# NEUROBEHAVIORAL OUTCOME AND SUBTHALAMIC DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

by

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# STATEMENT OF ETHICS APPROVAL

The author, whose name appears on the title page of this work, has obtained, for the research described in this work, either:

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# ABSTRACT

Subthalamic deep brain stimulation (STN DBS) is known to improve motor functioning in Parkinson's Disease (PD), but the neurobehavioral impact is less clear. This study examined neurobehavioral outcome of bilateral STN DBS in advanced PD. Study participants were assigned to either a Surgical Group (n=19) or a waitlist Control Group (n=16) and assessed twice. Between assessments, there was a two month interval during which the Surgical Group had STN DBS surgery, while the Control Group had no surgery. In comparison to the Control Group, the Surgical Group showed significant decline in executive functioning, verbal delayed memory, verbal working memory, and verbal fluency. Nevertheless, the Surgical Group also reported significantly improved health and quality of life in several domains including vitality, mental health, general health, and social functioning. In summary, this study revealed that despite declines on several cognitive measures, participants who underwent STN DBS also reported improved quality of life.

**Key words**

Parkinson's Disease; deep brain stimulation, subthalamic nucleus; neurosurgery; cognition; quality of life

# DEDICATION

To my parents and brother who have stood beside me every step of the way and who inspire me to live a life of compassion and hope. To those with Parkinson's Disease with whom I had the privilege to work.

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# INTRODUCTION

## General Overview of Parkinson's Disease

Parkinson's Disease (PD) is one of the most common neurodegenerative disorders in the world. It is estimated that on a global level, approximately 3,765,000 people have Parkinson's Disease and 305,000 people are diagnosed each year with the disease (http://www.phac-aspc.gc.ca). According to the Parkinson's Society of Canada, around 100,000 Canadians have Parkinson's Disease (http://www.parkinson.ca/pd/parkinson.html). Recent estimates suggest that approximately 5000 to 8000 people living in British Columbia have been diagnosed with Parkinson's Disease (Honey & Palur, 2001).

## Symptoms of Parkinson's Disease

Parkinson's Disease is a chronic, progressive disorder that involves several cardinal symptoms: tremor (i.e., often a resting tremor), rigidity (i.e., increased muscle tone and stiffness), and bradykinesia (i.e., slowness of motor movements) (Gelb, Oliver, & Gilman, 1999). Often, usually in the latter stages of the disease, patients may also experience postural instability, involving falls and subsequent injuries (Lang & Lozano, 1998; Gelb et al., 1999). Without doubt, these symptoms can interfere with and negatively affect patients' lives and medical treatments are needed to address these symptoms. Patients, however, are not the only ones negatively affected by the disease. Often, family members and other caregivers of the person with PD are also negatively

impacted by the disease, even if indirectly. For example, the burden may exist on several levels including extra financial stress, physical demands (i.e., helping the patient stand and walk), psychological burdens (i.e., trying to raise a patient's spirits when feeling sad about their condition), and restricted social freedom (i.e., finding it difficult to go out to socialize with friends if the patient requires constant in-home assistance) (Martinez-Martin et al., 2005).

Parkinson's Disease is also associated with several neuropsychological effects, including declines in executive functioning (Williams-Gray, Foltynie, Lewis, & Barker, 2006), decision-making (Mimura, Oeda, & Kawamura, 2006), visuospatial functioning (Williams-Gray et al., 2006), verbal fluency (Auriacombe et al., 1993), psychomotor functioning (Taylor, Saint-Cyr, & Lang, 1987), verbal recall (Auriacombe et al., 1993), and working memory (Gilbert, Belleville, Bherer, & Chouinard, 2005).

A variety of interventions, including medication and neurosurgery, have been developed and used to treat the motor symptoms of Parkinson's Disease (Marjama-Lyons & Koller, 2000).

## Use of Medications for Parkinson's Disease

A number of front line medications have been used to treat PD, including levodopa (L-Dopa), and other dopaminergic agents. Historically, the major medicinal breakthrough in the treatment of Parkinson's Disease was the discovery of L-Dopa. The drug was first used to treat Parkinson's Disease in 1961 (Tolosa, Marti, Valldeoriola, & Molinuevo, 1998) and "after three decades of universal use, the drug remains the most efficacious and symptomatic medication for treating patients with Parkinson's disease"

(Rascol et al., 2003, p. S3). Levodopa has been noted to significantly reduce motor symptoms, especially during the first few years of a patient's pharmacotherapy for PD (Rascol et al., 2003). With chronic use of levodopa and other dopaminergic agents, however, limitations are more evident, including debilitating side effects (such as dyskinesia and motor fluctuations), lack of effectiveness for several non-motor symptoms (such as mood and pain), and the failure of L-Dopa to stop the chronic advancement of PD (Rascol et al., 2003). In fact, as noted by Martinez-Martin et al. (2002), to date no pharmacotherapy has been shown to stop the disease's progression.

## Use of Surgical Intervention

Interestingly, many decades ago, prior to the development of medications to combat the symptoms of PD, neurosurgical techniques were commonly used in an attempt to ameliorate the symptoms of PD. The surgery involved permanent lesioning and ablation of select areas of the patient's brain. For example, pallidotomy was generally successful in improving motor symptoms and thalamotomy was used to reduce tremor (Samii, Nutt, & Ransom, 2004). However, as effective medications to combat symptoms of PD started being used in the 1960s, such as levodopa, which remains the so-called "gold standard" in the pharmaceutical treatment of PD, surgical intervention and their undeniable invasiveness rapidly fell out of favour (Samii et al., 2004).

Eventually, however, it became evident that PD patients on anti-parkinsonian medications for a long time may experience a decrease in the benefit of this drug treatment, due to decreased sensitivity (Ahmad, Mu, & Scott, 2001). As PD progresses, many patients become increasingly unresponsive to medications, or medications create incapacitating side effects (Sanghera, Desaloms, & Stewart, 2004). For example,

symptoms such as stooped posture and freezing may become less responsive to medicinal treatment (www.reutershealth.com/wellconnected/doc51.html). Also, some patients may develop other problems, such as motor fluctuations and dyskinesia (a condition involving involuntary motor movements), which are often not amenable to drug treatment (Samii et al., 2004). These poor outcomes highlight the potential limitations of pharmacotherapy to treat Parkinson's Disease, especially patients in the latter stages of the disease. Thus, recently, there has been renewed consideration of the use of surgical interventions to treat Parkinson's Disease (Thobois, Delamarre-Damier, & Derkinderen, 2005; Moretti et al., 2003).

