)
	Non-dominant time	12	11 (11)	7	8 (6)	13	14 (13)
MNO test	Micrographia	10	11 (10)	9	8 (8)	11	13 (11)
	Perseveration	10	11 (10)	8	8 (7)	10	13 (10)

Note. The numbers within the brackets indicate the number of participants included in the statistical analyses for each variable. For some variables the sample included in the statistical analysis was smaller than the smallest sample size during each of the assessments because different participants provided data in the baseline and follow up assessments. n/a = not applicable as these participants did not undergo dyskinesia assessment. Dominant PVP = surgery contralateral to dominant hand, non-dominant PVP = surgery ipsilateral to dominant hand.

provide data for the Trail Making Test Part B and the Tower of Toronto.

The relatively smaller sample sizes at baseline for the Delayed Alternation (DA) and Delayed Responding (DR) tests reflects the lower testing priority assigned to these measures due their long administration time. These measures were frequently not administered when assessment time was short.

Finally, Digit Span forwards and backwards was administered to roughly half of the participants as these measures were added mid-way through the study.

Missing data at follow-up

With few exceptions, participants who completed a measure during the baseline assessment also completed the measure at follow-up. Patient fatigue or limited availability for testing accounted for most of the isolated instances when this was not the case. Additionally, the small decline in the number of patients who completed the DA and DR tests at follow-up once again reflected the lower testing priority assigned to these measures.

However, two participants who underwent left PVP experienced significant difficulty performing a cognitive measure they were able to complete pre-operatively, and as a result the test had to be terminated. One of these participants was unable to perform the Trail Making Test Part B, and the second participant was unable to perform the Tower of Toronto.

QUESTION 1: GROUP ANALYSIS OF OUTCOME FROM PALLIDOTOMY

The goal of this portion of the thesis was to examine neurobehavioural outcome from left and right PVP in a manner that controlled for practice effects, and to then compare the observed post-operative changes in neurobehavioural functioning with the changes typically reported by previous studies that did not fully control for retesting effects.

Statistical Approach

For the cognitive, quality of life, and mood measures group-level changes over the baseline and follow-up assessments were investigated with SPSS repeated measures analysis of variance (MANOVA; Norusis, 1993). Assessment session (Baseline, Follow-up) served as a within-participant factor. A between participant factor of Group (left hemisphere PVP, right hemisphere PVP, waitlist group) was constructed by dividing the surgery group into participants who underwent left and right PVP.[7] For the measures of speeded manual dexterity, micrographia, and motor perseveration the same MANOVA model was employed, except a between participant factor of Group (dominant hemisphere PVP, non-dominant hemisphere PVP, waitlist group) was constructed by dividing the surgery group into participants who underwent PVP contralateral and ispsilateral to their dominant hand.

To account for the fact that there were different numbers of participants in each of the groups in the above MANOVA analyses, the regression method was used to calculate the sums of squares (Norusis, 1993, p. 48). Additionally, the multivariate approach to MANOVA was employed, as this approach is not based on assumptions about the variance-covariance matrix

[7] The pattern of cognitive, quality of life, and mood results obtained with this analysis did not change when the surgery group was divided into dominant and non-dominant hemisphere PVP based on participant handedness.

(such as symmetry), which are frequently not tenable in practice (Norusis, 1993, p. 116).

In the MANOVA models described above, performance by members of the surgery group before and after PVP was compared to performance by highly similar participants in the waitlist group who were assessed twice with the same test-retest interval. Therefore, an effect of PVP on a dependent variable would be reflected in an Assessment x Group interaction (Chelune, 2002; Keith et al., 2002; Sawrie, 2002; Smith, 2002). Consequently, discussion of the results of the MANOVA analysis is restricted to this higher-order interaction of principal interest. Significant Assessment x Group interactions were analyzed further with simple effect analyses followed by Newman-Keuls multiple comparisons (as described by Howell, 1987).

Given the relatively small clinical sample employed, and the need to preserve statistical power to detect effects of surgery, the alpha level was set at the .05 level for each test. The magnitude of statistically significant MANOVA effects was reported in the η^2 metric (the proportion of variance in the dependent variable explained by differences among the groups).

Clinical ratings of dyskinesia severity in the surgery group 2 months before and 2 months after surgery were compared using a paired sample *t*-test, and again alpha was set at the .05 level.

Statistical Power and Implications of the Missing Data

G*Power (Erdfelder, Faul, & Buchner, 1996) was used to compute the statistical power of this MANOVA analysis to detect a Group x Assessment interaction for each of the cognitive, quality of life, mood, and motor variables employed in the study. Statistical power was computed to detect small ($\eta^2 = .02$), medium ($\eta^2 = .15$), and large ($\eta^2 = .35$) effect sizes as defined by Cohen (1988). Alpha was set at the .05 level, and rho (the population correlation coefficient between scores at baseline and follow-up) was conservatively set at .50 for all the

variables.[8]

The results of this power analysis are presented in Table 5. Inspection of Table 5 suggests the MANOVA analysis had good power, as this analysis had a greater than 90% chance of detecting a medium- or large-sized effect of surgery on most variables. As described above, the sample size for a few measures was diminished, and these variables did have somewhat lower statistical power, but the probability of detecting a medium-sized effect of PVP was less than 90% for only Digit Span forwards and backwards and the Tower of Toronto.

However, it is worthy of note that this MANOVA analysis did not include pre- and post-operative data from the participant in the left PVP group who was unable to complete Trails B at follow-up and the other participant in the left PVP group who was unable to complete the Tower of Toronto at follow-up. As their poor post-operative performance on these measures was not captured by the MANOVA analysis, post-surgical decline on Trails B and the Tower of Toronto after left PVP was likely underestimated somewhat.

Results

Cognitive functioning

There were significant effects of PVP (i.e., Group x Assessment interactions) on verbal learning [RAVLT total trials 1-5, $F(2, 32) = 5.49$, $p = .009$, $\eta^2 = .26$], verbal fluency [COWA, $F(2, 33) = 8.82$, $p = .001$, $\eta^2 = .35$], verbal working memory [SOP words, $F(2, 31) = 8.01$, $p = .002$, $\eta^2 = .34$], and speed of color naming [Stroop color condition (non-interference), $F(2, 27) =$

[8] Amongst members of the waitlist group, the observed correlation between baseline and follow-up scores for the dependent measures ranged greatly. The mean correlation between performance at baseline and follow-up was $r = .54$ ($SD = .34$) for the cognitive variables, $r = .57$ ($SD = .24$) for the SF-36 subscales, $r = .66$ ($SD = .17$) for the POMS subscales, and $r = .59$ ($SD = .40$) for the motor measures.

Table 5. Power on Testing the Group x Assessment Interaction for the Cognitive, Quality of Life, Mood, and Motor Variables

Dependent variable			Power		
	N	*DF*	Small effect size $\eta^2 = .02$	Medium effect size $\eta^2 = .15$	Large effect size $\eta^2 = .35$
Digit Span backward	18	2,15	.15	.76	.98
Digit Span forward	18	2,15	.15	.76	.98
Tower of Toronto errors	23	2,20	.19	.87	.99
Tower of Toronto moves	23	2,20	.19	.87	.99
Tower of Toronto time	23	2,20	.19	.87	.99
Delayed Alternation	25	2,22	.20	.91	.99
Delayed Responding	25	2,22	.20	.91	.99
Motor perseveration	27	2,24	.22	.93	.99
Trails B	28	2,25	.22	.94	.99
Conditional Associative Learning Test	29	2,26	.23	.95	.99
Micrographia	29	2,26	.23	.95	.99
Grooved Pegboard dominant hand	30	2,27	.24	.96	.99
Grooved Pegboard non-dominant hand	30	2,27	.24	.96	.99
Stroop words	30	2,27	.24	.96	.99
Stroop colours	30	2,27	.24	.96	.99
Stroop colour-words	31	2,28	.25	.96	.99
SF-36 physical functioning	32	2,29	.26	.97	.99
Benton Visual Retention Test	33	2,30	.26	.97	.99
RAVLT Delayed recall List A	33	2,30	.26	.97	.99
SF-36 role-emotional	33	2,30	.26	.97	.99
SF-36 role-physical	33	2,30	.26	.97	.99
SF-36 vitality	33	2,30	.26	.97	.99
Judgment of Line Orientation	34	2,31	.27	.98	.99
POMS anger-hostility	34	2,31	.27	.98	.99
POMS confusion-bewilderment	34	2,31	.27	.98	.99
POMS depression-dejection	34	2,31	.27	.98	.99
POMS fatigue-inertia	34	2,31	.27	.98	.99
POMS tension-anxiety	34	2,31	.27	.98	.99
POMS vigor-activity	34	2,31	.27	.98	.99
RAVLT delayed recognition of List A	34	2,31	.27	.98	.99
SF-36 bodily pain	34	2,31	.27	.98	.99
SF-36 general health	34	2,31	.27	.98	.99
SF-36 mental health	34	2,31	.27	.98	.99
SF-36 social functioning	34	2,31	.27	.98	.99

Dependent variable			Power		
	N	*DF*	Small effect size $\eta^2 = .02$	Medium effect size $\eta^2 = .15$	Large effect size $\eta^2 = .35$
Subject Ordered Pointing designs	34	2,31	.27	.98	.99
Subject Ordered Pointing drawings	34	2,31	.27	.98	.99
Subject Ordered Pointing words	34	2,31	.27	.98	.99
Trails A	34	2,31	.27	.98	.99
Corsi Blocks backward	35	2,32	.28	.98	.99
Corsi Blocks forward	35	2,32	.28	.98	.99
Hooper Visual Organization Test	35	2,32	.28	.98	.99
RAVLT immediate recall List A	35	2,32	.28	.98	.99
RAVLT total recall trials 1-5	35	2,32	.28	.98	.99
SF-36 health in transition	35	2,32	.28	.98	.99
COWA	36	2,33	.29	.98	.99

Note. *N* = total sample size for variable; *DF* = degrees of freedom on Assessment x Group interaction in the MANOVA analysis. The variables are arranged in order of ascending sample size. SF-36 = Medical Outcomes Study Short Form; RAVLT = Rey Auditory Verbal Learning Test; POMS = Profile of Mood States; COWA = Controlled Oral Word Association.

3.89, $p = .03$, $\eta^2 = .22$]. The Group x Assessment interaction was not statistically significant for the remaining cognitive measures. The effects of surgery on verbal learning, fluency, working memory, and speed of colour naming are depicted in Figure 2. Significant performance decline after left but not right PVP was evident for all four variables.

The same general pattern of performance was evident for verbal learning, fluency, and verbal working memory. There were no significant performance differences between the groups in these abilities at baseline. Participants who underwent left PVP then exhibited a decline in performance, while performance by the right PVP and waitlist groups remained essentially unchanged. Consequently, performance differed significantly across the groups at follow-up [simple Group effects at follow-up for SOP words, RAVLT total trials 1-5, and COWA were $F(2, 31) = 7.14$, $p = .003$, $F(2, 33) = 17.8$, $p < .001$, and $F(2, 33) = 7.55$, $p = .002$ respectively]. For all three variables, at follow-up the performance of the waitlist and right PVP groups did not differ, but both of these groups outperformed the left PVP group ($p < .05$).

A slightly different pattern of results was obtained for speed of colour naming, although once again performance decline was evident after left but not right PVP. Group differences were evident in speed of color naming during the baseline and follow-up assessments [simple Group effects during the baseline and follow-up assessments were $F(2, 28) = 5.52$, $p = .01$ and $F(2, 28) = 19.12$, $p < .001$ respectively]. At baseline, the right PVP group performed better than the left PVP and waitlist groups ($p < .05$), while the left PVP and waitlist groups did not differ from each other. Performance then declined strongly in the left PVP group, while declines in the right PVP and waitlist groups were modest. At follow-up, all contrasts between the groups were significant, with the left PVP group now performing significantly below the waitlist and right PVP groups ($p < .05$).

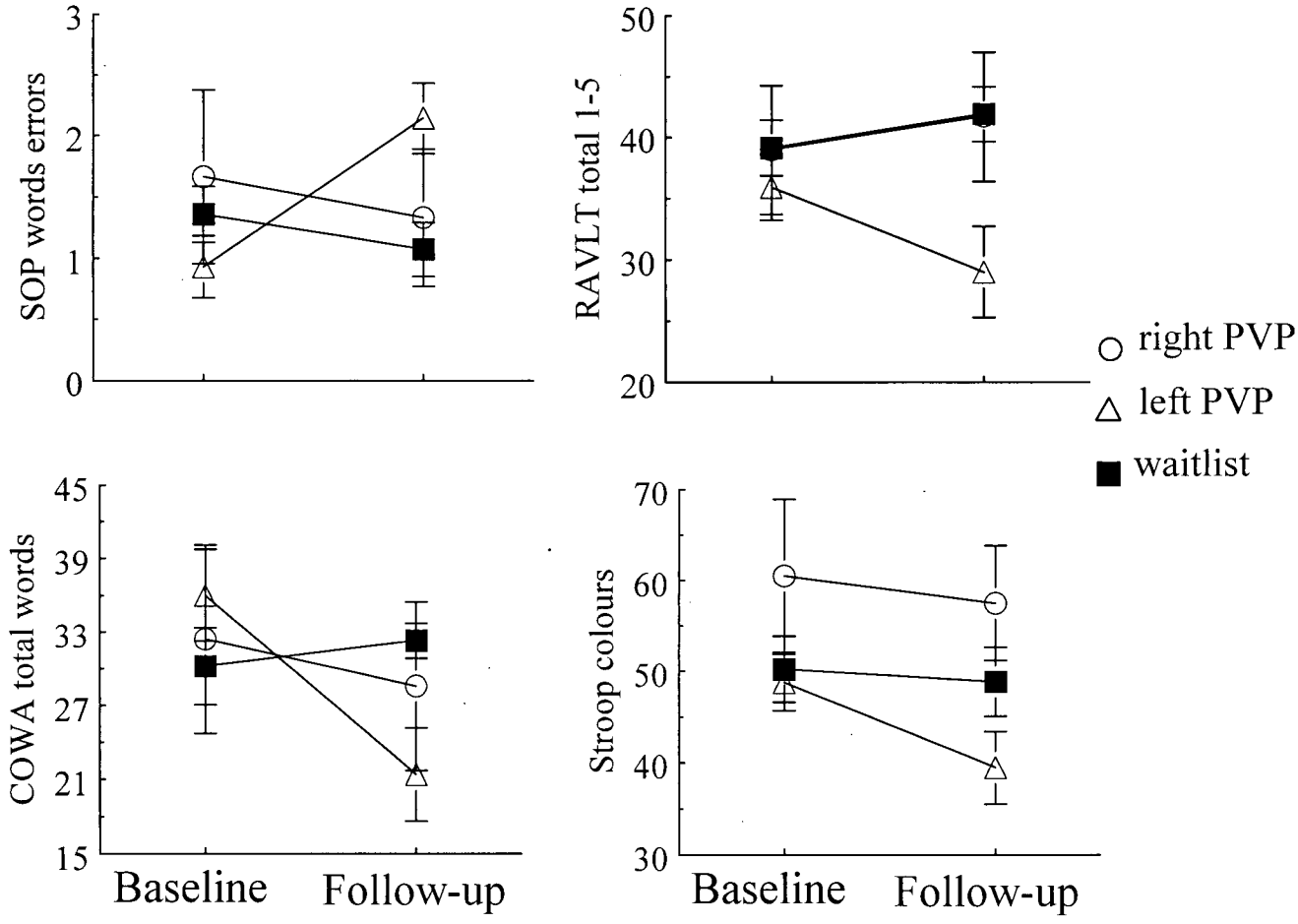

Figure 2. Mean performance by the right PVP, left PVP, and waitlist groups during the baseline and follow-up assessments on the verbal measures of working memory (SOP words), list learning (RAVLT total trials 1-5), fluency (COWA), and speed of colour naming (Stroop colours). With the exception of the working memory task (SOP words), a higher score on these measures reflects better performance. Error bars demarcate the standard error of the mean. Please note, the mean baseline and follow-up RAVLT total trials 1-5 scores for the right PVP and waitlist groups were virtually identical, and consequently the data points for these groups are superimposed in the figure.

Quality of life

There were significant effects of PVP on the bodily pain, $F(2, 31) = 3.62$, $p = .04$, $\eta^2 = .19$, and social functioning, $F(2, 31) = 4.17$, $p = .03$, $\eta^2 = .22$, subscales of the Medical Outcomes Study Short Form (SF-36). These effects of surgery on reported quality of life are depicted in Figure 3.

The groups did not differ at baseline in reported bodily pain. Reported functioning then declined in the waitlist group and improved in the groups that underwent PVP. As a result, the groups differed significantly at follow-up [simple effect of Group at follow-up was $F(2, 31) = 5.63$, $p = .008$]. At follow-up, reported bodily pain did not differ between the right and left PVP groups, but both of these groups reported better (i.e., less) bodily pain than the waitlist group ($p < .05$).

For reported social functioning, group differences were evident during the baseline and follow-up assessments [simple effects of Group during the baseline and follow-up assessments were $F(2, 31) = 4.71$, $p = .03$ and $F(2, 32) = 4.78$, $p = .02$ respectively]. At baseline, reported social functioning did not differ for the waitlist and left PVP groups, but both of these groups reported better social functioning than the right PVP group ($p < .05$). Reported social functioning then improved amongst those participants who underwent right PVP, remained essentially unchanged in the left PVP group, and declined in the waitlist group. As a result, at follow-up reported social functioning was not different for the left and right PVP groups, but both of these groups reported better social functioning than the waitlist group ($p < .05$).

Mood Functioning

PVP did not result in any significant changes at the group level in reported mood functioning, as measured by the subscales of the Profile of Mood States (all $\eta^2 \leq .12$).