In short, in recent years, the treatment tide has shifted slightly and surgery has been reconsidered and utilized not as a first treatment for Parkinson's Disease, but rather to be used in pharmacotherapy-refractory situations, with patients in the latter stages of the disease process. As noted by Nutt and Wooten (2005), surgical therapy is a treatment option usually for patients "in whom the response to anti-parkinsonian medications is complicated by severe motor fluctuations and dyskinesia", which is usually "absent in the early stage of the disease" and, thus, this therapeutic modality (e.g., surgery) has been noted to have "no role in early Parkinson's disease" (p. 1025). Similarly, Ardouin et al. (1999) comment "the failure of levodopa and dopaminergic therapy to achieve long-term symptom relief in patients with Parkinson's Disease (PD) and advances in stereotactic techniques have led to a renewed interest in surgical treatments" (Ardouin et al., 1999, p. 217).

Currently, an array of improved surgical techniques for PD is available, in comparison to the techniques used several decades ago. Surgical procedures involving

the permanent lesioning or ablation of select brain areas are still used. However, it has been noted that "modern ablative surgery for movement disorders probably results in less frequent and severe cognitive morbidity than seen in early surgical series" (Fields & Troster, 2000, p. 268). Nonetheless, the major drawback to the use of ablative surgery is that it is an irreversible procedure and can involve major complications, especially if the lesions are not created at the ideal target locations (Benabid et al., 2001). A very grave disadvantage of this surgery is that it may also irreversibly destroy healthy brain tissue and may permanently disrupt circuits required for cognitive functioning (Ardouin et al., 1999). As well, if an adverse event occurs during surgery and the brain site ameliorated is not the intended one, no further surgical correction or reversal is possible.

Fortunately, a new surgical option for Parkinson's Disease, deep brain stimulation, has been developed. Deep brain stimulation (DBS) is emerging as a preferred surgical option for intractable, medication-resistant conditions (Honey & Palur, 2001). In 1987, DBS was used for the first time to treat Parkinson's Disease (Thobois et al., 2005). Deep brain stimulation involves sending pulsed electrical current to the brain. To do this, current travels from a small device implanted below the patient's clavicle to electrodes implanted in the patient's brain. The current "stimulates" the brain, which is believed to decrease activity within neural areas close to the electrodes and, in turn, reduce symptoms (Samii et al., 2004).

Deep brain stimulation (DBS) is a great advance in surgical interventions for Parkinson's Disease because it does not create permanent brain lesions or ablations and is a reversible procedure, while being as clinically effective as a permanent lesion. Moreover, with DBS, side effects resulting from the stimulation can be ameliorated as the

stimulation parameters are amenable to adjustment (Thobois et al., 2005; Dujardin, Defebvre, Krystkowiak, Blond, & Destee, 2001). In essence, deep brain stimulation provides the effect of a permanent lesion while having the valuable advantage of being a reversible procedure (Benabid et al., 2001). As well, several stimulation parameters (such as the stimulation intensity and frequency) can be adjusted (Jahanshahi et al., 2000).

In general, there are three target sites for deep brain stimulation in patients with Parkinson's Disease: thalamus, globus pallidus internus, and subthalamic nucleus (Honey & Palur, 2001). Notably, however, subthalamic nucleus (STN) stimulation is the most frequently used surgical intervention to treat Parkinson's Disease (Ashkan, Wallace, Bell, & Benabid, 2004) and has "rapidly become the surgical treatment of choice for medically refractory PD" (Ashkan et al., 2004, p. 19). Perhaps not so coincidentally, the initial use of the thalamus and pallidum as surgical target sites was largely unanticipated, whereas the use of the subthalamic nucleus was more intentional, stemming from deeper understanding of anatomy and physiology (Ashkan et al., 2004). It is believed that overactivation of these sites in humans contributes to parkinsonian symptoms and that stimulation (e.g., via deep brain stimulation) decreases this activation, thus improving motor symptoms.

Benabid et al. (2001) hail the use of STN DBS as the "method of choice when a surgical procedure is indicated for the treatment of Parkinson's disease" (p. 37). As further reinforced by Breit, Schulz, and Benabid (2004), STN is the "most used target for DBS in the treatment of PD, due to the marked improvement of all cardinal symptoms of

the disease" (p. 275). It has even been "considered by many experts the best surgical option for patients with advanced Parkinson's disease" (Lezcano et al., 2004, p. 451).

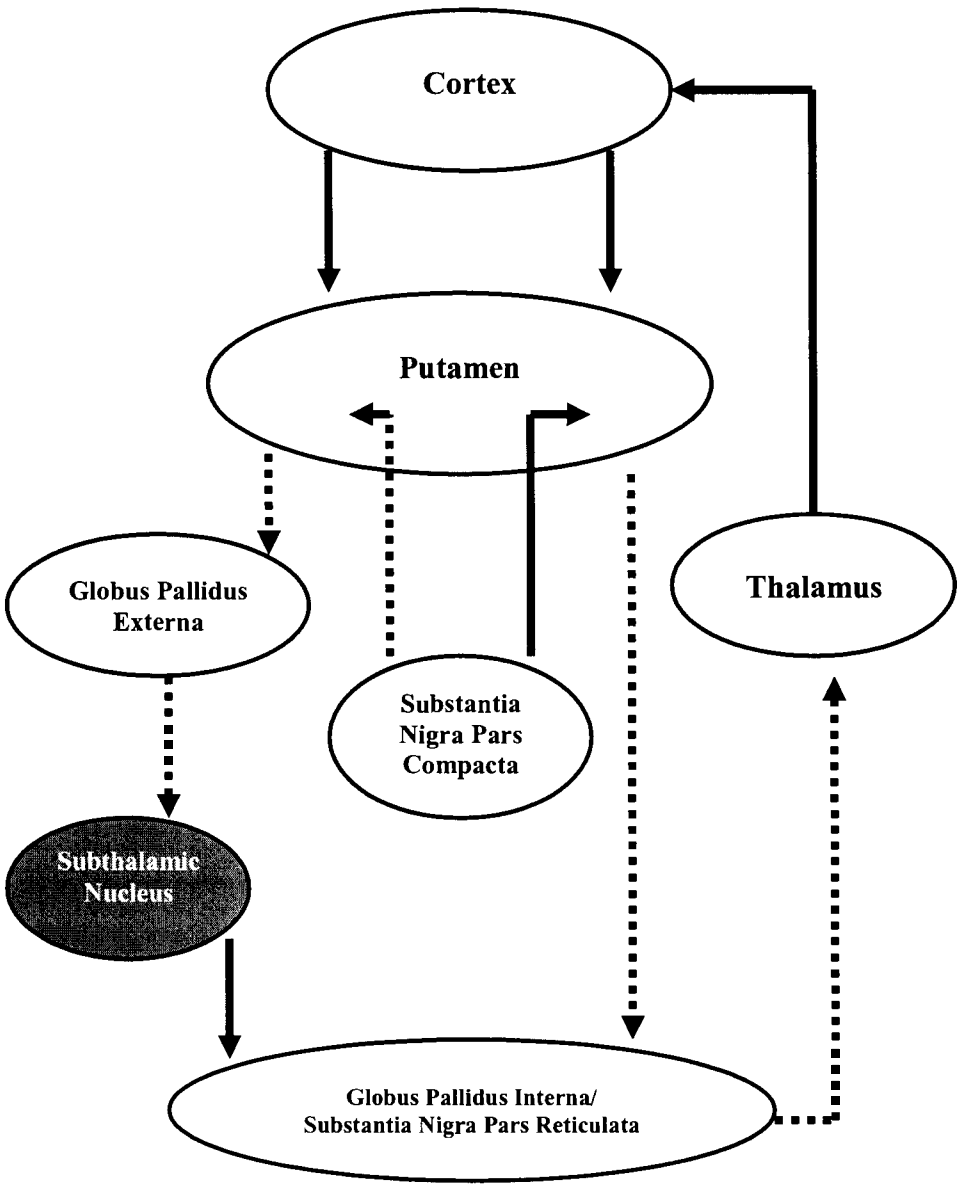
## Rationale in Using Deep Brain Stimulation of the STN to Treat Advanced PD