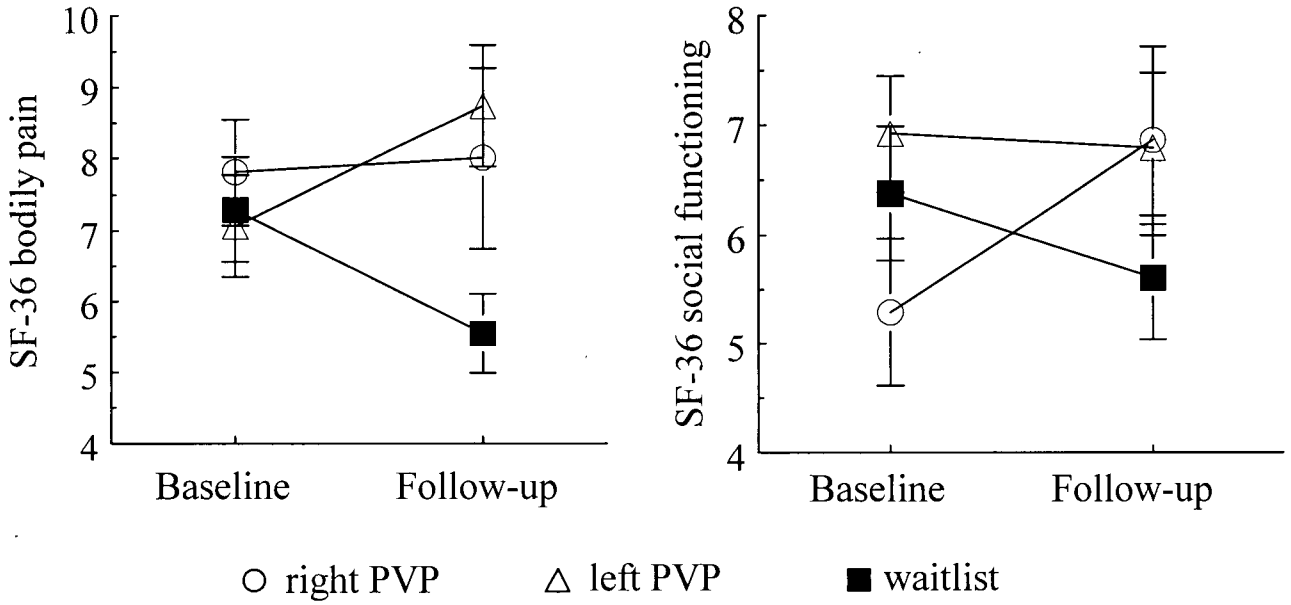

Figure 3. Mean scores obtained by the right PVP, left PVP, and waitlist groups during the baseline and follow-up assessments on the bodily pain and social functioning subscales of the Medical Outcomes Study Short Form (SF-36). Error bars demarcate the standard error of the mean. For both variables a higher score reflects better reported functioning.

Motor functioning

Clinical ratings of dyskinesia severity contralateral to PVP declined significantly after surgery, $t(21)= 8.8, p < .001$. However, there were no significant effects of PVP on grooved pegboard performance, or in the amount of micrographia or motor perseveration present in the handwriting samples (all $\eta^2 \leq .15$).

Discussion

Participants who underwent left PVP exhibited decline on verbal measures of list learning, fluency, working memory, and speed of color naming relative to waitlisted participants and participants who underwent right PVP. This pattern of cognitive decline is in keeping with the results of previous studies of the cognitive effects of PVP that did not control for practice effects. Indeed, declines in verbal learning, fluency, and working memory after left PVP are the most consistently reported negative cognitive sequelae of this procedure (see Table 1).

The declines observed after left PVP on verbal measures of list learning, fluency, working memory, and speed of color naming might reflect decline in a single cognitive process. Indeed, verbal retrieval appears to be central to the performance of all four tasks, raising the possibility that PVP in the left hemisphere disrupted the efficient retrieval of verbal information. Alternatively, the present findings may reflect post-surgical decline in multiple cognitive abilities such as verbal retrieval, working memory, and speed of information processing.

To examine whether disruption in one or many processes was responsible for the cognitive declines evident after PVP, I examined the correlations amongst the post-PVP change scores for the measures of list learning, fluency, working memory, and speed of color naming. I reasoned if post-surgical decline on these measures reflected disruption of a single cognitive process, post-operative change scores for these four measures should be strongly intercorrelated.

On the other hand, if post-surgical decline on these measures reflected compromise in multiple, at least partially dissociable cognitive processes, post-PVP change scores for these measures would be weakly or inconsistently intercorrelated.

The obtained pattern of intercorrelations suggests PVP altered at least two, partially dissociable cognitive processes (see Table 6). Change scores for verbal learning, fluency, and speed of colour naming were all significantly intercorrelated, while change scores for the measure of verbal working memory did not correlate significantly with the change scores for any of the other cognitive variables affected by PVP.

It is interesting that during the baseline and follow-up assessments the right PVP group performed better on Stroop colours than the left PVP and waitlist groups (see Figure 2). As noted above, PVP was usually performed in the hemisphere contralateral to the most affected side of the body. Given this, the side of PVP may provide a crude reflection of the more compromised cerebral hemisphere amongst the present PVP candidates. Perhaps then, the overall superiority in speed of colour naming exhibited by right PVP candidates reflects relative insensitivity on the part of Stroop colours to compromise within the right hemisphere. I note that the waitlist group contained a roughly equivalent number of participants who eventually underwent left and right PVP, and as would be expected on this basis, performance by the waitlist group fell between that of the left and right PVP groups.

Patients who underwent PVP reported lower bodily pain at follow-up than waitlisted patients. This is consistent with other reports of significant improvement in pain and bodily discomfort after PVP (Honey, Stoessl, Tsui, Schulzer, & Calne, 1999; Laitinen et al., 1992; Martinez-Martin et al., 2000; Scott et al., 1998). Honey et al. (1999) described several types of pain reported by patients with advanced PD including exacerbation of somatic pain (e.g., arthritis

Table 6. Correlations Amongst the Post-Surgical Change Scores for the measures of List Learning, Fluency, Working Memory, and Speed Of Color Naming

	COWA	Stroop colours	SOP words	RAVLT total trials 1-5
COWA		.42*	-.23	.55**
Stroop colours			-.18	.37*
SOP words				-.04
RAVLT total trials 1-5				

Note. * = $p < .05$, ** = $p < .01$; COWA = Controlled Oral Word Association; SOP = Subject Ordered Pointing; RAVLT = Rey Auditory Verbal Learning Test. For additional details regarding the COWA, Stroop, SOP, and RAVLT tests see Table 2 and the Appendix.

or tendonitis) due to repetitive movements such as dyskinesia, pain due to dystonia,[9] and musculoskeletal and dysesthetic[10] pain likely of central origin. Honey and colleagues argue that PVP may reduce pain in advanced PD by reducing movement disorder symptoms, and by altering the abnormal processing of sensory stimuli in the spinal cord and basal ganglia. Interestingly, in the present study improvement in the absolute level of reported bodily pain at follow-up was modest amongst participants who underwent PVP, and worsening of reported bodily pain amongst waitlisted participants appeared to contribute to the superiority of the surgical groups over the waitlist group at follow-up (see Figure 3).

At follow-up, participants who underwent PVP also reported better social functioning than waitlisted participants. This is consistent with other reports of improvement in reported social functioning after PVP (e.g., Baron et al., 1996; Martinez-Martin et al., 2000; Scott et al., 1998; Straits-Troster et al., 2000). Outcome with respect to social functioning appeared to differ depending on the hemisphere of PVP. Absolute level of reported social functioning appeared to increase at follow-up amongst participants who underwent right PVP. In contrast, reported social functioning changed little amongst participants who underwent left PVP, and decline in reported social functioning amongst waitlisted participants appears to account for the superiority of the left PVP group over the waitlist group at follow-up (see Figure 3).

Participants in the present study did not demonstrate post-operative improvement in their reported physical functioning (as measured by the physical functioning and role physical subscales of the SF-36), or in their reported mood functioning (as measured by the POMS subscales). Similarly, although participants demonstrated reduced levodopa-induced dyskinesia after surgery, speeded manual dexterity, micrographia, and motor perseveration did not improve after PVP.

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[9] Dystonia are slow, involuntary muscle contractions that produce postural distortion (Loring, 1999).
[10] Dysesthetic pain is a persisting painful sensation induced by a gentle touch of the skin (Miller & Keane, 1983).

The results of the power analysis reported above suggest the absence of significant improvement after surgery in complex motor performance and reported physical and emotional functioning does not likely reflect low statistical power. I suspect these findings reflect the nature and extent of the physical and emotional gains PVP offers patients with advanced PD. Although not formally measured, most participants in this study had Parkinsonian motor deficits such as gait and swallowing disorders not specifically targeted by PVP. These persisting disabilities, plus the effects of advanced age and other medical conditions, may have placed limits on the breadth of the physical and emotional gains participants were able to attain after they underwent PVP.

QUESTION 2: INDIVIDUAL PARTICIPANT ANALYSIS OF OUTCOME FROM PALLIDOTOMY

Clinicians are typically interested in how frequently individual patients exhibit effects that are present at the group level, as an effect that is statistically significant at the group level but infrequent at the individual patient level may have limited clinical significance. There have been very few attempts to study the incidence of significant individual change in neurobehavioural functioning after PVP (but see Green et al., 2002 and Lacritz et al., 2000), and none of this work has examined individual outcome from PVP after accounting for possible confounds to retesting such as baseline performance level, test practice, regression to the mean, and disease progression. Below I describe the results of a multiple regression-based analysis of individual outcome from PVP that accounts for the changes in test performance expected on retesting.

Statistical Approach

Outcome from PVP at the individual participant level was investigated using the Standardized Regression Based (SRB) technique. This procedure has been used successfully to investigate neurobehavioural outcome from other neurosurgical interventions such as temporal lobe resection for epilepsy (e.g., McSweeny, Naugle, Chelune, & Luders, 1993), and it is gaining acceptance as a preferred method of neuropsychological outcome analysis at the individual participant level (e.g., Temkin et al., 1999; Sawrie, 2002).

In the SRB technique an inferential statistical decision (change/no change) is made on the basis of each participant's performance on each variable examined. As a result, the familywise Type I error rate with this technique is typically high, and it climbs as the number of measures

and participants examined increase (Keith et al., 2002; Smith, 2002). Thus it has been recommended that the number of variables examined be held at "the lowest number possible to detect the cognitive or behavioural parameter of interest" (Sawrie, 2002). In light of these concerns, I restricted the SRB analysis to the cognitive and quality of life variables the MANOVA analysis indicated were significantly affected by PVP at the group level. When used in this way, the SRB technique served as a complement to the MANOVA analysis, characterizing the base rates of significant change on the subset of cognitive and quality of life variables the MANOVA analysis indicated were affected by PVP at the group level (Keith & Puente, 2002; Sawrie, 2002; Smith, 2002).

Linear regression equations were constructed that predicted follow-up performance by members of the waitlist group. The equations were constructed using data from the waitlist group in the following manner. The baseline score on a dependent variable was entered into a linear regression equation predicting follow-up scores for that variable. Then the incremental predictive ability of a set of clinical and demographic variables was examined using a stepwise approach to the addition and removal of variables from the regression equation. The *p*-values for inclusion and exclusion were set at .05 and .10 respectively. The clinical and demographic variables examined included planned hemisphere of surgery, age at surgery, gender, years of education, duration of PD, age at PD onset, North American Adult Reading Test (NAART) errors, and the total score on the Dementia Rating Scale (DRS). The total scores for the Medical Outcomes Study Short Form (SF-36) and Profile of Mood States (POMS) were also included as potential predictors of follow-up performance for the cognitive variables (see Table 2 and the Appendix for additional information regarding the NAART, DRS, SF-36, and POMS).

The regression equations constructed capture the net effect of factors such as baseline performance level, test practice, regression to the mean, and disease progression, on test performance at follow-up by the waitlisted participants (Sawrie, Marson, Boothe, &

Harrell, 1999). These equations were then used to predict the scores members of the surgery group would have obtained on the cognitive and quality of life measures at follow-up had they not undergone PVP. Subtracting predicted from observed follow-up scores yielded individual estimates of the full effect of PVP on each variable. These individual estimates of the effect of PVP were then divided by the standard error of the estimate from the associated regression equation. This yielded a *Z*-score based SRB change score for each variable for each participant in the surgery group (McSweeny et al., 1993; Sawrie et al., 1999).[11] It is important to appreciate that these SRB-based Z-scores reflect the discrepancy between an individual's actual and predicted follow-up performance, with respect to the variability in prediction associated with the SRB regression equations. Consequently, an SRB change score of –1 reflects performance 1 standard deviation (*SD*) below expected follow-up performance. The SRB change scores do not reflect deviation in follow-up performance with respect to variability in baseline performance. Cumulative histograms of the obtained SRB change scores were then constructed for each cognitive and quality of life variable. Individual SRB change scores that fell outside a 95% confidence interval (i.e., $Z = +/- 1.96$) were taken to be significantly higher or lower than would be expected on retesting if PVP had no effect on the variable.

Results

The regression equations that best predicted follow-up scores for members of the waitlist group are presented in Table 7. As a robust regression equation was not constructed for RAVLT total trials 1-5, this variable had to be omitted from the rest of the SRB analysis. For all other variables, the regression equations constructed accounted for a significant proportion of the

[11] The order of subtraction was reversed for the negatively-keyed SOP words data, thus for all measures a negative SRB change score represents performance or reported functioning at follow-up that fell below expectations.

variance in follow-up scores (with R^2 ranging from .56 to .93). As is typically found in applications of the SRB technique, baseline scores were the most powerful predictors of follow-up scores (e.g., McSweeny et al., 1993; Temkin et al., 1999). For four of the six cognitive and quality of life variables subjected to SRB analysis, demographic and clinical variables enhanced prediction over baseline scores alone (see regression equations presented in Table 7).

Cumulative histograms of the obtained SRB change scores for the measures of verbal fluency (COWA), working memory (SOP words), and speed of colour naming (Stroop colours) are presented in Figure 4. As left PVP appeared to have greater effects on verbal fluency, working memory, and speed of colour naming than right PVP (see Figure 2), the SRB change scores for participants who underwent left and right PVP are presented in separate plots.

Significant post-surgical declines in verbal fluency were common after left PVP, and only slightly less so after right PVP. Verbal fluency performance decreased significantly for 12 of 15 (80%) members of the left PVP group, and for 5 of 7 (71%) members of the right PVP group. However, the overall magnitude of the decline in fluency was several *SD* greater amongst participants who underwent left PVP. Significant declines in verbal working memory and speed of color naming were somewhat less common overall, and for these variables significant individual decline was more common in the left PVP group. Working memory performance decreased significantly for 12 of 14 (86%) members of the left PVP group, and for 1 of 6 (17%) members of the right PVP group. Speed of color naming declined significantly for 6 of 12 (50%) participants in the left PVP group, but for only 1 of 4 (25%) members of the right PVP group.

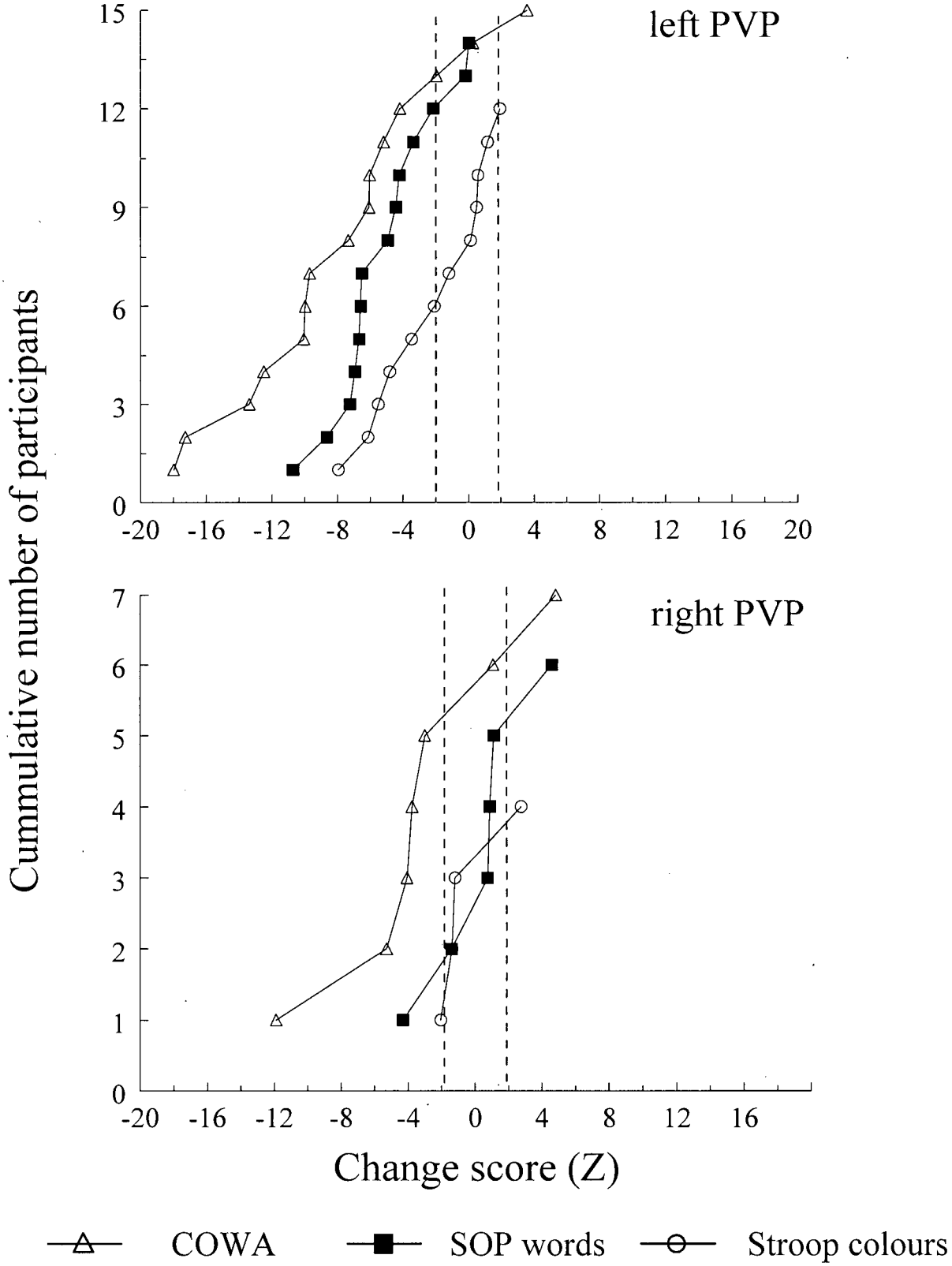
Cumulative histograms of the obtained SRB scores for the bodily pain and social functioning subscales of the SF-36 are presented in Figure 5. As right PVP appeared to have

Table 7. Regression Equations Predicting Scores for Waitlisted Participants at Follow-Up

Variable	p	R^2	R^2_{adj}	C	$\beta_{baseline}$ score	$\beta_{duration}$ of PD	β_{DRS} total score	$\beta_{SF\text{-}36\ total}$ score
Quality of life variables								
SF 36 Bodily pain	.001	.78	.73	.89	.35	.21		
Social functioning	.005	.56	.52	1.22	.71			
Cognitive variables								
COWA	.001	.92	.90	14.52	.53	.23		
Stroop colors	.001	.93	.91	16.87	.92			-.03
RAVLT total trials 1-5	.14	.26	.16	20.46	.52			
SOP words	.001	.83	.78	6.01	.49		-.04	

Note. R^2 = coefficient of determination; R^2_{adj} = R^2 corrected to more closely reflect the goodness of fit of the model in the population. C = constant; $\beta_{variable}$ = unstandardized beta weight for the indicated variable; SF-36 = Medical Outcomes Study Short Form; COWA = Controlled Oral Word Association; SOP = Subject Ordered Pointing; RAVLT = Rey Auditory Verbal Learning Test.