Understanding the use of STN DBS to treat the motor symptoms of Parkinson's Disease requires knowledge of the pathways between brain cortical and subcortical areas, which are often referred to as frontal-subcortical brain circuitry. A model that has been proposed and generally well-received purports the existence of five frontal-subcortical circuits (Weingarten & Cummings, 2001; Lichter, 2001; Tekin & Cummings, 2002). One of these circuits, the motor circuit, is most critical in motor functioning. It has both a direct and an indirect pathway. The direct pathway arises from neurons in the supplementary motor area, premotor cortex, and somotosensory cortex, and proceeds to the putamen, which is located in the striatum (Bronstein & Cummings, 2001). From the putamen, the circuit continues to the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr), then to the thalamus, and finally continuing on to the frontal cortex (Lichter, 2001; Lichter & Cummings, 2001). The secondary pathway arises from the same areas of the cortex. This indirect pathway, however, proceeds from the putamen (in the striatum) to the globus pallidus externa and the STN before advancing to the GPi and the SNr, onto the thalamus, and then, like the direct pathway, concludes in the frontal cortex (Weingarten & Cummings, 2001; Lichter, 2001).

The balance between the direct and indirect pathways is critical to understanding motor function and dysfunction; the direct pathway is thought to facilitate cortical activity while the indirect pathway inhibits it (Lichter, 2001). According to this model,

as outlined by Lichter (2001), in Parkinson's Disease, the STN is overactive in the indirect pathway which, in turn, leads to increased GPi activation, increased thalamic inhibition, and finally insufficient excitatory influence on the cortex in areas needing activation for proper motor functioning (Lichter, 2001; Breit et al., 2004). The use of STN DBS is congruent with this model. According to this model, inhibiting the STN with high frequency DBS reduces the overactivity of the STN (Romito et al., 2003). This, in turn, allows for improved balance between the inputs of the direct and indirect pathways, resulting in an appropriately sufficient level of thalamic activation. The diagram on the following page outlines the steps noted above as part of the dominant model of select pathways within the motor circuit. The diagram is adapted from Lichter (2001) and has been simplified to highlight the closed loop connections of interest to this research study. In reality, it is believed that there are also open loops, connections with other non-basal ganglia brain areas (such as parietal lobes, temporal lobes, and hippocampus), and several other interconnections between basal ganglia (Weingarten & Cummings, 2001).

**Figure 1: Motor Circuitry in the Human Primate**

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**Based on Lichter (2001). Black arrows represent excitatory connections. Dashed arrows represent inhibitory connections. The subthalamic nucleus, highlighted in grey, represents the STN DBS stimulation site.**

Many clinical studies have found support for the use of STN DBS to treat motor symptoms in Parkinson's Disease. Evidence for clinical improvement following STN DBS is derived from the following studies: Obeso et al. (2001) found that patients with PD that underwent STN DBS showed a mean motor score improvement of 43% on the Unified Parkinson's Disease Rating Scale (UPDRS) and, moreover, lower rates of complications. A study by Limousin et al. (1998) found that one year following STN DBS surgery, PD patients showed significant improvement. Specifically, they had motor score improvement in the range of 10 to 60%. In another study, Katayama and colleagues (2001) also found significant improvement in motor score symptoms (UPDRS motor scores improved by 27%) in PD patients who underwent STN DBS. Kumar et al. (1998) echoed the conclusion of significant motor improvement in PD patients who had STN DBS, with UPDRS motor score increase of 41% post-operatively.

Although these studies examined post-operative changes in motor functioning, the researchers either incompletely examined or conducted no evaluation of post-operative changes in cognitive functions, such as memory, executive functioning, or visuospatial abilities (Obeso et al., 2001; Katayama et al., 2001). Cognitive functioning, however, is important to evaluate in order to ascertain whether the surgery affects patients' mental status. If, for example, surgery improves motor symptoms but harms cognitive functioning, this knowledge would be important when weighing treatment options and evaluating whether the potential motor benefits outweigh the potential costs in the cognitive domain. Further, a negative change in cognition could have a negative impact on quality of life, which could outweigh potential motor benefits. However, neither Obeso et al. (2001), Katayama et al. (2001), nor Kumar et al. (1998) studied cognitive

functioning. Though Limousin et al. (1998) examined cognition, mainly frontal lobe functioning, the evaluation was not a comprehensive one and did not appear to include some important areas of cognitive functioning, such as verbal memory. Also, the Limousin et al. (1998) study did not use a control group.

In general, cognitive functioning can be assessed by administering standardized clinical neuropsychological tests. Ideally, this battery of tests comprises a range of measures from a variety of cognitive domains, including memory, mental speed, attention, working memory, executive functioning, verbal fluency, and motor functioning.

In contrast to the studies noted above which primarily focused on motor functioning, some recent studies have placed more focus on studying the potential cognitive impact of STN DBS in PD patients. The following pages outline several cognitive domains and associated research findings (see Table 1).