Figure 4. Standardized regression-based change scores for the participants who underwent left (upper panel) and right (lower panel) PVP on the measures of verbal fluency (COWA), working memory (SOP words), and speed of colour naming (Stroop colours). For all variables, a positive change score indicates better than expected performance on retesting, while a negative change score reflects lower than expected performance on retesting. Scores below and above the area bounded by the dashed vertical lines at -1.96 and +1.96 are significantly lower and higher respectively than would be expected on retesting if PVP had no effect on the variable. Due to missing data there are differences in the number of participants who provided data for each measure.


left PVP
right PVP
Cummulative number of participants
Change score (Z)
COWA
SOP words
Stroop colours

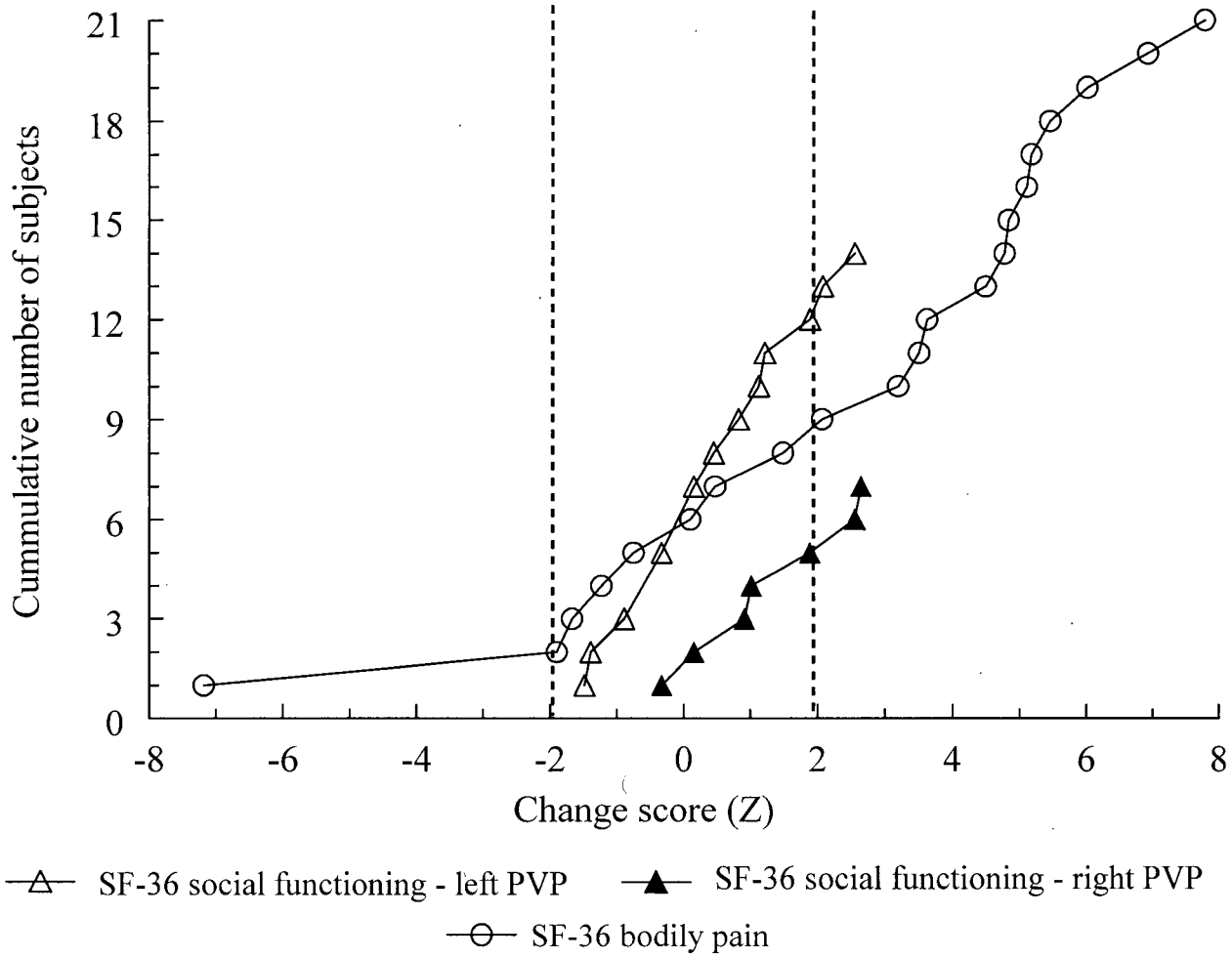


Figure 5. Standardized regression-based change scores for the participants who underwent PVP on the bodily pain and social functioning subscales of the SF-36. For all variables, a positive change score indicates better than expected reported functioning on retesting, while a negative change score reflects lower than expected reported functioning on retesting. For social functioning, separate plots are provided for the participants who underwent left and right PVP. Scores below and above the area bounded by the dashed vertical lines at -1.96 to +1.96 are significantly lower and higher respectively than would be expected on retesting if PVP had no effect on the variable.

greater beneficial effects on social functioning than left PVP (see Figure 3), the social functioning SRB change scores for the participants who underwent left and right PVP are presented in separate plots.

Significant post-PVP improvements in reported bodily pain were quite common, as 13 of 21 (62%) members of the surgery group exhibited significant improvement in their reported level of bodily pain. Significant improvements were less common for social functioning. Reported social functioning increased significantly for 2 of 14 (15%) participants who underwent left PVP, and for 2 of 7 (29%) participants who underwent right PVP. However, the magnitude of the improvement in social functioning was typically 1 to 2 *SD* greater amongst patients who underwent right PVP.

As mentioned above, I was unable to construct a regression equation that adequately predicted follow-up verbal learning (RAVLT total trials 1-5) scores for the waitlist group. This reflects RAVLT total trials 1-5's relatively low test-retest reliability between the baseline and follow-up assessments amongst waitlisted participants, $r(11) = .46$, $p = .11$.[12] In order to generate an estimate of the incidence of individual post-operative decline in verbal learning, I calculated the number of participants in the surgery and waitlist groups whose verbal learning performance declined by greater than 1 *SD* at follow-up, a technique that has been used elsewhere in this literature (e.g., Lacritz et al., 2000).[13] For the surgery group, 5 of 22 (22%) participants exhibited a decline in verbal learning of greater than 1 *SD*, all of whom underwent left PVP. Declines at follow-up of this magnitude were only observed in 1 of 14 (7%) participants in the waitlist group. When the criterion for decline was relaxed to .5 *SD*, 10 of 22 (45%) participants in the surgery group exhibited decline in verbal learning, of whom 8

[12] Lower reliability for memory measures as compared to measures of other cognitive abilities has been previously reported (e.g., Dikmen et al., 1999; McCaffrey et al., 1995), and this may reflect variability in memory functioning as well as methodological issues such as lack of equivalence of alternate versions of test stimuli.

[13] This was computed using the standard deviation of the baseline RAVLT total trials 1-5 data for all study

underwent left PVP. In contrast, declines in verbal learning at follow-up of greater than .5 *SD* were observed for only 2 of 14 (14%) participants in the waitlist group.

Discussion

The incidence of significant individual post-operative decline in verbal fluency, list learning, working memory, and speed of colour naming was high amongst members of the left PVP group. Indeed, almost all of the participants who underwent left PVP exhibited significant post-operative decline in verbal fluency and working memory. Decline in verbal fluency was also common after right PVP (occurring in 71% of the right PVP group). However, the decline in fluency was several *SD* larger amongst participants who underwent left PVP.

Almost two-thirds of the surgical group exhibited post-operative improvement in reported bodily pain. However, the incidence of significant post-operative improvement in reported social functioning was low, and the magnitude of improvement in social functioning was marginally larger for members of the right PVP group.

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participants, which equaled 10.3 words.

QUESTION 3: CHANGES IN TEST PERFORMANCE DISPLAYED BY WAITLISTED PARTICIPANTS ON RETESTING

Below I quantify the direction and magnitude of the changes in test performance members of the waitlist group exhibited on retesting, and characterize how correcting for these retesting effects alters the profile of cognitive, quality of life, mood, and motor changes observed after PVP.

Statistical Approach

For the waitlist, left PVP, and right PVP groups mean baseline to follow-up difference scores were computed for each cognitive, quality of life, and mood variable. These changes on retesting were expressed in the effect size metric using the formula effect size = (mean score at follow up - mean score at baseline) / pooled *SD* at baseline.[14]

I present the effect sizes of the changes exhibited by the waitlist group on retesting, and classify the magnitude of these changes using a system based on Cohen's (1988) effect size criteria (Bezeau & Graves, 2001).[15] I then present graphs depicting the magnitude of change after left and right PVP on the cognitive, quality of life and mood measures before and after correcting for the changes on retesting displayed by the waitlist group.

The same analysis was conducted with the measures of speeded manual dexterity, micrographia, and motor perseveration, except for these variables mean difference scores

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[14] The pooled *SD* at baseline for each variable was calculated using the procedure described by Howell (1987, p. 170-171). The order of score subtraction in this formula was reversed for negatively keyed tests (i.e., mean score at baseline - mean score at follow-up), so for all dependent measures a positive effect size reflected an improvement in performance or reported functioning on retesting.

[15] Cohen (1988) defined small (.2 *SD*), medium (.5 *SD*), and large (.8 *SD*) levels of effect size for the difference between two means. As I wanted to classify observed effect sizes into ranges, I defined the middle value between adjacent levels of effect size as the boundary between the effect size ranges. Therefore, small effects ranged from 0

between the baseline and follow-up assessments were computed separately for the waitlist, dominant PVP, and non-dominant PVP groups.

Results

Cognitive measures

The waitlist group displayed mixed, typically small-sized improvements and declines at follow-up in their performance on most cognitive measures, with improvement and decline being evident on a roughly equivalent number of variables (see Table 8). Exceptions were a large-sized improvement at follow-up in the number of errors made on the Tower of Toronto test, and a medium-sized worsening in the time taken to complete the Tower of Toronto test. Changes at follow-up on the cognitive variables affected by PVP at the group level (RAVLT total trials 1-5, COWA, SOP words, Stroop colors) were mixed, and they ranged from -.20 to +.25 *SD*.

Waitlisted participants tended to exhibit decline at follow-up on cognitive measures that incorporate time in their dependent variable and consequently place a premium on speed of responding. This included measures for which the number of correct responses in a defined time period served as the dependent variable (e.g., Stroop), and measures for which the time to complete the task served as the dependent variable (e.g., Trail Making Test). The cognitive measures with a timed dependent variable are indicated with an asterisk in Table 8.

Figure 6 depicts the magnitude of post-operative change on the cognitive measures before and after correcting for the changes displayed by the waitlist group on retesting. The data for the left and right PVP groups are presented in separate panels. In Figure 6 the cognitive variables are ordered with respect to the magnitude of the change displayed by the waitlist group on

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to |.35| *SD*, medium effects ranged from |.36| to |.65| *SD*, and large effects ranged upwards from |.66| *SD*.

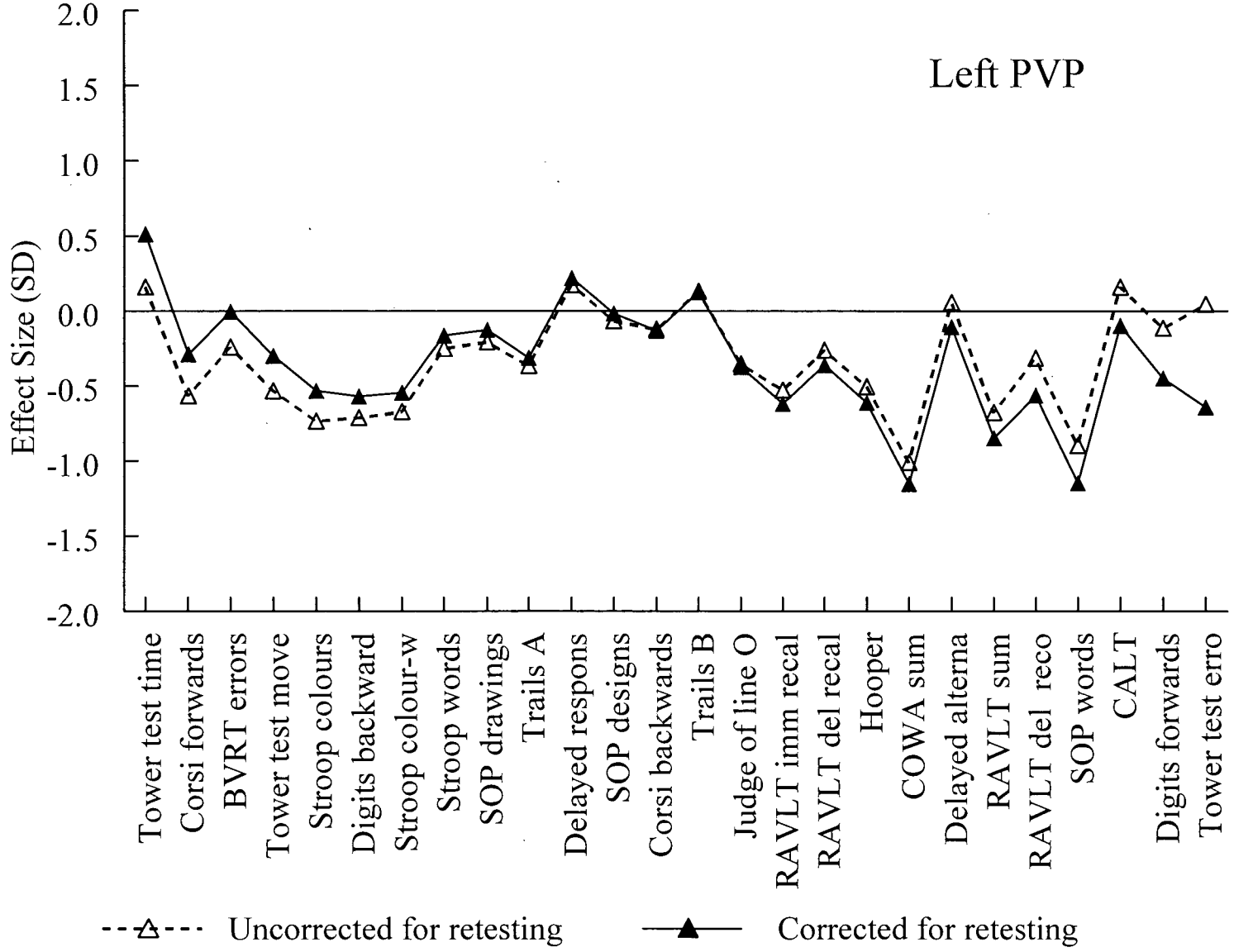
Table 8. Effect Size of the Changes Displayed by the Waitlist Group at Follow-Up on the Cognitive Measures

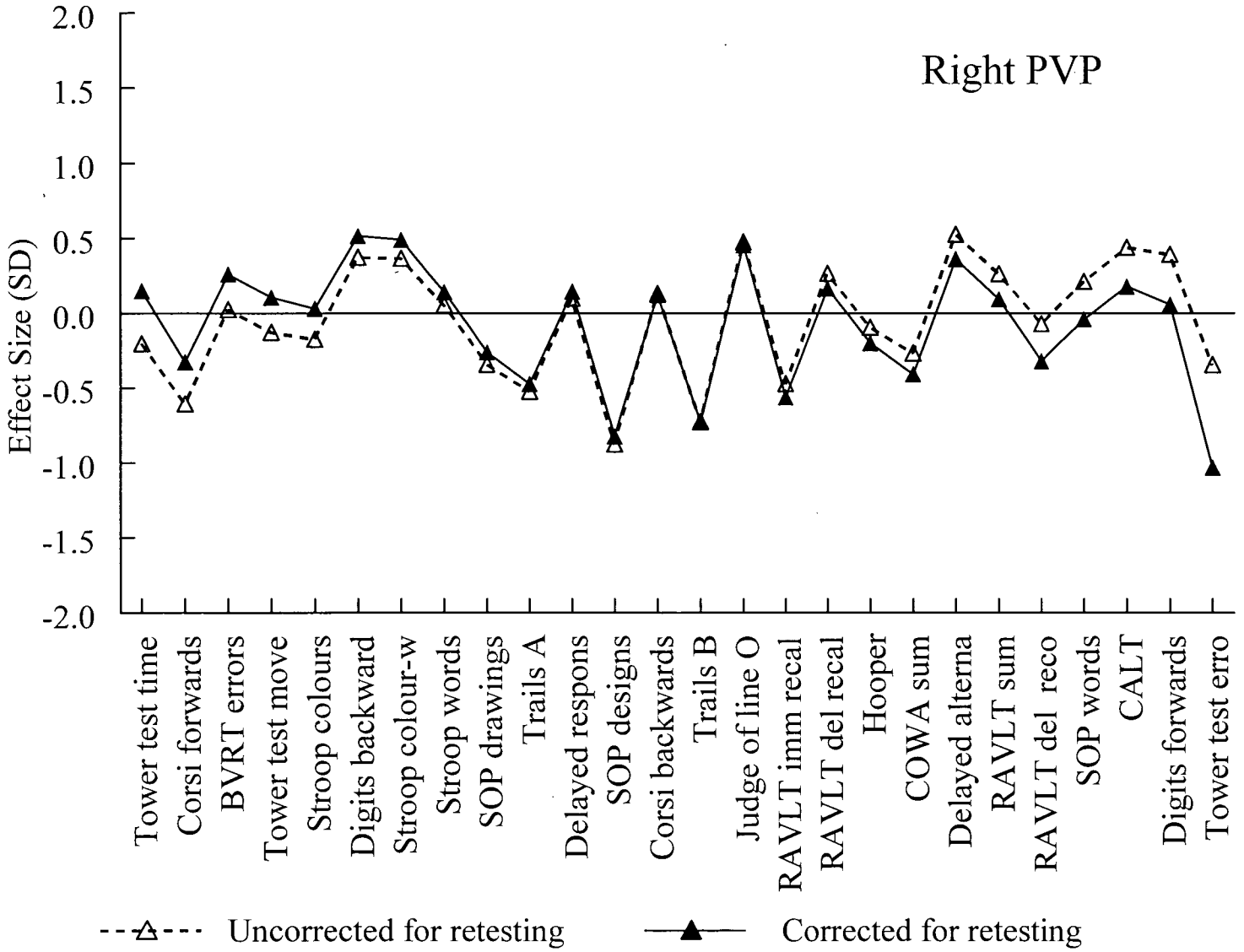
Variable	Effect size of change on retesting	Classification of effect size
* Tower of Toronto time	-0.35	Medium decline
Corsi blocks forwards	-0.28	Small decline
BVRT errors	-0.24	Small decline
Tower of Toronto moves	-0.23	Small decline
* Stroop colours	-0.20	Small decline
Digit Span backwards	-0.14	Small decline
* Stroop colour-words	-0.12	Small decline
* Stroop words	-0.09	Small decline
SOP drawings	-0.08	Small decline
* Trails A	-0.05	Small decline
Delayed Responding	-0.05	Small decline
SOP designs	-0.05	Small decline
Corsi blocks backwards	+0.01	Small improvement
* Trails B	+0.01	Small improvement
Judgment of Line Orientation	+0.02	Small improvement
RAVLT immediate recall	+0.09	Small improvement
RAVLT delayed recall	+0.10	Small improvement
Hooper Visual Organization Test	+0.11	Small improvement
* COWA sum	+0.14	Small improvement
Delayed Alternation	+0.16	Small improvement
RAVLT total trials 1-5	+0.17	Small improvement
RAVLT recognition	+0.25	Small improvement
SOP words	+0.25	Small improvement
CALT	+0.26	Small improvement
Digit Span forwards	+0.34	Small improvement
Tower of Toronto errors	+0.69	Large improvement

Note. Effect sizes were computed for each variable using the formula: effect size = (mean score at follow up minus mean score at baseline) / pooled *SD* at baseline. The pooled *SD* at baseline for each variable was computed as described by Howell, (1987, p. 170-171). The order of score subtraction was reversed for negatively keyed tests (i.e., mean score at baseline minus mean score at follow-up), so for all dependent measures a positive effect size reflected an improvement in performance on retesting. Small effects ranged from 0 to |.35| *SD*, medium effects ranged from |.36| to |.65| *SD*, and large effects ranged upwards from |.66| *SD*. BVRT = Benton Visual Retention Test; SOP = Subject Ordered Pointing; RAVLT = Rey Auditory Verbal Learning Test;

COWA = Controlled Oral Word Association; CALT = Conditional Associative Learning Test; * = timed test.

Figure 6. Effect sizes of the post-operative changes on the cognitive measures that were displayed by participants who underwent PVP before and after controlling for the changes on retesting demonstrated by the waitlist group. The data for the right and left PVP groups are presented in separate panels.


Left PVP
Effect Size (SD)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Tower test time
Corsi forwards
BVRT errors
Tower test move
Stroop colours
Digits backward
Stroop colour-w
Stroop words
SOP drawings
Trails A
Delayed respons
SOP designs
Corsi backwards
Trails B
Judge of line O
RAVLT imm recal
RAVLT del recal
Hooper
COWA sum
Delayed alterna
RAVLT sum
RAVLT del reco
SOP words
CALT
Digits forwards
Tower test erro
Uncorrected for retesting
Corrected for retesting


Right PVP
Effect Size (SD)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Tower test time
Corsi forwards
BVRT errors
Tower test move
Stroop colours
Digits backward
Stroop colour-w
Stroop words
SOP drawings
Trails A
Delayed respons
SOP designs
Corsi backwards
Trails B
Judge of line O
RAVLT imm recal
RAVLT del recal
Hooper
COWA sum
Delayed alterna
RAVLT sum
RAVLT del reco
SOP words
CALT
Digits forwards
Tower test erro
Uncorrected for retesting
Corrected for retesting

retesting, with greater improvement on retesting being evident as one moves from left to right. This method of data presentation allows the reader to appreciate visually the relative frequency of sizable declines and improvements in the performance of the waitlist group on re-testing, and to see how correcting for the changes on retesting exhibited by the waitlist group alters the overall profile of measured cognitive outcome from left and right PVP.

Figure 7 presents the magnitude of post-operative change on the cognitive measures displayed by members of the left and right PVP groups, after correcting for the retesting effects displayed by the waitlist group. In Figure 7 the cognitive variables are ordered by domain, following the order set out in Table 2. This method of data presentation allows the reader to appreciate visually the overall profile of measured cognitive outcome from left and right PVP after retesting effects have been accounted for.

Inspection of the data presented in Figure 7 reveals that the left PVP group exhibited greater post-operative decline than the right PVP group on most measures examined. However, the right PVP group did exhibit sizable declines (.75 *SD* or larger) on three cognitive measures, declines that were not evident in the MANOVA analysis reported above. These measures were the Trail Making Test Part B (Trails B), Subject Ordered Pointing with abstract designs (SOP designs), and the total number of errors made on the Tower of Toronto (Tower Test errors). Post-surgical declines on these three measures were more modest for the left PVP group.

Quality of life measures

On retesting, the waitlist group exhibited declines in reported functioning on most subscales of the Medical Outcomes Study Short Form (SF-36), and these declines were typically .25 *SD* or larger (see Table 9). Declines at follow-up were medium-sized for the role-emotional and social functioning subscales, while the worsening in reported bodily pain was large-sized,

Figure 7. Effect sizes of the post-operative changes on the cognitive measures that were displayed by participants who underwent left and right PVP after controlling for the changes on retesting demonstrated by the waitlist group.

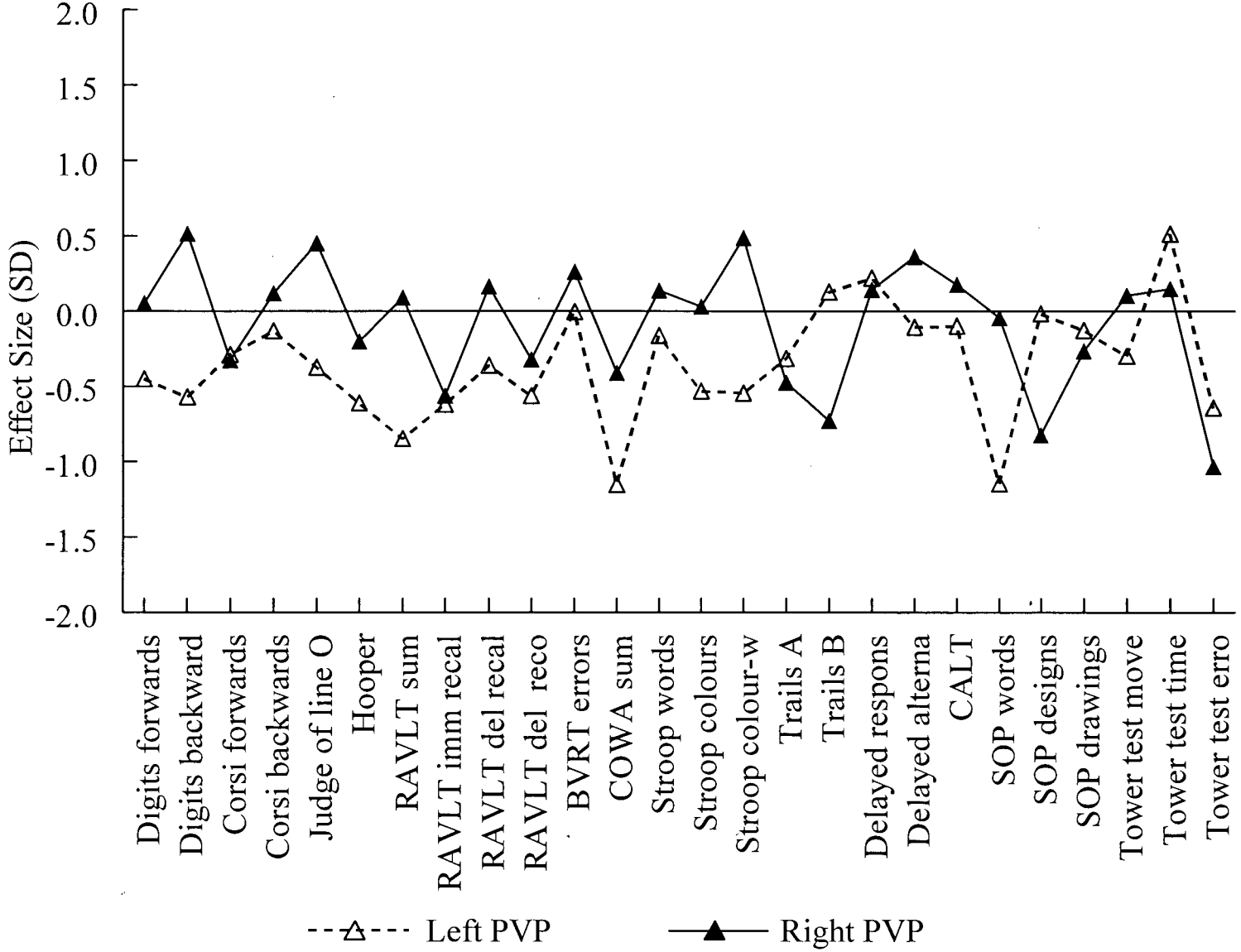

2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Effect Size (SD)
Digits forwards
Digits backward
Corsi forwards
Corsi backwards
Judge of line O
Hooper
RAVLT sum
RAVLT imm recal
RAVLT del recal
RAVLT del reco
BVRT errors
COWA sum
Stroop words
Stroop colours
Stroop colour-w
Trails A
Trails B
Delayed respons
Delayed alterna
CALT
SOP words
SOP designs
SOP drawings
Tower test move
Tower test time
Tower test erro
Left PVP
Right PVP

Table 9. Effect Size of the Changes Displayed by the Waitlist Group at Follow-Up on the Subscales of the SF-36 and Profile of Mood States

Variable	Effect size of change on retesting	Classification of effect size
Quality of life variables		
SF-36 Bodily pain	-0.68	Large decline
SF-36 Social functioning	-0.43	Medium decline
SF-36 Role emotional	-0.40	Medium decline
SF-36 Physical functioning	-0.25	Small decline
SF-36 Role physical	-0.25	Small decline
SF-36 General health	-0.25	Small decline
SF-36 Vitality	-0.25	Small decline
SF-36 Health in transition	-0.12	Small decline
SF-36 Mental health	+0.13	Small improvement
Mood variables		
POMS Confusion-bewilderment	-0.33	Small decline
POMS Anger-hostility	-0.18	Small decline
POMS Depression-dejection	-0.10	Small decline
POMS Fatigue-inertia	-0.09	Small decline
POMS Tension-anxiety	+0.15	Small improvement
POMS Vigor-Activity	+0.59	Medium improvement

Note. Effect sizes were computed for each variable using the formula: effect size = (mean score at follow up minus mean score at baseline) / pooled *SD* at baseline. The pooled *SD* at baseline for each variable was computed as described by Howell, (1987, p. 170-171). The order of subtraction was reversed for negatively keyed tests (i.e., mean score at baseline minus mean score at follow-up), so for all dependent measures a positive effect size reflected an improvement in reported functioning on retesting. Small effects ranged from 0 to |.35| *SD*, medium effects ranged from |.36| to |.65| *SD*, and large effects ranged upwards from |.66| *SD*. SF-36 = Medical Outcomes Study Short Form; POMS = Profile of Mood States.

being .68 *SD*. Declines in reported functioning at follow-up were largest for the bodily pain and social functioning subscales, the SF-36 subscales the MANOVA analysis indicated were significantly affected by PVP at the group level.

Accounting for the changes in reported quality of life demonstrated by waitlisted participants on retesting had a quite consistent positive effect on measured quality of life outcome, typically doubling the post-surgical improvement evident on any given SF-36 subscale (see Figure 8).

Mood measures

The waitlist group displayed mixed, typically small-sized changes on the subscales of the Profile of Mood States (POMS) at follow-up (see Table 9). Small-sized declines in reported mood functioning were evident for four of the six subscales, the greatest being a .33 *SD* increase in reported confusion/bewilderment. A small improvement was evident in reported tension-anxiety on retesting, while reported vigor-activity increased by almost .60 *SD* at follow-up.

Accounting for the changes in reported mood functioning demonstrated by waitlisted participants on retesting typically had a modest effect on measured mood outcome in the left and right PVP groups, the largest effect being to attenuate what might otherwise be taken to be post-operative improvement in vigor-activity in the right PVP group (see Figure 9).

Motor measures

The effect sizes of the changes the waitlisted participants exhibited on the motor measures at follow-up are presented in Table 10. Changes in grooved pegboard performance with the dominant and non-dominant hands were small and positive, while micrographia and motor perseveration in the writing samples worsened by roughly 1/3 of a *SD*. As a result,

Figure 8. Effect sizes of the post-operative changes on the subscales of the SF-36 that were displayed by participants who underwent PVP before and after controlling for the changes on retesting demonstrated by the waitlist group. The data for the right and left PVP groups are presented in separate panels.

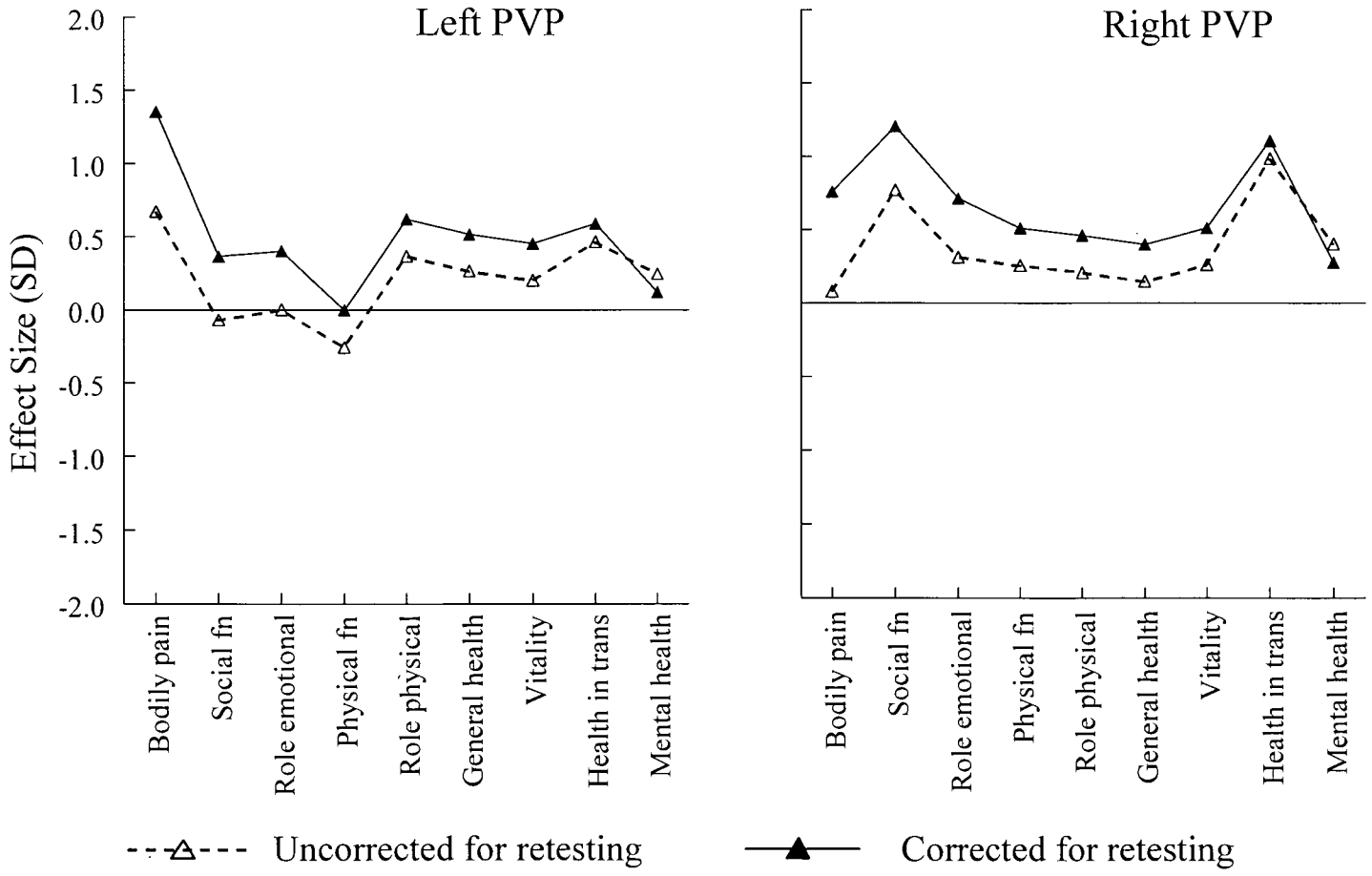

Left PVP
Right PVP
Effect Size (SD)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Bodily pain
Social fn
Role emotional
Physical fn
Role physical
General health
Vitality
Health in trans
Mental health
Uncorrected for retesting
Corrected for retesting

Figure 9. Effect sizes of the post-operative changes on the subscales of the POMS that were displayed by participants who underwent PVP before and after controlling for the changes on retesting demonstrated by the waitlist group. The data for the right and left PVP groups are presented in separate panels.