**Table 1: Findings of Previous Studies Examining Cognitive Outcome Following Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease**

| Cognitive Domain | Reports of Improvement | Reports of Decline |
|---|---|---|
| Learning and Memory<br><br>*Definition:*<br><br>Learning is generally defined as the process of acquiring knowledge and skills.<br><br>Memory tasks involve the consolidation, retention, retrieval, and recognition of presented information.<br><br>Tests used to assess learning and memory include:<br>• Rey Auditory Verbal Learning Test<br>• Benton Visual Retention Test | | • Alegret et al. (2001): Significant decline in performance (RAVLT)<br>• Morrison et al. (2004): Reduction in verbal memory (delayed recall)<br>• Saint-Cyr et al. (2000): Significant decline in encoding of visuospatial information (BEM) at 3-6 months post-op. Some improvement at 9-12 months post-op.<br>• Saint-Cyr et al. (2000): 3-6 months post-op, significant reduction in verbal memory (delayed recall on the CVLT), though some improvement at 9-12 months post-op.<br>• Dujardin et al. (2001): 3 months post-op: significant decline in performance on delayed free recall (Grober & Buschke delayed free recall)<br>• Trepanier et al. (2000): 3-6 months post-op: significantly worsened performance on verbal learning tasks (CVLT delayed free recall and CVLT delayed cued recall) |
| | **Conclusion**: These research findings suggest that STN DBS is associated with decline in verbal learning and memory. No research articles reviewed note improvement in learning and memory following STN DBS for advanced Parkinson's Disease. | |

| Cognitive Domain | Reports of Improvement | Reports of Decline |
|---|---|---|
| Mental Speed<br><br>*Definition:*<br><br>Mental speed is generally defined as the rate at which ("how fast") a person is able to process information.<br><br>Tests to assess mental speed include:<br>• Stroop Word Reading<br>• Stroop Color Naming<br>• Trail Making Test A<br>• Symbol Digit Modalities Test | • Dujardin et al. (2001): A trend for improved psychomotor speed<br>• Pillon et al. (2000): A significant improvement in information processing speed | • Alegret et al. (2001): Statistically significant worsened performance (Stroop color test)<br>• Saint-Cyr et al. (2000): 3-6 months post-surgery, significant decrease in mental processing speed. Decline still seen 6-9 months later at final testing sessions. |
| | **Conclusion**: Based on these research studies, no general consensus exists as to whether STN DBS for advanced Parkinson's Disease is associated with improvement or deterioration in mental processing speed. | |

| Cognitive Domain | Reports of Improvement | Reports of Decline |
|---|---|---|
| Attention<br><br>*Definition:*<br><br>The ability to concentrate selectively on particular stimuli, while ignoring other stimuli.<br><br>Tests to assess attention include:<br>• Corsi Blocks (Forward)<br>• WAIS-R Digit Span (Forward) | • Jahanshahi et al. (2000): Improvement in attention | |
| | **Conclusion**: There is sparse support that STN DBS is associated with improvement in attention. No research studies examined offered support that STN DBS was linked to improvement in attention. | |

| Cognitive Domain | Reports of Improvement | Reports of Decline |
|---|---|---|
| Working Memory<br><br>*Definition:*<br><br>Working memory involves the temporary mental storage and management of information in order to do certain tasks, such as reasoning and learning.<br><br>Tests to assess working memory include:<br>include:<br>• Corsi Blocks (Backward)<br>• WAIS-R Digit Span (Backward) | • Jahanshahi et al. (2000): Improved working memory<br>• Pillon et al. (2000): Significant improvement in spatial working memory | • Hershey et al. (2004): Reduced working memory (on a spatial delayed response task involving a high memory load)<br>• Saint-Cyr et al. (2000): 3-6 months post-op: significantly worsened performance on working memory tasks (declines still seen 9-12 months after surgery)<br>• Trepanier et al. (2000): 3-6 months post-op: trend toward a significant decline (Digit Span Backward) |
| | **Conclusion**: Based on these research studies, there appears to be a lack of consensus as to whether STN stimulation helps or hinders working memory in patients with advanced Parkinson's Disease. | |

| Cognitive Domain | Reports of Improvement | Reports of Decline |
|---|---|---|
| Executive Functioning<br><br>*Definition:*<br><br>Executive functioning is generally defined as related higher-order cognitive processes, including planning, decision making, and mental flexibility (Spreen & Strauss, 1991).<br><br>Tests to assess executive functioning include:<br><br>• Trail Making Test B<br>• Stroop Color/Word<br>• Tower of Toronto<br>• Conditional Associative Learning Task*<br>• Subject Ordered Pointing*<br>• Delayed Responding*<br>• Delayed Alternation*<br><br>* experimental measures | • Alegret et al. (2001): Significant improvement (Trail Making Test B)<br><br>• Daniele at al. (2003): Significant improvement on an executive functioning task (a modified Wisconsin card sorting test)<br><br>• Pillon et al. (2000): Statistically significant improvement on stimulation (Trail Making Test B, Stroop colour and word tasks)<br><br>• Witt et al. (2004): Improved mental flexibility (Random Number Generator Task) | • Dujardin et al. (2001): Slightly impaired performance on executive functioning tasks (the only actually significantly worse was the Stroop Test, Interference trial)<br><br>• Hershey et al. (2004): Reduced performance on response inhibition task (Go-No-Go task)<br><br>• Jahanshahi et al. (2000): Worsened performance on a task of response inhibition (Interference trial of the Stroop Test)<br><br>• Saint-Cyr et al. (2000): Significant deterioration in set-shifting performance<br><br>• Trepanier et al. (2000): Diminished performance on a set-shifting task (Trail Making Test B)<br><br>• Witt et al. (2004): Diminished performance on response inhibition task (Interference trial of the Stroop Test) |
| | **Conclusion**: There is a lack of consensus as to whether or not STN stimulation is associated with improvement or decline in executive functioning in people with advanced Parkinson's Disease. | |