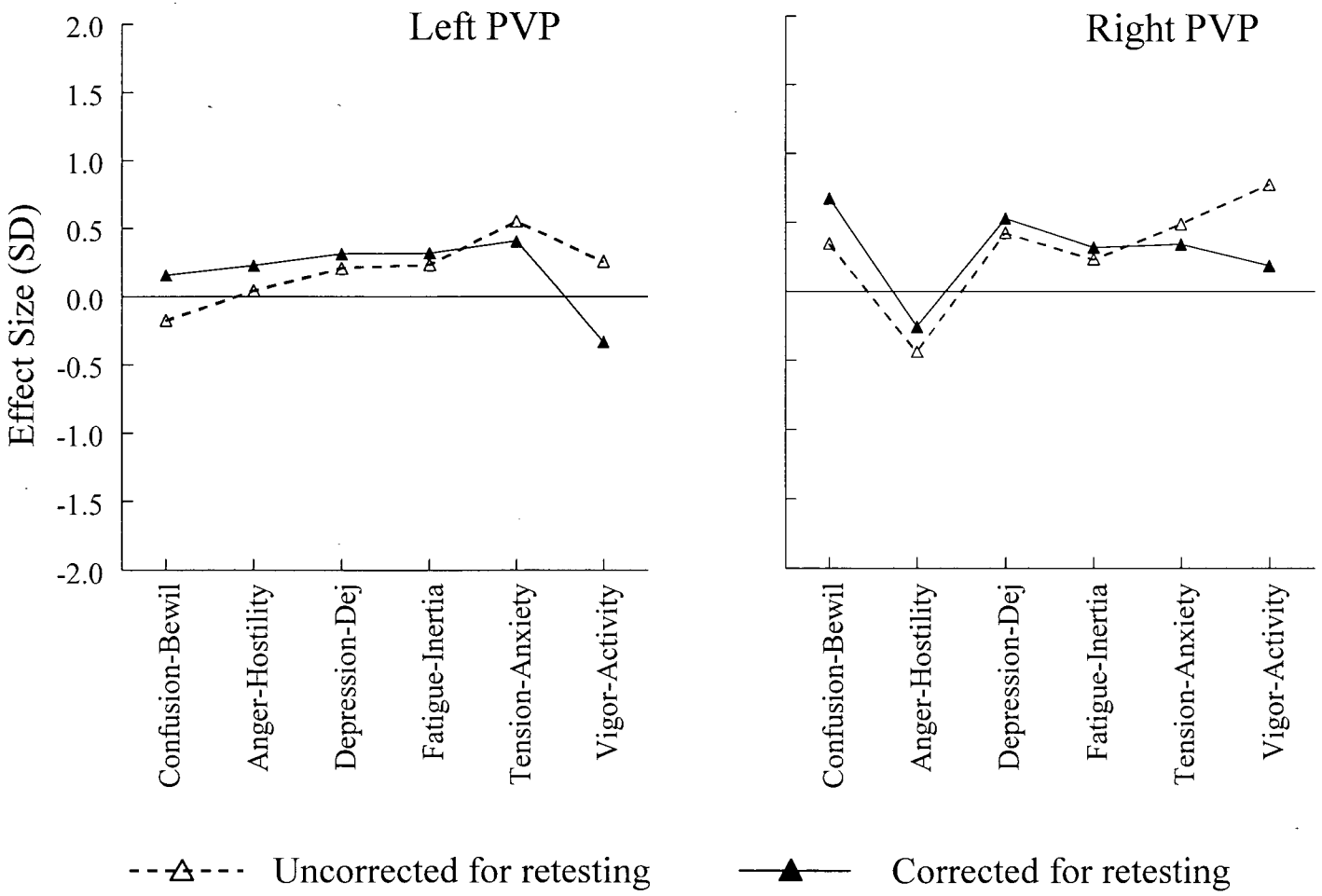

Left PVP
Right PVP
Effect Size (SD)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Confusion-Bewil
Anger-Hostility
Depression-Dej
Fatigue-Inertia
Tension-Anxiety
Vigor-Activity
Uncorrected for retesting
Corrected for retesting

Table 10. Effect Size of the Changes Displayed by the Waitlist Group at Follow-Up on the Measures of Speeded Manual Dexterity, Micrographia and Motor Perseveration

Variable	Effect size of change on retesting	Classification of effect size
Grooved pegboard – dominant hand	+0.01	Small improvement
Grooved pegboard – non dominant hand	+0.19	Small improvement
Micrographia	-0.32	Small decline
Motor perseveration	-0.39	Medium decline

Note. Effect sizes were computed for each variable using the formula: effect size = (mean score at baseline minus mean score at follow-up)/pooled *SD* at baseline. The pooled *SD* at baseline for each variable was computed as described by Howell, (1987, p. 170-171). For all dependent measures a positive effect size reflected an improvement in performance on retesting. Small effects ranged from 0 to |.35| *SD*, medium effects ranged from |.36| to |.65| *SD*, and large effects ranged upwards from |.66| *SD*.

accounting for the changes displayed by the waitlist group on retesting had a modest impact on measured outcome on the grooved pegboard but improved outcome with respect to micrographia and perseveration (see Figure 10).

Discussion

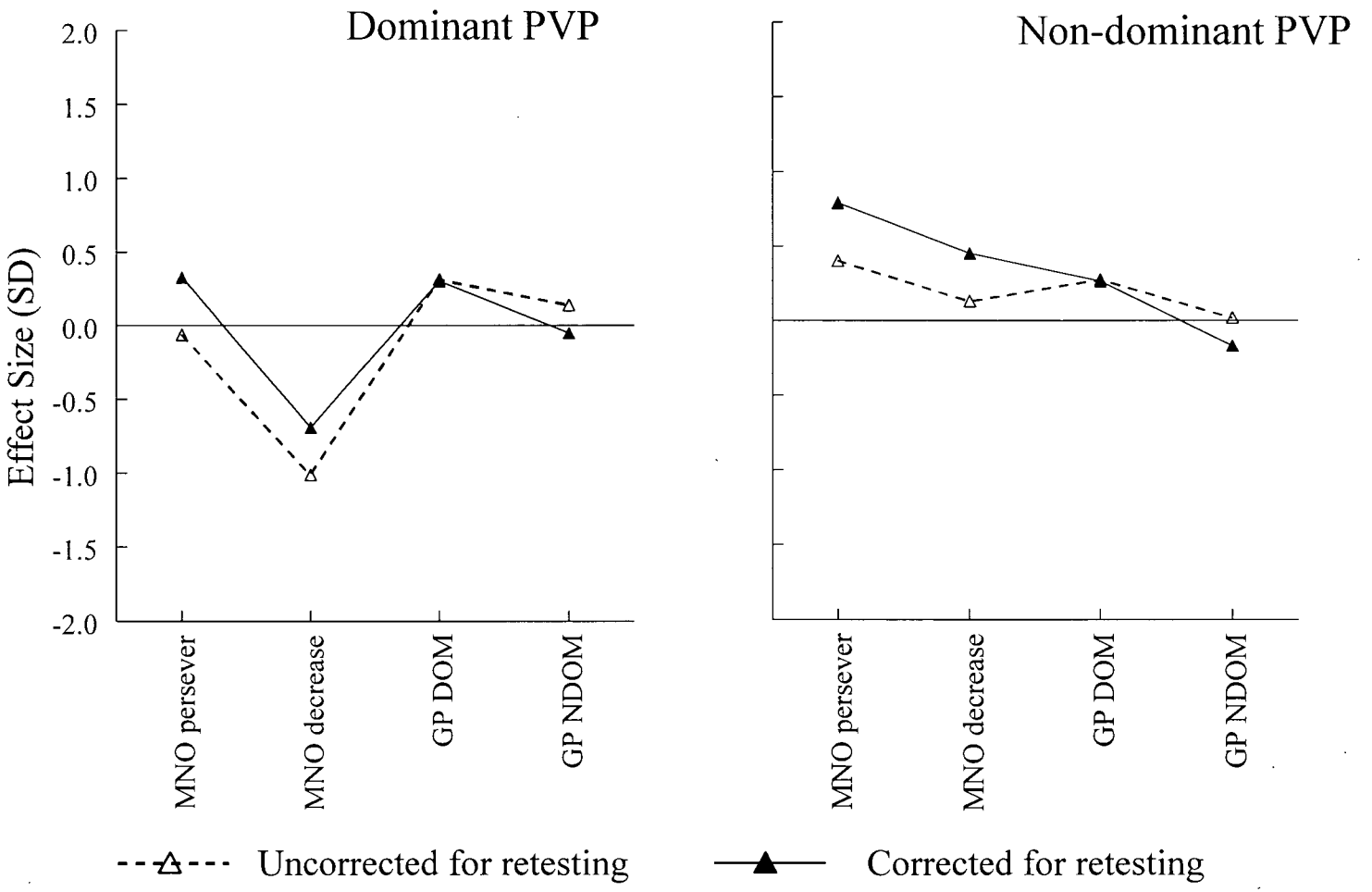
At follow-up, the waitlist group exhibited mixed changes in their performance on the cognitive measures, with small-sized improvement and decline being evident on a roughly equivalent number of tests. Changes on retesting ranged from near zero to two-thirds of a *SD*, and they were greater than or equal to .25 *SD* for 7/26 (27%) of the cognitive measures. Declines at follow-up tended to be largest on tests that incorporate time in their dependent variable and consequently place a premium on speed of responding.

After correcting for retesting effects, the left PVP group exhibited greater post-operative decline than the right PVP group on most measures examined. However, the right PVP group did exhibit sizable declines on measures of working memory with abstract designs, divided attention and speeded visual-spatial sequencing, and problem solving. These declines were not statistically significant in the MANOVA analysis reported above.

At follow-up, the waitlist group exhibited declines in reported functioning on most SF-36 subscales, and these declines were typically .25 *SD* or larger. For most subscales of the SF-36, the declines at follow-up exhibited by waitlisted participants were as large or larger than the improvements at follow-up exhibited by the surgical group. As a result, when the changes on retesting demonstrated by waitlisted participants were accounted for, the measured magnitude of the effect of surgery doubled on most SF-36 subscales.

The waitlist group displayed mixed, typically small-sized changes on the mood and motor

Figure 10. Effect sizes of the post-operative changes on the motor measures that were displayed by participants who underwent PVP before and after controlling for the changes on retesting demonstrated by the waitlist group. The data for the dominant and non-dominant PVP groups are presented in separate panels. Non-dominant PVP = surgery ipsilateral to dominant hand, dominant PVP = surgery contralateral to dominant hand.


Dominant PVP
Non-dominant PVP
Effect Size (SD)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
MNO persever
MNO decrease
GP DOM
GP NDOM
Uncorrected for retesting
Corrected for retesting

measures at follow-up, and accounting for these changes had a modest effect on the profiles of mood and motor outcome from PVP.

QUESTION 4: RELATIONSHIP BETWEEN PRE-OPERATIVE LEVEL OF COGNITIVE FUNCTIONING AND OUTCOME FROM PALLIDOTOMY

The goal of this portion of the thesis was to investigate whether preoperative level of cognitive functioning was related to the changes in cognition, quality of life, mood, and motor functioning members of the surgery group exhibited after they underwent PVP.

Statistical Approach

Participants' raw change scores (score at follow up – score at baseline) for each of the cognitive, quality of life, mood, and motor measures were correlated with their pre-operative total score on the Dementia Rating Scale (DRS; see Table 2 and the Appendix for a description of the DRS). This analysis was conducted first with the change scores for the surgery group as a whole, and in follow-up analyses the same sets of correlations were examined for the left and right PVP groups separately. The follow-up analyses were conducted as a relationship between preoperative level of cognitive functioning and cognitive outcome from PVP might be most evident in the data from the participants who underwent left PVP, as this group exhibited relatively larger cognitive declines after surgery. The same correlation analysis was conducted with the data from the motor measures, except during the follow-up analyses the surgery group was subdivided into dominant and non-dominant PVP groups based on participant handedness.[16]

As the present correlation analysis was conducted three times with 45 dependent variables the probability of Type I errors would appear to be very high. However, as described below, this correlation analysis had modest statistical power. Consequently, to protect my ability

[16] Scatter plots of the relationship between pre-operative DRS total score and post-operative change on each variable were also examined to verify that there were no non-linear relationships present that might not be detected by a

to detect a relationship between preoperative level of cognitive functioning and surgical outcome, I held alpha at the .05 level for each test.

Statistical Power and Implications of the Missing Data

G*Power (Erdfelder et al., 1996) was used to compute the statistical power of this analysis to detect a correlation between participants' pre-operative DRS total score and the post-operative change they displayed on each cognitive, quality of life, and mood measure. Statistical power to detect small ($r = .10$), medium ($r = .30$), and large ($r = .50$) effect sizes as defined by Cohen (1988) was computed. Alpha was set at the .05 level. This analysis was conducted with the surgery group as a whole, and then with the left PVP and right PVP groups separately. The results of this power analysis are presented in Table 11.

The same power analysis was conducted for the motor measures, except the analysis was first conducted with the surgery group as a whole, and was then conducted with the dominant and non-dominant PVP groups separately. The results of this analysis are presented in Table 12.

Inspection of Tables 11 and 12 suggests the present correlation analysis had modest power to detect a relationship between participants' pre-operative DRS total score and the post-operative change they displayed on individual dependent measures. For the entire surgery group, the correlation analysis had a 50-70% chance of detecting a large-sized effect on most cognitive, quality of life, mood, and motor variables. At best, this analysis had a 30% chance of detecting a medium-sized effect on any given variable.

As would be expected, statistical power was lower for the follow-up correlation analyses.

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correlation analysis.

Table 11. Power on Testing the Correlation Between DRS Total Score and Post-Operative Change on the Cognitive, Quality of Life, and Mood Variables

	Entire surgery group				Left PVP only				Right PVP only			
Variable correlated with DRS total score	*N*	Small effect size *r*=.10	Medium effect size *r*= .30	Large effect size *r*=.50	*N*	Small effect size *r*=.10	Medium effect size *r*= .30	Large effect size *r* =.50	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50
Digit Span Backward	10	.06	.14	.36	6	.05	.09	.20	4	.05	.07	.11
Digit Span Forward	10	.06	.14	.36	6	.05	.09	.20	4	.05	.07	.11
Tower of Toronto errors	11	.06	.15	.40	8	.06	.12	.28	3	.05	.06	.07
Tower of Toronto moves	11	.06	.15	.40	8	.06	.12	.28	3	.05	.06	.07
Tower of Toronto time	11	.06	.15	.40	8	.06	.12	.28	3	.05	.06	.07
DA	14	.06	.19	.51	10	.06	.14	.36	4	.05	.07	.11
Trails B	14	.06	.19	.51	10	.06	.14	.36	4	.05	.07	.11
DR	15	.07	.20	.54	11	.06	.15	.40	4	.05	.07	.11
CALT	17	.07	.23	.61	13	.06	.18	.48	4	.05	.07	.11

	Entire surgery group				Left PVP only				Right PVP only			
Variable correlated with DRS total score	*N*	Small effect size *r*=.10	Medium effect size *r*= .30	Large effect size *r*=.50	*N*	Small effect size *r*=.10	Medium effect size *r*= .30	Large effect size *r* =.50	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50
Stroop color-words	17	.07	.23	.61	13	.06	.18	.48	4	.05	.07	.11
Stroop colours	17	.07	.23	.61	13	.06	.18	.48	4	.05	.07	.11
Stroop words	18	.07	.24	.63	14	.06	.19	.51	4	.05	.07	.11
BVRT	19	.07	.25	.66	12	.06	.17	.44	7	.05	.11	.24
SF-36 physical functioning	19	.07	.25	.66	12	.06	.17	.44	7	.05	.11	.24
JOL	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
POMS anger-hostility	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
POMS confusion-bewilderment	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
POMS depression-dejection	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
POMS fatigue-inertia	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
POMS tension-anxiety	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
POMS vigor-	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20

	Entire surgery group				Left PVP only				Right PVP only			
Variable correlated with DRS total score	*N*	Small effect size *r*=.10	Medium effect size *r*= .30	Large effect size *r*=.50	*N*	Small effect size *r*=.10	Medium effect size *r*= .30	Large effect size *r* =.50	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50
activity												
SF-36 role-emotional	20	.07	.27	.69	13	.06	.18	.48	7	.05	.11	.24
SF-36 role-physical	20	.07	.27	.69	13	.06	.18	.48	7	.05	.11	.24
SF-36 vitality	20	.07	.27	.69	13	.06	.18	.48	7	.05	.11	.24
SOP Designs	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
SOP Drawings	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
SOP Words	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
Trails A	20	.07	.27	.69	14	.06	.19	.51	6	.05	.09	.20
Corsi Blocks backward	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
Corsi Blocks forward	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
COWA	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
Hooper	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
RAVLT delayed recall	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
RAVLT delayed recognition	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24

	Entire surgery group				Left PVP only				Right PVP only			
Variable correlated with DRS total score	*N*	Small effect size *r*=.10	Medium effect size *r*= .30	Large effect size *r*=.50	*N*	Small effect size *r*=.10	Medium effect size *r*= .30	Large effect size *r* =.50	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50
RAVLT immediate recall	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
RAVLT total recall trials 1-5	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
SF-36 bodily pain	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
SF-36 general health	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
SF-36 health in transition	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
SF-36 mental health	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24
SF-36 social functioning	21	.07	.28	.71	14	.06	.19	.51	7	.05	.11	.24

Note. Variables listed in order of ascending sample size. BVRT = Benton Visual Retention Test; SOP = Subject Ordered Pointing; RAVLT = Rey Auditory Verbal Learning Test; COWA = Controlled Oral Word Association; CALT = Conditional Associative Learning Test; DA = Delayed Alternation; DR = Delayed Response; JOL = Judgment of Line Orientation; Hooper = Hooper Visual Organization Test; SF-36 = Medical Outcomes Study Short Form; POMS = Profile of Mood States.