| Cognitive Domain | Reports of Improvement | Reports of Decline |
|---|---|---|
| Expressive Language<br><br>*Definition:*<br><br>Expressive language is commonly assessed by examining verbal fluency, which is the ease and quantity of production of words that begin with a certain letter of the alphabet (phonemic fluency) or which belong to a certain category (semantic fluency).<br><br>Tests to assess expressive language include:<br><br>• Controlled Oral Word Association Test (COWA) | | • Alegret et al. (2001): Significant decline in both phonemic and semantic verbal fluency<br>• Daniele et al. (2003): Significant decline in phonemic verbal fluency (at 3, 6, and 12 months post-op)<br>• Dujardin et al. (2001): A trend toward a significant decline in semantic verbal fluency<br>• Funkiewiez et al. (2004): Significant worsening in semantic verbal fluency and in total verbal fluency (semantic fluency combined with phonemic fluency)<br>• Gironell et al. (2003): Significant decline in semantic verbal fluency<br>• Pillon et al. (2000): Mild deficit in semantic verbal fluency<br>• Saint-Cyr et al. (2000): Significantly worsened phonemic verbal fluency<br>• Trepanier et al. (2000): Significant decline in phonemic verbal fluency |
| | **Conclusion**: The research studies unequivocally suggest that STN stimulation is associated with a decline in expressive language in patients with advanced Parkinson's Disease. | |

| Cognitive Domain | Reports of Improvement | Reports of Decline |
|---|---|---|
| Visuospatial Functioning<br><br>*Definition:*<br><br>Visuospatial functioning is generally defined as the type of processing that focuses on the positioning of visual stimuli in relation to one another, as well as the positioning of different parts of the same object or stimulus.<br><br>Tests to assess visuospatial functioning include:<br><br>• Hooper Visual Organization Test (HVOT)<br>• Judgment of Line Orientation (JLO) | | • Alegret et al. (2001): Significant decline in visuospatial functioning (Line Orientation Test) |
| | **Conclusion**: There is sparse support that STN DBS is associated with decline in visuospatial functioning. No research studies examined offered support that STN DBS was linked to improvement in visuospatial functioning. | |

As noted earlier in this review, much research has been conducted examining the impact of STN DBS on motor functioning. Although the prevailing clinical opinion supported by research findings is that STN DBS improves motor symptoms, the effects of STN DBS on specific cognitive functions in patients with Parkinson's Disease is much less clear. To date, few studies have been published examining the impact of STN DBS on cognition, generally or specifically. As noted in Table 1, although some rudimentary consensus appears to be forming for a number of cognitive domains, no firm conclusions have been reached. As well, in some cognitive domains, study results appear to conflict with each other.

By way of summary review, in the first cognitive domain of interest, **verbal learning and memory**, research findings suggest that STN stimulation is associated with decline (Alegret et al., 2001; Morrison et al., 2004; Saint-Cyr et al., 2000; Dujardin et al., 2001; Trepanier et al., 2000). No research articles have noted improvement in verbal learning and memory following STN DBS in Parkinson's Disease. The next domain of interest is **mental speed**. In this domain, some studies purport finding declines in mental speed (Pillon et al., 2000; Dujardin et al., 2001) while others suggest improvements (Saint-Cyr et al., 2000; Alegret et al., 2001). Thus, no general consensus seems to exist as to whether STN stimulation is associated with improvement or deterioration in mental processing speed. In the **attention** domain, one study reports improvement (Jahanshahi et al., 2000) and no studies report decline. In the domain of **working memory**, there are equivocal findings, as some studies report improvement (Jahanshahi et al., 2000; Pillon et al., 2000) while other studies report deterioration (Saint-Cyr et al., 2000; Hershey et al., 2004; Trepanier et al., 2000). In terms of performance on **executive functioning** tasks,

some support exists for STN DBS being associated with improvement (Alegret et al., 2001; Daniele et al., 2003; Pillon et al., 2000; Witt et al., 2004) while other studies show decline (Dujardin et al., 2001; Hershey et al., 2004; Jahanshahi et al., 2000; Saint-Cyr et al., 2000; Trepanier et al., 2000; Witt et al., 2004). Thus, for executive functions, no strong conclusion regarding the impact of STN DBS can be made. In the domain of **expressive language**, all studies examined report declines in performance following STN DBS (Alegret et al., 2001; Daniele et al., 2003; Dujardin et al., 2001; Funkiewiez et al., 2004; Gironell et al., 2003; Pillon et al., 2000; Saint-Cyr et al., 2000; Trepanier et al., 2000). Lastly, in terms of **visuospatial functioning**, negligible research exists. No studies were found to suggest improvement in this domain, whereas only one study noted decline in performance on visuospatial functioning tasks (Alegret et al., 2001).

In conclusion, given that the jury is still out regarding the effect of STN DBS upon various cognitive functions, further research is needed. Moreover, many of the studies noted above have a number of drawbacks. Although the vast majority of these studies utilized a pre-post design for comparison purposes, most of them did not use matched control groups, which would have managed possible practice effects (Alegret et al., 2001; Witt et al., 2004; Ardouin et al., 1999; Jahanshahi et al., 2000; Funkiewiez et al., 2004; Pillon et al., 2000; Saint-Cyr et al., 2000; Limousin et al., 1998). Most likely, research designs deploying controls would have produced more accurate estimates of the impact of STN DBS surgery on cognitive functioning for PD patients. A review article examining studies of cognitive functioning in PD patients has echoed the sentiment that neurobehavioral research in this area has yet to sufficiently tackle the issue of "outcome relative to appropriate control groups" (Fields & Troster, 2000, p. 268). Moreover, and

quite crucially, by not utilizing control groups, there is a significant risk for underestimating the effect that the surgery has on cognitive functioning (and may not be detecting potential dysfunction). For example, if performance during post-surgical assessments is expected to reflect practice effects (and, thus, enhanced performance on some measures) and expected improvements are not seen post-surgically, perhaps the surgery is actually exerting a negative effect on cognitive functioning. Thus, a finding of "no cognitive change" post-operatively may actually more accurately be interpreted as a decline in cognitive functioning. As well, those studies without a control group may actually be underestimating the magnitude and breadth of cognitive decline. Also, none of these studies have seemed to account for disease progression, even those that involve long-term follow-up occurring a year or more after surgery.

The quality of life experienced by PD patients pre- and post-treatment is another area of research interest. Quality of life is important to assess because medical treatment for PD should not only improve motor symptoms, but also strive to improve the lives that patients lead. A drawback of many studies thus far examining the effect of STN DBS is that few, if any, of them incorporated measures to assess the patients' reported quality of life. Interestingly, improved motor functioning does not necessarily translate into improved quality of life for patients. If, for example, a patient has improved motor ability but deteriorated cognitive functioning after surgery, then the patient may not experience increased quality of life and lifestyle (regardless of improved motor functioning). Quality of life evaluations also provide an opportunity for patients to voice their own views of their health and for health care professionals to see whether patients believe their lives have gotten better after surgery (Behari, Srivastava, & Pandey, 2005).