Table 12. Power on Testing the Correlation Between DRS Total Score and Post-Operative Change on the Motor Variables

Variable correlated with DRS total score	Entire surgery group			Dominant PVP only				Non-dominant PVP only			
	N	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50
Perseveration	18	.07	.24	.63	10	.06	.14	.36	8	.06	.12	.28
GP non-dominant	19	.07	.25	.66	12	.06	.17	.44	7	.05	.11	.24
Micrographia	19	.07	.25	.66	10	.06	.14	.36	9	.06	.13	.32
GP dominant	20	.07	.27	.69	12	.06	.17	.44	8	.06	.12	.28
Clinical rating of dyskinesia	21	.07	.28	.71	12	.06	.17	.44	9	.06	.13	.32

Note. GP = Grooved Pegboard. Variables listed in order of ascending sample size. Non-dominant PVP = surgery ipsilateral to dominant hand, dominant PVP = surgery contralateral to dominant hand.

For the left PVP group, the correlation analysis had a 40-50% chance of detecting a large-sized effect on most variables. For the smaller right PVP group, the correlation analysis had only a 20% chance of detecting a large-sized effect on most measures. Similarly, for the dominant PVP group, the correlation analysis had a 30-40% chance of detecting a large-sized effect on the motor variables. For the smaller non-dominant PVP group, this analysis had only a 20-30% chance of detecting a large-sized effect on the motor measures.

As described above under the heading Participant Retention and Missing Data, some participants with a relatively low pre-operative level of cognitive functioning were unable to complete the Trail Making Test Part B (Trails B) and the Tower of Toronto at baseline, and consequently they did not provide pre- and post-PVP data for these measures. This likely attenuated the range of pre-operative DRS total scores amongst the participants who provided data for Trails B and the Tower of Toronto, diminishing further my ability to detect a relationship between pre-operative level of cognitive functioning and post-operative change on these two measures.

Results

Cognitive functioning

There was little evidence that magnitude of post-operative change in cognitive performance was related to participants' pre-surgical level of cognitive functioning. For the surgery group as a whole, the correlation between pre-operative DRS total score and post-operative change was only significant for one of the twenty-six cognitive variables studied, namely Corsi blocks forwards, $r(19) = .48, p < .03$. Given the number of correlations examined, one significant finding would be expected on the basis of chance alone.

For the left PVP group, the correlation between pre-operative DRS total score and post-

operative change was not significant for any of the cognitive variables. For the right PVP group, the correlation between pre-operative DRS total score and post-operative change was only significant for Corsi blocks forwards, $r(5) = .78$, $p = .04$.

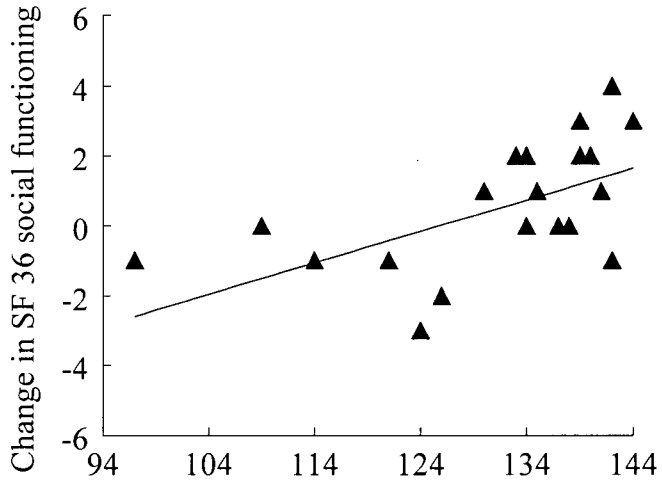
Quality of life

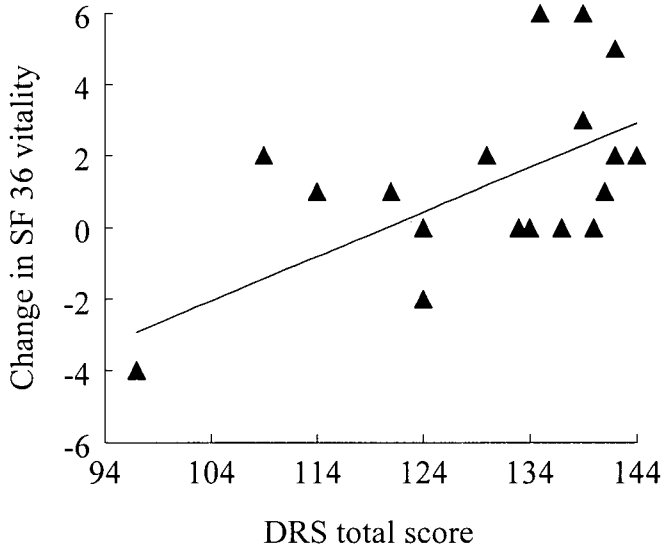
There was evidence that magnitude of post-operative change in reported quality of life was related to participants' pre-surgical level of cognitive functioning. Significant positive correlations were obtained between participants' baseline DRS total score and their post-operative change scores for the vitality, $r(18) = .45$, $p = .05$, and social functioning, $r(19) = .57$, $p = .007$, subscales of the Medical Outcomes Study Short Form (SF-36). The same pattern of correlations was obtained when this analysis was conducted separately for the participants who underwent left and right PVP. However, the correlations with baseline DRS total score were only statistically significant for reported social functioning.

The vitality and social functioning subscales of the SF-36 are positively keyed, so these positive correlations between pre-operative level of cognitive functioning and post-surgical change suggest participants with a higher overall level of cognitive functioning before surgery tended to exhibit a more positive outcome with respect to reported vitality and social functioning.

Figure 11 presents a scatter plot of the relationship between pre-operative level of cognitive functioning and post-operative change on the social functioning and vitality subscales of the SF-36 for the surgery group as a whole. Inspection of Figure 11 suggests the relationship between pre-operative DRS total score and post-operative change in vitality was driven principally by the data from one participant with a DRS total score well below that of most participants. For reported social functioning, the relationship between pre-operative level of cognitive functioning and post-operative change appears less dependent on a single observation,

Figure 11. A scatter plot of the relationship between pre-operative level of cognitive functioning (DRS total score) and change (follow-up minus baseline) on the social functioning and vitality subscales of the Medical Outcomes Study Short-Form (SF-36) for the entire surgery group. The solid lines are linear regression lines fit to the data.


Change in SF 36 social functioning
6
4
2
0
-2
-4
-6
94
104
114
124
134
144


Change in SF 36 vitality
6
4
2
0
-2
-4
-6
94
104
114
124
134
144
DRS total score

as the data points are more evenly distributed along the length of the regression line. Consistent with these visual impressions, when the data from the participant with the lowest DRS total score were excluded, the correlation between pre-operative DRS total score and post-operative change remained statistically significant for reported social functioning but not for reported vitality [being $r(17) = .60, p = .005$ and $r(18) = .31, p = .20$ respectively].

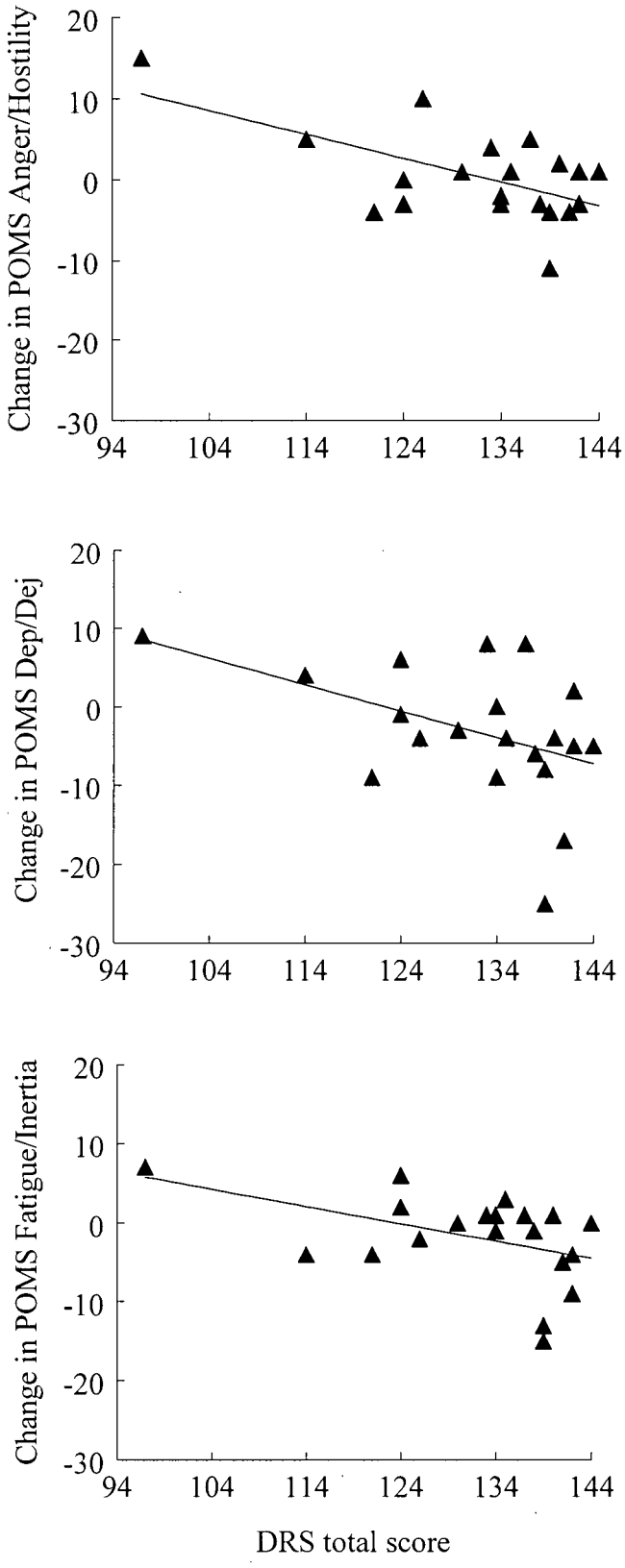
Mood functioning

There was also evidence that magnitude of post-operative change in reported mood functioning was related to participants' pre-surgical level of cognitive functioning. Significant negative correlations were obtained between participants' baseline DRS total score and their post-operative change scores for the depression/dejection, $r(18) = -.46, p = .04$, anger/hostility, $r(18) = -.60, p = .005$, and fatigue/inertia, $r(18) = -.45, p = .05$, subscales of the Profile of Mood States (POMS). While the correlations failed to reach statistical significance, the same pattern of correlations was obtained when the relationship between baseline level of cognitive functioning and post-operative change on the POMS subscales was examined separately for the participants who underwent left and right PVP.

The depression/dejection, anger/hostility, and fatigue/inertia subscales of the POMS are negatively keyed, so these negative correlations between pre-operative level of cognitive functioning and post-surgical change suggest participants with a higher overall level of cognitive functioning before surgery tended to exhibit a more positive outcome with respect to their reported mood functioning.

Figure 12 presents a scatter plot of the relationship between pre-operative level of cognitive functioning and change on the depression/dejection, anger/hostility, and fatigue/inertia

Figure 12. A scatter plot of the relationship between pre-operative level of cognitive functioning (DRS total score) and change (follow-up minus baseline) on the anger/hostility, depression/dejection, and fatigue/inertia subscales of the Profile of Mood States (POMS) for the entire surgery group. The solid lines are linear regression lines fit to the data.


Change in POMS Anger/Hostility
20
10
0
-10
-20
-30
94
104
114
124
134
144
Change in POMS Dep/Dej
20
10
0
-10
-20
-30
94
104
114
124
134
144
Change in POMS Fatigue/Inertia
20
10
0
-10
-20
-30
94
104
114
124
134
144
DRS total score

subscales of the POMS for the surgery group as a whole. Inspection of Figure 12 suggests for all three POMS subscales, the relationship between baseline DRS total score and post-operative change in reported mood functioning was principally driven by the data from the same participant with a DRS total score well below that of most participants. When the data from this participant were excluded, the correlations between baseline DRS total score and post-operative change in depression/dejection, anger/hostility, and fatigue/inertia were no longer statistically significant [being $r(17) = -.33$, $p = .17$, $r(17) = -.30$, $p = .22$, and $r(17) = -.28$, $p = .24$ respectively].

Motor functioning

There was no evidence that magnitude of post-surgical change in motor performance was related to participants' pre-surgical level of cognitive functioning. Participants who underwent dominant and non-dominant PVP were considered separately, and for both groups there were no significant correlations between baseline DRS total score and post-PVP change in dominant and non-dominant speeded manual dexterity, micrographia, motor perseveration, or dyskinesia contralateral to PVP.

Discussion

There was little evidence post-surgical change in cognitive or motor performance was related to participants' pre-surgical level of cognitive functioning. The correlation between pre-operative level of cognitive functioning (as measured by the DRS total score) and post-operative change on the thirty-one cognitive and motor variables studied was only statistically significant for a single measure of visual-spatial attention and working memory. Given the number of measures included in this analysis, this isolated finding provides little support for the notion that

change in cognitive or motor functioning after PVP is related to individuals' pre-operative level of cognitive functioning.

Low statistical power does not likely account for the present failure to detect a relationship between pre-operative level of cognitive functioning and cognitive or motor outcome from PVP. Individual measures did have modest statistical power, particularly when the surgery group was subdivided during the follow-up analyses. However, given the number of variables included in this analysis, even a weak relationship between pre-operative level of cognitive functioning and cognitive or motor outcome would surely have been evident in the outcome data for more than one measure.

The present sample did not, however, contain many individuals who were significantly cognitively impaired before surgery, as only 4 of the 22 (18%) of members of the surgery group obtained baseline DRS total scores below the recommended cut-off score for impairment. Consequently, it is possible the present failure to detect a relationship between pre-operative level of cognitive functioning and cognitive or motor outcome from PVP reflects range restriction in participants' pre-operative level of cognitive functioning.

There was evidence post-surgical change in aspects of reported quality of life and mood functioning was related to participants' pre-surgical level of cognitive functioning. As participants' pre-operative level of cognitive functioning increased they tended to exhibit a more positive outcome with respect to social functioning, vitality and fatigue/inertia, depression/dejection, and anger/hostility. However, the under representation of individuals with significant pre-operative cognitive impairment was again problematic, as the relationship between pre-operative level of cognitive functioning and post-operative change on most of these quality of life and mood variables appeared to be driven principally by the data from a single individual with a pre-operative level of cognitive functioning well below that of most participants.

QUESTION 5: RELATIONSHIP BETWEEN COGNITIVE AND QUALITY OF LIFE OUTCOMES FROM PALLIDOTOMY

If PVP is followed by cognitive decline that prevents patients from translating post-operative motor improvement into enhanced performance of their daily activities, patients may ultimately fail to demonstrate post-operative improvement in their perceived quality of life (Cahn, Sullivan, Shear, Pfefferbaum, et al., 1998; Koplas et al., 1999; Schrag, Jahanshahi, & Quinn, 2000; Trepanier et al., 1998). The goal of this portion of the thesis was to examine whether participants who exhibited relatively larger post-operative cognitive declines also reported relatively smaller post-operative improvement in their quality of life.

Statistical Approach

Participants' post-surgical change scores on the measures of verbal fluency (COWA), list learning (RAVLT total trials 1-5), verbal working memory (SOP words), and speed of colour naming (Stroop colours) were correlated with the post-operative change they displayed in the total score for the Medical Outcomes Study Short Form (SF-36). This analysis was first conducted with the change scores for the surgery group as a whole, and in follow-up analyses the same correlations were examined with the left and right PVP groups separately. These follow-up analyses were conducted as a relationship between cognitive and quality of life outcomes from PVP might be most evident in the left PVP group, as these participants exhibited relatively larger cognitive declines after surgery.[17]

As described below, this correlation analysis had modest statistical power. Consequently,

[17] I also examined scatter plots of the relationship between participants' post-surgical change in SF-36 total score and post-surgical change on each of the cognitive measures, to verify that there were no non-linear relationships

to protect my ability to detect a relationship between cognitive and quality of life outcome from PVP, I held alpha at the .05 level for each test.

Statistical power

G*Power (Erdfelder et al., 1996) was used to compute the statistical power of this analysis to detect a correlation between post-operative change on the measures of verbal fluency, list learning, verbal working memory, and speed of colour naming and post-operative change in the total score for the SF-36. Statistical power was computed to detect small ($r = .10$), medium ($r = .30$), and large ($r = .50$) effect sizes as defined by Cohen (1988). Alpha was set at the .05 level. This analysis was conducted with the surgery group as a whole, and then with the left PVP and right PVP groups separately. The results of this analysis are presented in Table 13. Inspection of Table 13 suggests this correlation analysis had modest power to detect a relationship between the post-operative cognitive and quality of life changes exhibited by members of the surgery group. For the surgery group as a whole, this analysis had a 50-60% chance of detecting a large-sized relationship, and a 20% chance of detecting a medium-sized relationship. As would be expected, the correlation analysis conducted with the left and right PVP groups had weaker statistical power. For the left PVP group, the correlation analysis had a 40-50% chance of detecting a large-sized correlation. For the smaller right PVP group, the analysis had only a 10-20% chance of detecting a large-sized relationship for most measures.

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present that might not be detected by a correlation analysis.

Table 13. Power on Testing the Correlation Between Post-Operative Change in Verbal Fluency, List Learning, Working Memory, and Speed of Colour Naming and Post-Operative Change in the SF-36 Total Score

	Entire surgery group				Left PVP only				Right PVP only			
Variable correlated with SF-36 total score	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50	*N*	Small effect size *r* =.10	Medium effect size *r* = .30	Large effect size *r* =.50
Stroop colours	15	.06	.20	.54	11	.06	.15	.40	4	.05	.07	.11
SOP words	17	.07	.23	.61	11	.06	.19	.51	6	.05	.09	.20
COWA	18	.07	.24	.63	11	.06	.19	.51	7	.05	.11	.24
RAVLT total trials 1-5	18	.07	.24	.63	11	.06	.19	.51	7	.05	.11	.24

Note. Correlations are listed in order of ascending sample size. SOP = Subject Ordered Pointing; SF-36 = Medical Outcomes Study Short Form; COWA = Controlled Oral Word Association; RAVLT = Rey Auditory Verbal Learning Test.

Results

No statistically significant relationships were evident when the change scores for verbal fluency, list learning, verbal working memory, and speed of colour naming for the entire surgery group were correlated with post-operative change in the total score for the SF-36 (all $r < .40$, all $p > .10$). Similarly, no significant correlations were obtained when the data from participants who underwent left and right PVP were examined separately (all $r < .52$, all $p > .49$).

Discussion

Magnitude of cognitive decline following PVP was not related to magnitude of post-operative change in reported quality of life. This suggests the decline in cognitive test performance that follows PVP does not have significant negative consequences for patients' perceived quality of life. However, modest statistical power likely limited my ability to detect any relationships present.

GENERAL DISCUSSION AND FUTURE DIRECTIONS

Individuals with advanced idiopathic Parkinson's disease (PD) frequently experience disabling medically-refractory motor symptoms and medication side effects. Unilateral posteroventral pallidotomy (PVP) has become an important symptomatic treatment for these complications of advanced PD, especially levodopa-induced dyskinesia (Lang, 2000). Regions of the GPi adjacent to the posteroventrally-located sensori-motor region targeted in PVP are thought to lie in cortical-basal ganglia circuits that subserve cognitive and affective functions (see Figure 1), and interest in the psychological sequelae of PVP is high. Recently several groups have begun to describe the effects of PVP on cognitive functioning in advanced PD (Alegret et al., 2000; Baron et al., 1996; Cahn, Sullivan, Shear, Heit, et al., 1998; Demakis et al., 2002; Green et al., 2002; Jahanshahi et al., 2002; Junque et al., 1999; Kubu et al., 2000; Lacritz et al., 2000; Masterman et al., 1998; Obwegeser et al., 2000; Perrine et al., 1998; Rettig et al., 2000; Riordan et al., 1997; Schmand et al., 2000; Scott et al., 1998; Soukup et al., 1997; Stebbins et al., 2000; Trepanier et al., 1998; Uitti et al., 1997; Yokoyama et al., 1999).

The present research had two principal goals: to determine whether controlling for test practice and other retesting effects increases the measured cognitive effects of PVP beyond those typically reported in the literature, and to examine the notion that a lower preoperative level of cognitive functioning is associated with poorer outcome from PVP.

Impact of Accounting for Retesting Effects on Measured Outcome from Pallidotomy

When tested with an extensive battery of cognitive tests, participants who underwent left PVP exhibited decline on verbal measures of list learning, fluency, working memory, and speed of color naming relative to waitlisted participants and participants who underwent right PVP.

This pattern of cognitive decline after left PVP is in keeping with the results of previous studies that did not control for retesting effects. Indeed, declines in verbal learning, fluency, and working memory after left PVP are amongst the most consistently reported negative cognitive sequelae of this procedure (see Table 1).

Schmand et al. (2000) and Green et al. (2002) described similar results in their reports of the only other waitlist control-group studies of cognitive outcome from PVP. Schmand and colleagues found left PVP was followed by significant declines in phonemic and semantic verbal fluency. Green at al. found participants who underwent left PVP exhibited poorer verbal fluency, problem solving, working memory, and verbal learning and memory after surgery than participants who underwent right PVP and members of a medical management group. Consequently, when the accumulated evidence is taken together, it appears unlikely that failure to control for retesting effects in much of the previous literature resulted in significant under-reporting of the breadth of cognitive decline following PVP.

Several studies have reported cognitive improvements after PVP (e.g., Alegret et al., 2000; Baron et al., 1996; Cahn, Sullivan, Shear, Heit, et al., 1998; Junque et al., 1999; Lacritz et al., 2000; Obwegeser et al., 2000; Rettig et al., 2000; Riordan et al., 1997; Trepanier et al., 1998; Uitti et al., 1997), and it has been suggested these post-surgical improvements in test performance reflect the additional attentional resources available to patients following reduction of their distracting dyskinesia (Obwegeser et al., 2000; Scott et al., 1998; Trepanier et al., 1998). The present results suggest, however, that these post-surgical improvements in test performance represent practice effects. I did not detect improvement after PVP on any cognitive measure that exceeded the improvement demonstrated on retesting by a group of highly similar waitlisted participants who were tested twice with the same test-retest interval.

Changes Displayed by the Waitlist Group on Retesting

At follow-up, the waitlist group exhibited mixed changes in their performance on the cognitive measures, with small-sized (i.e., less than .35 *SD*) improvement and decline being evident on a roughly equivalent number of tests. Waitlisted participants tended to exhibit decline at follow-up on cognitive measures that incorporate time in their dependent variable, and consequently place a premium on speed of responding. This observation contrasts with the usual finding that performance improves on retesting with speeded tests (reviewed by Lezak, 1995 and McCaffrey & Westervelt, 1995), and suggests that progression of the psychomotor slowing associated with PD (reviewed by Smith, Goldman, Janer, Baty, & Morris, 1998) can be measured in patients with advanced PD over periods as short as 2 months.

For most subscales of the Medical Outcomes Study Short Form (SF-36), the declines in reported quality of life exhibited by waitlisted participants at follow-up were as large or larger than the improvements exhibited by the surgical group at follow-up. In particular, lower bodily pain and better social functioning in the surgical group at follow-up reflected improvement or stability in reported functioning amongst participants who underwent PVP, and decline in reported functioning amongst waitlisted participants.

Factors such as aging and disease progression might be expected to produce decline in reported quality of life over time, and the present findings underscore the importance of including an appropriate control group when studying interventions for PD (Gray et al., 2001). However, the magnitude of the declines on the subscales of the SF-36 exhibited by waitlisted participants was typically .25 *SD*, which appears quite large given the 2-month follow-up period. Perhaps the declines in reported quality of life exhibited by waitlisted participants also reflect some form of retesting effect? For example, it seems possible waitlisted participants were more

likely to report difficulties at follow-up because they were more comfortable with the assessment process, or perhaps because repeat assessment increased their frustration with their difficulties, leading them to report lower perceived levels of functioning.

Pre-Operative Level of Cognitive Functioning and Outcome from Pallidotomy

Some recent research publications and consensus statements have advocated that dementia should be a contraindication for PVP, as patients functioning pre-operatively at a low cognitive level have a poorer surgical outcome (e.g., Baron et al., 1996; Bronstein et al., 1999; Masterman et al., 1998; Mendis et al., 1999; Scott et al., 1998). This suggestion appears to be based largely on clinical observations of significant post-operative cognitive decline in a few patients noted to be overtly demented before surgery (e.g., Baron et al., 1996, Masterman et al., 1998). However, attempts to address this question systematically have failed to find a relationship between pre-operative level of cognitive functioning and post-PVP change in cognitive (Rettig et al., 2000) or motor (Riordan et al., 1997) functioning.

In the present study, participants' pre-operative level of cognitive functioning was not related to their cognitive or motor outcome from PVP. However, there was evidence pre-operative level of cognitive functioning was positively related to aspects of quality of life and mood outcome from surgery. These results are consistent with Rettig et al.'s (2000) suggestion that individuals with a low pre-operative level of cognitive functioning may have insufficient cognitive resources and preserved activities to support improvement in their quality of life after surgical treatment of their motor deficits.

It is possible the present failure to detect a relationship between pre-operative level of cognitive functioning and cognitive or motor outcome from PVP reflects range restriction in participants' pre-operative level of cognitive functioning, as the present sample did not contain

many individuals with significant pre-operative cognitive impairment. Similarly, the present evidence for a positive relationship between pre-operative level of cognitive functioning and post-operative improvement in aspects of quality of life and mood functioning is heavily dependent on the data from a single participant with a pre-operative level of cognitive functioning well below that of most participants. Additional research examining neurobehavioural outcome from PVP in individuals with a lower pre-operative level of cognitive functioning is needed.

Functional Implications of the Cognitive Declines that Follow Pallidotomy

Patients who underwent left PVP exhibited decline on verbal measures of list learning, fluency, working memory, and speed of color naming relative to waitlisted patients and patients who underwent right PVP. It is important to consider, however, that these statistically reliable cognitive declines after surgery do not automatically imply decline in participants' daily functioning and quality of life (Keith et al., 2002; Stebbins et al., 2000). To understand fully the functional implications of these changes in cognitive performance after PVP, these changes in test performance need to be empirically related to changes in real world functioning.

In the present study, magnitude of cognitive decline following PVP was not correlated with magnitude of post-operative change in reported quality of life. One interpretation of this finding is that the decline in cognitive test performance observed following PVP does not have significant negative consequences for patients' real world functioning. However, as noted above, this analysis had modest statistical power, and further research is needed that examines the relationship between neuropsychological and functional outcome from PVP in greater detail. In particular, the present research was limited to a self-report measure of quality of life. It will be important in future research to include measures of specific adaptive skills completed by patients

and their spouses and/or caregivers. Given the present findings, it may be helpful to focus this research on aspects of daily functioning that depend heavily on the recall and manipulation of verbal information and the production of speech. Socialization is particularly dependent on these abilities, and therefore potentially at particular risk after left PVP. In support of this notion, I note the present evidence that reported social functioning improved relatively more after right than left PVP.

Cognitive Effects of Right Pallidotomy

The MANOVA analysis employed in the present study did not reveal any significant cognitive declines at the group level after right PVP. This is not an unusual finding, and many researchers have concluded that cognitive decline is greater following left PVP (e.g., Kubu et al., 2000; Obwegeser et al., 2000; Riordan et al., 1997; Schmand et al., 2000; reviewed by York et al., 1999). However, other data analysis techniques employed in the present research did reveal evidence for cognitive decline after right PVP. In particular, when I examined the effect size of post-operative change on the cognitive measures (to address Question 3), sizable (.75 *SD* or larger) decline was evident after right PVP on measures of working memory for abstract designs, divided attention and speeded visual-spatial sequencing, and problem solving. Post-surgical declines on these three measures were more modest for the left PVP group, suggesting that different types of cognitive changes may follow left and right PVP. Additionally, while statistically significant decline in verbal fluency after right PVP was not evident at the group level, results of the individual participant analysis suggested decline in fluency after right PVP was quite common (occurring in 71% of right PVP patients).

The MANOVA, effect size of post-operative change, and individual participant analyses are based on different analytical procedures and they provided different types of information.

Consequently, it is not surprising that their results differ somewhat. Given the evidence for cognitive decline after right PVP described above, it seems premature to conclude right PVP posses no risk for cognitive decline. The relatively small number of participants in the right PVP group may have contributed to my inability to consistently detect cognitive effects of right PVP, and in future research it will be important to study outcome in a larger sample of patients undergoing right PVP.

The present evidence for greater cognitive decline following left PVP may also reflect the fact that the present test battery was more sensitive to cortical-basal ganglia dysfunction in the left than the right hemisphere. York et al. (1999) suggested this criticism might be applied to the PVP outcome literature as a whole, as their review suggested measures of non-dominant hemisphere functioning are under-represented in this literature. This likely reflects the difficulties inherent in using measures that are sensitive to non-dominant fronto-subcortical dysfunction, such as Design Fluency (Jones-Gotman & Milner, 1977), with this population due to the demands these measures typically place on drawing ability (Green & Barnhart, 2000).

Our understanding of cognitive outcome from right PVP would be improved by focusing research efforts on measures that are sensitive to non-dominant cortical-basal ganglia functioning and require minimal motor skill. The Subject Ordered Pointing task (SOP) with words and abstract designs as stimuli may be one such measure. This measure is differentially sensitive to lesions within left and right prefrontal systems (e.g., Petrides and Milner, 1982), and given the minimal demands it places on motor functioning, it is particularly well-suited for use with individuals with advanced PD. Furthermore, the results of the present study suggest this measure may indeed be sensitive to the cognitive changes that follow right PVP. Inspection of Figure 7 reveals a dissociation in the effects of right and left PVP on SOP performance, with performance on SOP with abstract designs declining after right but not left PVP, and performance on SOP with words declining after left but not right PVP. However, only the effect of left PVP on

performance of SOP with words reached statistical significance in the MANOVA analysis, and future research with this measure is warranted.

Implications for Clinical Practice

The present research makes several contributions to the information available to patients and health care providers regarding neurobehavioural outcome from PVP. One principal finding is that the cognitive effects of PVP depend on the hemisphere operated on, and in particular, candidates for left PVP should expect to sustain some post-operative decline in their verbal abilities, perhaps particularly in the retrieval of verbal information. Indeed, the results of the individual participant outcome analysis suggest that most participants who underwent left PVP exhibited post-operative verbal decline, particularly in verbal fluency and working memory.

The results of the present study also suggest refinements to the broad notion that a low pre-operative level of cognitive functioning is associated with poorer outcome from PVP. While pre-operative level of cognitive functioning did not predict degree of post-operative change in cognitive or motor functioning, surgical candidates functioning at a lower level cognitively before surgery did exhibit smaller post-surgical improvements in aspects of their mood functioning and quality of life. This finding raises the possibility that there may be a critical pre-operative level of cognitive functioning, and patients functioning below this level before surgery may not accrue sufficient post-operative improvement in their quality of life and mood functioning to justify exposing them to the morbidity risks associated with PD (Rettig et al., 2000). This is likely an important point clinically, as the morbidity risks associated with PVP are not trivial, and include hemiparesis, visual defects, dysarthria, hypophonia, and dysphagia. Indeed, after aggregating published data de Bie et al. (2002) estimated that roughly 30% of patients experience an adverse effect as a result of PVP, and that adverse effects are permanent

(i.e., last greater than 3 months) in 14% of patients.

The present results also suggest a cautionary note is in order regarding the breadth of the improvements in physical functioning that patients and their caregivers should expect after PVP. As would be expected, PVP was followed by reduction in contralateral levodopa-induced dyskinesia. Additionally, participants who underwent PVP exhibited better reported social functioning and bodily pain than waitlisted participants. However, there were no statistically reliable post-operative improvements in participants' reported level of physical functioning (as measured by subscales of the SF-36), nor did participants' performance improve significantly after surgery on measures of speeded manual dexterity, micrographia, or motor perseveration. The absence of significant post-operative improvement in these objective and subjective measures of complex motor functioning may reflect persisting Parkinsonian motor impairments, such as tremor, rigidity, and bradykinesia, that were not targeted by PVP. To facilitate informed decision making before surgery, and to guard against disappointment after surgery, it will be important to be very clear with patients and their caregivers regarding the motor deficits that will be targeted by PVP, and to be clear they should not expect a global increase in patients' motor functioning after surgery (Bronstein et al., 1999).

Limitations of the Present Research

This study has two limitations that should be borne in mind when considering the results obtained. First, due to the relatively small clinical sample employed, the statistical power for some analyses was low. As described above, the within-subjects design used to examine group outcome from PVP (i.e., Question 1) had good statistical power, having a greater than 90% chance of detecting a medium- or large-sized effect of surgery on most variables (see Table 5). However, the correlational analysis conducted to examine the relationship between

neurobehavioural outcome and pre-operative level of cognitive functioning (Question 4), and the correlational analysis conducted to examine the relationship between cognitive and quality of life outcomes from PVP (Question 5) had modest statistical power (see Tables 11-13). Consequently, my failure to detect a relationship between cognitive and motor outcome from PVP and pre-operative level of cognitive functioning, or a relationship between cognitive and quality of life outcomes from surgery, may represent Type II error due to low statistical power. This possibility underscores the importance of future research with larger samples sizes.

The absence of precise information regarding the location of surgical lesions represents a second important limitation of the present study. The fact that dyskinesia declined significantly after surgery suggests surgical lesions typically included the sensori-motor region of the GPi. However, I cannot exclude the possibility that lesions extended beyond the posteroventral GPi, into regions of this nucleus that subserve cognitive and emotional processes. Surgical error of this nature might be expected to negatively impact cognitive and quality of life outcome from surgery. The post-operative improvements in quality of life found in the present study were more circumscribed than is typically reported (e.g., Martinez-Martin et al., 2000; Straits-Troster et al., 2000), raising the possibility of less than optimal lesion placement. As noted above, however, the cognitive declines detected after surgery are in keeping with the exisiting literature, a finding that suggests surgical lesions were generally well placed. Nevertheless, the absence of precise information regarding lesion location limits the information that this study can provide about the neurobehavioural functions of the GPi, and caution should be used when generalizing the present findings regarding neurobehavioural outcome from PVP to predict outcome at other surgical centers.