Amongst the aforementioned studies, only a few of them have measured post-operative mood changes in PD patients. This is a grave oversight because the research literature suggests that some mood states, such as depression, negatively impact executive functioning and memory in PD patients (Norman, Troster, Fields, & Brooks, 2002). Thus, changes in mood from pre- to post-surgery may influence changes in cognitive performance. As well, studies failing to concurrently study motor improvement, cognitive functioning, mood, and quality of life of their patients miss a valuable opportunity to examine relationships among these variables. For example, it is not inconceivable that a patient's post-operative mood change may be directly related to their quality of life.

In summary, there have been many limitations of past research examining motor and cognitive functions, as well as quality of life for patients following STN DBS. Few previous studies have used matched control groups. Most have used a narrow range of measures to examine cognitive functioning, and few have concurrently examined motor and cognitive functioning. Moreover, quality of life and mood measures have largely been ignored and need to be further explored. Clearly, there may be benefit to being rather inclusive and broad in terms of assessment measures utilized. As well, the use of a control group in clinical trials seems well warranted, given the associated potential for improved accuracy of test result interpretation.

## STN DBS Influence on Cognition

In trying to understand the impact DBS may have on cognition, consideration of frontal-striatal circuitry is warranted. As mentioned earlier, research has been conducted to examine the association between neuronal circuitry (specifically frontal-subcortical circuitry) and motor functioning in Parkinson's Disease. Similarly, examination of the neuronal circuitry aids in understanding how STN DBS may impact cognitive functioning in Parkinson's Disease. All five frontal-striatal circuits have an indirect pathway that includes the STN. Although Lichter and Cummings (2001) purport that each circuit operates in a fully segregated way, this view may not be accurate (Percheron & Filion, 1991; Woods, Fields, & Troster, 2002). Echoing this point, Kolomiets et al. (2001) note that information proceeding from the motor cortex to the striatum, for example, may not be totally segregated once it is in the subthalamic nucleus. As well, since the STN is quite compact and the frontal-striatal circuits are parallel and situated adjacent to one another, it seems possible that electrical stimulation to one circuit may impact nearby circuits. As noted by Saint-Cyr et al. (2000) in discussing stimulation to improve motor functioning, "it may prove impossible for the current to avoid impinging on sectors that are associated with cognitive functions" (p. 2101). One circuit adjacent to the motor circuit, the dorsolateral prefrontal cortex (DLPC) circuit, is believed to play a major role in cognition, notably in executive functioning tasks, such as planning strategies, mental flexibility, initiating and planning behaviour, and organizing information (Tekin & Cummings, 2002; Lichter & Cummings, 2001). Like all frontal-striatal circuits, the DLPC circuit has two pathways: a direct pathway and an indirect pathway. Its direct pathway involves a direct connection between the striatum (more

specifically, the caudate's dorsolateral region) and the globus pallidus interna/substantia nigra pars reticulata complex and then onward to the thalamus and cortex. The indirect pathway proceeds from the striatum (the dorsolateral region of the caudate nucleus), to the globus pallidus externa, then to the STN, then to the globus pallidus interna/substantia nigra pars reticulata complex, then to the thalamus and, finally, completing the circuit via projections from the thalamus to the cortex (Lichter & Cummings, 2001). By stimulating the STN to improve motor symptoms, it is plausible that activity may be upset in nearby areas of the STN associated with cognition, such as executive functioning. In fact, as noted in Table 1, evidence has been accumulating that suggests STN DBS interferes with executive functioning (Dujardin et al., 2001; Trepanier et al., 2000; Witt et al., 2004; Jahanshahi et al., 2000; Hershey et al., 2004). As well, research suggests that stimulation of the STN can lead to "further deterioration of processes normally though to be dependent on the functional integrity of these circuits" (Trepanier et al., 2000, p. 341). Clearly, given past research noting the potential impact that STN DBS may have on cognition, further research is warranted.

In summary, Parkinson's Disease is a progressive neurological disorder for which medication is usually the initial treatment of choice. For individuals in the advanced stages of the disease, however, pharmacotherapy is often limited or ineffective and causes debilitating side effects. To counter such limitations, there is renewed clinical interest in surgical intervention for advanced PD. One type of surgical intervention is the use of STN DBS, which has been consistently shown to improve motor functioning. Models have been applied to explain motor dysfunction in PD and how STN DBS improves motor functioning by stimulating the motor circuitry at the STN site. As it has been

reported that the neural circuitry may not be fully segregated, however, it may be possible that stimulating circuitry involved in motor functioning may also affect adjacent brain circuitry involved in other areas of functioning, such as cognition. Although research finds that STN DBS has a positive impact on motor functioning, more research is needed on the impact of STN DBS on cognition, and other areas of psychosocial functioning, such as mood and quality of life.

# THE PRESENT STUDY

## Purpose of the Study

The present study examines the impact of STN DBS on the motor functioning, cognitive functioning, mood states, and quality of life in patients with Parkinson's Disease, while controlling for the impact of retesting by using a wait-list control group.

## Specific Hypotheses

**Hypothesis 1**: Patients undergoing bilateral STN DBS will show a significant improvement in motor functioning test scores post-surgically.

**Hypothesis 2**: Patients who undergo bilateral STN DBS will show declines in test performance in the domain of executive functioning and verbal fluency, post-surgically.

**Hypothesis 3**: Patients undergoing bilateral STN DBS will report improved quality of life, particularly in the areas having to do with physical functioning, perceived health, and social functioning.

## Context for the Present Study

The present study is part of a larger investigation of deep brain stimulation being conducted at the Vancouver General Hospital, within the Surgical Centre for Movement Disorders (SCMD). The SCMD receives referral of patients with Parkinson's Disease from throughout the province as it is the only site in British Columbia that offers deep brain stimulation surgery for PD patients.

At the SCMD, there is usually an unavoidable gap of several months between pre-operative neurosurgical evaluations, when patients' suitability for STN DBS is evaluated, and their surgery dates. Patients can be enrolled in the present study at the time of their initial evaluation and the pre-surgical neuropsychological assessment would occur shortly thereafter. Although the neuropsychological assessment is quite extensive and comprehensive, it is easily completed in a few hours.

# METHOD

## Overview

In British Columbia, patients who are referred to receive deep brain stimulation are seen at the Surgical Centre for Movement Disorders (SCMD) at the Vancouver General Hospital. At this surgical centre, patient suitability for DBS treatment is determined. Patients deemed eligible for the surgery are placed on a surgical waitlist. Patients scheduled for surgery were approached and asked to participate in the present study. Consenting patients were placed randomly into either the Surgical Group or the Control Group.