The Use of a Waitlist Control-Group Design in Future Research

I have suggested that future research should examine outcome from PVP in individuals with pre-operative cognitive impairment, and that greater insight into outcome from right PVP might be obtained by studying larger samples of individuals undergoing right PVP, and by employing cognitive measures, such as Subject Ordered Pointing, that are both sensitive to dysfunction in non-dominant fronto-subcortical systems, and compatible with the motor deficits associated with advanced PD. Should this research employ a waitlist control-group design to control for the effects of retesting and disease progression? This methodology has drawbacks that likely account for the infrequent application of waitlist control-group designs in the PVP literature to-date. In particular, this methodology requires enrollment of greater numbers of participants, and it typically requires the investment of more time and resources in scheduling and assessment. Additionally, the use of a waitlist control group design may be ethically problematic in settings where the waiting time for surgery is short, and participants in the waitlist group would have to wait longer than they might otherwise to undergo PVP.[18]

Given these drawbacks of waitlist control-group designs, the reader may wonder whether one should use this methodology when studying outcome from PVP, particularly as a principal conclusion drawn from the present research is that accounting for re-testing effects does not increase the breadth of cognitive decline measured after PVP. I would suggest, however, that there are at least two reasons to include a waitlist control-group in future studies of neurobehavioural outcome from PVP. First, controlling for re-testing effects allows for more accurate measurement of neurobehavioural outcome from PVP. As described above, waitlisted participants exhibited mixed improvements and declines on the cognitive measures at follow-up, and these changes were greater than or equal to .25 *SD* for roughly one quarter of the variables. Similarly, at follow-up, the waitlist group exhibited declines in reported functioning on most

[18] As described above, at the center whether this research was conducted all surgical candidates had to wait 2 to 3 months to undergo PVP. Consequently, it was possible to conduct baseline and follow-up assessments on members

subscales of the SF-36. These declines were typically .25 *SD* or larger, and after accounting for these changes the magnitude of the effect of surgery doubled on most SF-36 subscales. By accounting for these changes in cognitive performance and reported functioning expected on re-testing, I was able to more accurately measure neurobehavioural outcome from PVP. Second, full assessment of neurobehavioural outcome from medical interventions includes characterization of outcome at the individual participant level (Chelune, 2002; Lacritz et al., 2000; Sawrie, 2002). There are ways to measure significant individual change in the absence of a control group, such as defining significant change as performance on re-testing that deviates from baseline performance by more than 1 *SD* (reviewed by Keith et al., 2002). However, this approach does not account for factors such as baseline performance level, test practice, regression to the mean, and disease progression. The use of more sophisticated techniques that do account for these potential confounds inherent in re-testing, such as the standardized regression-based technique employed in the present research, necessitates the inclusion of a group of patients as similar as possible to the experimental group, ideally differing only in the timing of intervention delivery (Chelune, 2002; Sawrie, 2002).

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of the waitlist group during this period and not delay when they underwent PVP.

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APPENDIX: DESCRIPTION OF THE MEASURES EMPLOYED

Premorbid Intellectual Functioning

The *North American Adult Reading Test (NAART)* is composed of phonetically irregular words read aloud by participants (Blair & Spreen, 1989). The number of words pronounced correctly is predictive of premorbid cognitive functioning (especially of verbal IQ, with which NAART performance has been found to correlate at roughly .70 levels, see Lezak, 1995). The NAART was only administered during the baseline assessment, and the number of errors served as the dependent variable.

Preoperative Overall Level of Cognitive Functioning

The *Dementia Rating Scale (DRS)* measures attention, initiation/perseveration, constructional ability, conceptual functioning (abstraction), and memory and was designed to measure overall level of cognitive functioning in cognitively suspect populations (Mattis, 1988). This scale is widely used, has good psychometric properties, and is predictive of functional status (Baird, Podell, Lovell, & McGinty, 2001; Lezak, 1995). The DRS was only administered in the baseline assessment, and the total score served as the dependent variable.

Clinical Measures of Cognitive Functioning

The following tests were selected because they are extensively used clinically, are compatible with the cognitive and motoric deficits typical of individuals with advanced PD undergoing PVP, and they have been used in many of the previous studies of psychological

outcome from PVP. When available, alternate versions of test stimuli were used across the two assessments, and the presentation order of the alternate versions was counterbalanced across the participants. The measures for which alternate forms were available is detailed in Table 2.

Attention and Working Memory

WAIS-R Digit Span provides a measure of verbal attention and short-term memory (Wechsler, 1981). Participants were verbally presented strings of numbers (1/second) and asked to repeat the same numbers in the same order (or in the case of Digits Backwards in the reverse order). Participants were presented with two trials of increasingly longer strings of numbers, and testing was terminated when participants failed both trials of a given length. The total number correct in the digits forwards and digits backwards conditions served as dependent variables.

Corsi Blocks is a test of visual-spatial attention and short-term memory (Milner, 1971). Subjects were presented a board upon which nine cubes were mounted in a random configuration. During each trial an examiner touched blocks in a set order and the participants then touched the same blocks in the same order (or in the case of Corsi Blocks backwards in the reverse order.) Participants were presented with two trials of increasingly longer sequences, and testing was terminated when participants failed both trials of a given length. The total number correct in the forwards and backwards conditions served as dependent variables.

Visual-Spatial Processing and Synthesis

Judgment of Line Orientation tests a participant's perception of angular relationships (Benton, Hamsher, Varney & Spreen, 1983). On each trial participants were presented with two test lines on a page and eleven comparison lines radiating out from a central point on a second page. Participants indicated which two comparison lines were orientated the same as the two test lines. Fifteen trials were administered during each assessment (either all the even or all the odd

items from the test). The dependent variable was the number of trials when participants provided both correct comparison lines.

The *Hooper Visual Organization Test* measured participants' ability to identify depicted objects that have been fragmented and rearranged in a manner analogous to a mental jigsaw puzzle (Hooper, 1983). This test is thought to measure visual perception, analysis, and synthesis plus naming abilities. The number of correct responses served as the dependent variable.

Verbal and Visual Learning and Memory

The *Rey Auditory Verbal Learning Test (RAVLT)* is a measure of verbal learning and memory (Lezak, 1995). Participants were verbally presented a list of 15 unrelated words (List A) and then instructed to recall as many words as they could in any order. Participants were given four additional learning trials with List A and were then tested with a second 15-item list (List B). Recall of List A after distraction with List B, and recall and recognition of List A after a half-hour delay were then tested. Dependent variables included the total number of words recalled from List A over trials 1 through 5 (RAVLT total trials 1-5), immediate recall of List A after distraction with List B, recall of List A after a half-hour delay, and true-positives minus false-positives on testing of recognition memory for List A after a half hour delay.

The *Benton Visual Retention Test: Administration A* is a measure of the ability to reproduce increasingly complex visual stimuli (abstract line drawings with one to three elements) after a 10-second exposure (Sivan, 1992). In addition to short-term visual memory, this test draws upon visual-spatial constructional skill and visual conceptualization. During scoring attention was focused on the degree to which participants reproduced the gestalt of the design(s), and minor imperfections attributable to tremor or dyskinesia were ignored. The number of errors served as the dependent variable.

Executive Functioning

The *Controlled Oral Word Association test* (Benton & Hamsher, 1989) is a measure of lexical access and verbal production. Participants were asked to quickly say aloud words that begin with a target letter (e.g., 'c'). Three 60-second long trials were given, each with a different phonemic cue, and participants were asked to not provide proper nouns or words with the same prefix. The total number of correct words provided served as the dependent variable.

The *Stroop Test* is a measure of speeded lexical access, and in the colour-word trial the ability to inhibit a prepotent or over-learned cognitive response. Three 45-second long trials were administered (Golden, 1978). In the first trial (Stroop words) participants read aloud as quickly as they could the words 'red', 'green' and 'blue' typed in black ink arranged randomly in columns on a page. In the second trial (Stroop colours) participants named the colour of the ink (red, green, or blue) used to print 'XXXX's arranged in columns on a page. In the third trial (Stroop colour-words) participants named the colour of the ink in which the words 'red', 'green', and 'blue' were printed. The word printed and the colour of the ink used conflicted on every trial. The colour-word trial required participants to inhibit the over-learned response of reading the words, and to instead say the colour of the ink the words were printed in. The number of correct utterances during each of the three 45-second trials served as dependent variables.

The *Trail Making Test Part A (Trails A)* is thought to be principally sensitive to deficits in psychomotor speed, sustained attention, and/or visual-motor coordination (Reitan & Wolfson, 1985). Participants were presented with a sheet of paper that displayed numbered circles (1-25) arranged in a pseudorandom configuration. As quickly as possible participants drew a line connecting the circles in ascending numerical order (i.e., 1 to 2 to 3 ...). In the *Trail Making Test Part B (Trails B)*, participants were presented a paper displaying circles containing either a number (1-13) or a letter (A-L), arranged in a pseudorandom configuration. As quickly as possible participants drew a line connecting the circles in ascending numerical and alphabetic

order, alternating between numbers and letters (i.e., 1 to A to 2 to B to 3, and so on). Trails B taps psychomotor speed, sustained attention, and visual-motor coordination but also requires participants to flexibly shift conceptual sets (number to letter and back again), and to remember their position in the sequence. The total time taken to complete Trails A and B served as dependent variables.

Experimental Neuropsychology Tasks Sensitive to Dysfunction in Associative Cortical-Basal Ganglia Circuits

The following tasks have been used in the human and animal experimental neuropsychology literature, and they have been found to be sensitive to dysfunction within the associative cortical-basal ganglia circuits described above. Therefore, post-operative alterations in the functioning of these cortical-basal ganglia circuits would be expected to alter performance on these tests. Surprisingly, these tests have been used infrequently in previous investigations of the psychological effects of PVP (York et al., 1999; Jahanshahi et al., 2002). For a recent review of these measures see Stuss and Levine (2002).

The testing procedures for the *Delayed Responding (DR)* and *Delayed Alternation (DA)* tests have been adapted from those used with laboratory animals (see Freedman & Oscar-Berman, 1986; Oscar-Berman, McNamara, & Freedman, 1991). In both DR and DA the participant and examiner sat facing each other, separated by a wooden apparatus. A guillotine-type door was mounted in the apparatus. When the door was raised a stimulus board could be slid towards the participant and the participant could see the examiner's hands (but not his or her face). The stimulus board contained two shallow wells. The wells could be covered with identical black plaques. When the stimulus board was pulled back towards the examiner and the guillotine-type door was lowered the participant could not see the two wells.

The DR task draws heavily upon visual-spatial discrimination skills and short-term memory for spatial information (Oscar-Berman et al., 1991). In the DR task the door was raised, the stimulus board was pushed towards the participants, and the participants were instructed to watch the examiner place a penny in one of the two wells. The examiner then covered both wells with the black plaques, retracted the stimulus board, and lowered the door. After a set delay had elapsed the door was raised, the stimulus board was slid towards the participant, and he or she indicated where the penny was hidden.

Each participant was tested at increasing delays on the DR task (0, 10, 30, and 60 s), and testing at each delay was terminated when a participant was either correct on nine of ten consecutive trials, or received 40 trials at that delay. All delays were tested for each participant during each assessment. The total number of errors made across the four delay intervals served as the dependent variable.

The Delayed Alternation (DA) task is thought to draw upon visual-spatial discrimination skills and short-term memory for spatial information (where the penny was on the last trial), plus the ability to inhibit the previously rewarded response (Oscar-Berman et al., 1991). In the DA task trials began with the door lowered and the stimulus board pulled towards the examiner. Out of the participant's view the examiner put a penny into a well. The wells were then covered with the identical black plaques, the door was raised, and the stimulus board was slid towards the participant. The participants showed the examiner where they thought the penny was hidden and the contents of the selected well were then exposed. Participants had to learn using only this feedback that the baited well alternated across trials (i.e., right then left then right and so on).

Testing on the DA task was terminated when a participant was either correct on 15 consecutive trials, or received 40 trials. The total number of errors made served as the dependent variable.

The *Conditional Associative Learning* task required participants to learn by trial and error

the one-to-one pairings, or "associations", between six colours and six abstract designs (Petrides, 1991). It is thought to place demands on basic associative processes and the strategic control of memory. Participants were presented with a stimulus card displaying six abstract designs. Participants were then presented a smaller coloured card, and asked to indicate which design they thought 'went with' with the colour. If they provided the correct response they were told they were correct, and the process began again with a different coloured card. If they provided an incorrect response, participants were told they were wrong, and they were asked to select another design. This process continued until participants chose the correct design for each of the six coloured cards. Participants then received five additional trials with five other stimulus cards. Each stimulus card displayed the same six abstract designs (in a novel spatial configuration), and participants had to continue to indicate the design paired with each of the six coloured cards. No changes were made to the design-colour associations over the course of the six learning trials. Learning of the colour-design associations was reflected in a decline in the number of errors made over the six trials. The total number of errors made over the six trials served as the dependent variable.

The *Subject Ordered Pointing (SOP)* test required participants to organize and carry out an internally developed sequence of responses, and this test is thought to place demands on working memory and executive functioning (Milner, Petrides, & Smith, 1985). At the beginning of each trial participants were presented with a stack of twelve cards. The same stimuli were printed in a novel spatial configuration on each of the twelve cards. Participants looked at each card in turn and selected a different stimulus - one they had not chosen before. Versions of the SOP task incorporating words (SOP words), representational drawings (SOP drawings), and abstract designs (SOP designs) as stimuli were administered. The number of errors (stimuli selected more than once) for SOP words, SOP drawings, and SOP designs served as the dependent variables.

The *Tower of Toronto* is thought to be sensitive to deficits in planning/problem solving (Lezak, 1995; Saint-Cyr et al., 1988). Participants were presented with a board mounting three pegs. Three circular wooden rings painted different colours (white, gray, and black) were positioned on one peg. The rings were arranged according to colour (with lighter rings on top of darker rings, so black was on the bottom, then gray, then white was on the top). During each trial participants were instructed to rebuild the tower of rings exactly as it was on an indicated peg. They were cautioned to obey three rules: 1) they could only move one ring at a time; 2) once they took a ring off a peg they had to place it on a peg before moving another ring; and 3) no ring could be placed on top of a ring painted a lighter colour (i.e., the white ring could sit on the gray ring, but the reverse was not permissible). Three trials were administered per assessment, and the pattern of tower movement was counterbalanced across the participants. The total number of moves, the total time required, and the number of errors made summed across the three trials served as dependent variables.

Quality of Life

The *Medical Outcomes Study Short Form (SF-36)* is a self-report measure of health-related quality of life (Ware et al., 1993). Ware and colleagues documented the reliability and validity (including sensitivity to change) of this scale. The SF-36 is currently one of the most popular generic measures of quality of life in the neurological literature, and has been described as the 'international measure of the future' (Murrell, 1999). The SF-36 provided separate indices of physical functioning, social functioning, role-physical, role-emotional, bodily pain, general health, vitality, mental health, and health in transition. With the exception of the health in transition subscale, the SF-36 subscales are all positively keyed. The SF-36 has been selected by Vancouver Hospital for in-house investigations of health-related quality of life, and it is one of

the more frequently used quality of life measures in the PVP literature. Raw scores for each of the nine indices served as the principal dependent variables. Additionally, the total score for the SF-36 was computed as described in the manual and used as a measure of overall reported quality of life.

Mood

The *Profile of Mood States (POMS)* served as a self-report measure of mood state. Respondents were presented a list of 65 adjectives (e.g., happy, sad) and instructed to indicate using a 5-point scale the extent to which each adjective applied to how they felt during the past week. The scale provided six mood indices: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. With the exception of the Vigor-Activity subscale, these mood indexes are negatively keyed (i.e., a higher score reflects greater reported negative mood). McNair et al. (1981) have documented the reliability and validity of the POMS. This measure has been used to study treatment outcome for neurological disorders such as epilepsy and HIV-related dementia (Lezak, 1995), and the POMS has been used in several previous studies of outcome from PVP. Raw scores for each of the six mood indices served as the principal dependent variables. Additionally, the total score for the six indices (with the keying of the Vigor-Activity scale reversed) was used as a measure of overall reported mood dysfunction.

Motor Functioning

Clinical rating of dyskinesia. Levodopa-induced dyskinesia was assessed by the neurosurgeon two months before and two months after surgery using the rating scale of Goetz et al. (1994). This measure grades dyskinesia on a scale of increasing severity from 0-4. Patients

were assessed while in an 'on' state.

The *Grooved Pegboard* test provides a measure of psychomotor speed and manual dexterity (Lafayette Instrument Company, 1995; Lezak, 1995). Participants were presented with an apparatus comprising a board with a 5 x 5 array of slotted holes angled in different directions and a shallow well containing numerous small metal pegs. Each peg was circular with a square protrusion. Every peg fits into every hole, but each peg must be rotated so the square protrusion is aligned with the slot in the hole. Grooved pegboard performance is strongly correlated with motor symptoms in PD (Matthews & Haaland, 1979). The time taken to complete the first two rows of the board with the dominant and then the non-dominant hand served as dependent variables.

The *MNO* test provides for quantitative assessment of micrographia and motor perseveration (Lezak, 1995 pg. 670-671). Participants wrote "*MNO*" over and over again in cursive script for roughly 250 mm without lifting their pencil off the page. Two writing samples were obtained. Micrographia was assessed for each sample by computing the difference (in mm) between the height of the first and last "*MNO*". The average change value for the two samples served as the dependent variable. Motor perseveration was operationally defined as a repeated inappropriate element within a "*MNO*", and the total number of perseverations in the two samples served as the dependent variable.