Neuropsychological assessments were conducted according to two different schedules. Half of the patients enrolled in the study, those in the Control Group, were tested two months prior to DBS surgery and again during the week before surgery. During these two pre-surgical assessments, patients were on medications. The other half of the patients in the present study, those in the Surgical Group, was tested during the week before surgery (while on medication) and then two months post-surgically (while on medication and with their deep brain stimulation activated). Thus, as a consequence of this research design, this repeated measures study included a waitlist control group in order to evaluate practice effects and disease progression. As noted by Fields and Troster (2000), using a control group of patients with Parkinson's Disease would "be appropriate in studies of long-term outcomes, because it is necessary to account for the neurobehavioral effects of disease progression" (p. 284). However, although a surgical

waitlist is ideal as a control group from a research-design standpoint, it can be difficult to implement for ethical reasons (Fields & Troster, 2000). For example, if a patient with Parkinson's Disease needs surgery and surgical time is available, it would be unethical to withhold surgery for the sake of methodological rigor. Given that the waitlists for surgery at the Surgical Centre for Movement Disorders (SCMD) are often several months in duration, fortunately no patients participating in the present study had their surgery delayed for research purposes.

## Patient Selection

Ethical approval for this study was received from the research ethics boards at the Vancouver General Hospital, the University of British Columbia, and Simon Fraser University. The type of DBS surgery offered to PD patients depends on their symptom constellation. Typically, patients experiencing tremor only are offered thalamic DBS. Patients with outstanding dyskinesia (e.g., uncontrolled, involuntary movements), but with little slowness of movement (e.g., bradykinesia) are typically offered pallidal DBS. Finally, STN DBS is typically offered to patients with predominant bradykinesia.

Only patients scheduled to receive STN DBS were asked to participate in the present study and, upon their consent, were placed in one of the two study groups. Recruitment took place at the Surgical Centre for Movement Disorders between May 2001 and December 2005. Occasionally, if patients resided at a great distance from Vancouver and were unable to attend two neuropsychological assessments before surgery, they were placed (non-randomly) in the Surgical Group and this was recorded in the study files. In turn, there was a greater proportion of patients from rural areas in the

Surgical Group, relative to the Control Group, however not at a statistically significant level (as determined via chi-square testing).

Patients considered for STN DBS had been clinically diagnosed with Parkinson's Disease and experienced predominant slowness of movement (bradykinesia). Given the speech requirements of the neurobehavioral assessments, patients unable to speak English fluently were to be excluded from the study. However, over the course of the study, no patients were excluded due to this criterion as all were able to speak English. In total, 44 consecutive STN DBS patients were asked to participate in the study. All 44 patients agreed to study participation and, for the most part, were randomly assigned to either the Control Group or the Surgical Group. However, not all 44 patients completed the two assessments. Nine patients failed to complete the full research protocol for various reasons: One patient died prior to the second assessment being completed. Another was excluded due to participation in another study. Two patients were unable to complete a second assessment within the study's time frame. One experienced surgical complications and declined a second assessment. Two had their surgeries cancelled. One declined a second assessment (due to experiencing behavioral disturbances after surgery and the necessity of moving into a care home) and one patient was not followed. Data collected from these nine patients were not included in any of the data analyses outlined in this study. Thus, at final tally, the study comprised 35 participants, with 16 subjects in the Control Group and 19 subjects in the Surgical Group. Table 2 provides information on these 35 subjects regarding various clinical and demographic variables. T-tests and chi-square analyses were conducted on these variables to determine if significant differences existed between the two study groups.

**Table 2: Comparison of the Control and Surgical Groups on a Variety of Demographic and Clinical Variables**

| VARIABLE | CONTROL GROUP | SURGICAL GROUP |
|---|---|---|
| Gender | Male = 13, Female = 3 | Male = 14, Female = 5 |
| Mean Age | 60.19<br>(SD = 11.46) | 60.89<br>(SD = 9.68) |
| Race | White = 11, Other = 5 | White = 16, Other = 3 |
| Psychiatric History (%) | 4 (25%) | 5 (26%) |
| Residence | Rural = 0 Urban = 16 | Rural = 3 Urban = 16 |
| Marital Status | Married/CL = 14 (88%)<br>Separated/Divorced = 1 (6%)<br>Widowed = 1 (6%) | Married/CL = 13 (68%)<br>Separated/Divorced = 4 (21%)<br>Single = 2 (11%) |
| Mean Years of Education | 14.69<br>(SD = 3.79) | 13.84<br>(SD = 2.93) |
| Handedness | Right = 14, Left = 2 | Right = 18, Left = 1 |
| Smoking Status | Never Smoked = 9 (56%)<br>Currently Smokes = 2 (13%)<br>Quit = 5 (31%) | Never Smoked = 10 (53%)<br>Currently Smokes = 0 (0%)<br>Quit = 9 (47 %) |
| Mean Duration of PD in Years | 11.56<br>(SD=4.1) | 12.79<br>(SD = 5.44) |
| Mean Age of PD Diagnosis In Years | 48.63<br>(SD=11.30) | 48.11<br>(SD = 8.76) |
| Non-English First Language | 5 (31%) | 3 (16%) |
| Mean Number of Errors Made on the NAART | 25.0<br>(SD=11.66) | 22.9<br>(SD=10.26) |
| Mean DRS Total Score* | 129.13<br>(SD=8.33) | 136.26<br>(SD = 5.51) |
| Number Impaired on the DRS | 3 (18.8%) | 1 (5.3%) |
| Mean Number of Days Between Baseline and Follow-up Assessments | 83.25<br>(SD = 51.73) | 114.37<br>(SD= 80.49) |
| Mean SF-36 Total Score at Baseline Assessment | 362.82<br>(SD = 127.21) | 390.39<br>(SD = 119.83) |
| Mean POMS Total Score at Baseline Assessment | 47.13<br>(SD = 43.25) | 37.21<br>(SD = 32.91) |

Note: SD = Standard Deviation; Rural = Population under 2500, Urban = Population over 2500, * refers to probability less than 0.05 via t-test analysis; PD = Parkinson's Disease; NAART = North American Adult Reading Test; DRS = Dementia Rating Scale (A total score of less than 123/144 on the DRS is suggestive of impairment); SF-36 = Medical Outcomes Survey – Short Form; POMS = Profile of Mood States.

## Surgical Procedure

Typically, patients were admitted to the Vancouver General Hospital the day before their surgery. All anti-parkinsonian medications taken by the patient were stopped the evening before the surgery. Just prior to the surgery's commencement, the patient was fitted with a stereotactic head frame to prevent head movement during the surgery. An MRI was completed the morning of the surgery in order to accurately determine the location of the target site, the STN. Once the STN location was determined, the surgery began. In the first phase of the surgery, while the patient was alert but under local anesthetic, the neurosurgeon drilled a small hole through the patient's skull in order to insert the electrodes. Test electrodes were slowly inserted into the patient's brain and directed toward the STN site. Use of cellular recordings of neural signals and stimulation aided in determining when the STN was reached. Once the target site had been reached, electrodes designed for more permanent long-term stimulation were inserted and secured, in place of the temporary test electrodes.

During the second phase of the surgery, when the patient was generally anesthetized, a pulse generator (the "stimulator") was implanted below the patient's clavicle. Then, a wire was directed subcutaneously from the patient's clavicle, extending up the neck and behind the ear, to the electrodes in the patient's brain. Typically, the patient left the hospital the next day and returned approximately 6 to 8 weeks post-surgery for activation of the DBS system. This approximate two month delay allowed for the patient's recuperation and for any post-surgical swelling to diminish. As the DBS system was activated and the stimulation parameters were adjusted during several visits to the neurosurgeon, the patient's anti-parkinsonian medications taken were also reduced.

## Motor Testing

Patients in the study underwent two tests during the neuropsychological testing that were specific to motor functioning. These tests were the Grooved Pegboard and the MNO Test. The Grooved Pegboard measures how quickly pegs can be picked up and placed into a pegboard. The MNO Test involves repeatedly writing the letter combination of "mno" in order to detect changes in writing height, as well as the presence of perseverations.

## Neurobehavioral Assessments

As described earlier, many studies examining the cognitive impact of STN DBS surgery have limitations. These limitations include failing to incorporate a control group into the study design (so as to quantify practice effects), utilizing a narrow range of measures to assess cognitive functioning, and failing to incorporate items that assess mood or quality of life.

In the present study, each participant underwent two neurobehavioral assessments. Each assessment took approximately 3 to 4 hours to complete. The time duration varied depending on symptom severity and time needed for breaks. Each assessment was undertaken when participants were in their optimal motor state (often referred to as "on" periods). Each participant in the Control Group completed two assessments with no neurosurgical intervention between assessments, which were approximately 8 weeks apart. This time frame was achieved by having each Control Group participant evaluated two months in advance of surgery and then, once again, in the week before to surgery. The Surgical Group was assessed in the week before surgery and then, once again, two months following surgery. Neuropsychological measures that

can detect cognitive changes in PD patients were selected. Alternate forms of tests were incorporated into the research design, whenever possible, in order to minimize practice effects. The tests comprising the neuropsychological battery were selected to tap a wide range of cognitive functions, as well as measure mood and quality of life. All tests were given twice to each subject with the exception of the North American Adult Reading Test and the Mattis Dementia Rating Scale, which were used only in the first assessment as measures of premorbid functioning.

## Test Selection

In each assessment, a variety of tests were utilized from a range of psychological domains including mood, quality of life, mental speed, attention, working memory, executive functioning, language, visuospatial functioning, and motor functioning. The Appendix identifies the tests used and summarizes the cognitive and psychological domains which they tap.

In the **mood** and **quality of life (QoL)** domains, the tests used were the Profile of Mood States (POMS), the Medical Outcomes Survey Short Form (SF-36), and the Affect/Arousal Scale. The POMS is a 65-item questionnaire in which participants are provided with adjectives describing affective states and asked how frequently, over the past week, they have experienced such emotions. In short, the POMS evaluates participants' mood (Spreen & Strauss, 1991; Curran, Andrykowski, & Studts, 1995). The SF-36 is a questionnaire that assesses a participant's perspective about his or her health and well-being in several areas including social and physical functioning (Ware, Snow, Kosinski, & Gandek, 1993; Ware & Sherbourne, 1992). The Affect/Arousal Scale assesses the participant's current mood and consists of 13 questions (Brown, Marsden,

Quinn, & Wyke, 1984). Each question reflects a continuum, which has opposite feelings as anchor-points. For each question, the participant is required to make a vertical line at the point on the continuum that denotes how he or she feels (Brown et al., 1984).

In the domain of **learning and memory**, the tests utilized were the Rey Auditory Verbal Learning Test and the Benton Visual Retention Test. The Rey Auditory Verbal Learning Test is a list learning task designed to assess verbal memory and ability to learn lists of words (Spreen & Strauss, 1991; Lezak, 1995). In the Benton Visual Retention Test, participants are shown a series of designs. After a brief presentation of each design, the participant is immediately asked to draw as much of the design that he or she can remember. This test "assess(es) visual memory, visual perception, and visuoconstructive ability" (Spreen & Strauss, 1991, p. 119).

In the domain of **mental speed**, the assessment measures used were the Trail Making Test A, Stroop Test (colors), Stroop Test (words), and Symbol Digit Modalities Test (oral administration). The Trail Making Test A is a measure of mental processing speed, visuospatial sequencing, and attention (Spreen & Strauss, 1991). The Stroop Test (colors) is a timed color-naming task (Lezak, 1995). The Stroop Test (words) is a timed word-reading task (Lezak, 1995). The Symbol Digit Modalities Test is a speed test that measures components of visual attention, including scanning and tracking of visual information (Smith, 1995; Uchiyama et al., 1994; Lezak, 1995).

In the domain of **attention**, the tests utilized were Corsi Blocks (forward) and Digit Span (forward) from the Wechsler Adult Intelligence Scale – Revised (WAIS-R). Corsi Blocks involves the examiner touching blocks on a board, immediately followed by the examinee being required to touch the blocks in the same sequence. In essence, this is

a test of visuospatial attention and memory (Sivan, 1992; Lezak, 1995). The Digit Span (forward) test assesses attention span for verbally presented items (Wechsler, 1981).

In the domain of **working memory**, the tests used were Corsi Blocks (backward) and Digit Span (backward) from the WAIS-R. Corsi Blocks (backward) is a test involving visuospatial working memory. Digit Span (backward) is a task of verbal working memory (Wechsler, 1981).

In the domain of **executive functioning**, assessment measures used were the Stroop Test (color-word), the Trail Making Test B, and the Tower of Toronto Test. The Stroop Test evaluates the ability to shift cognitive sets and to inhibit a dominant response and provide an unusual response instead (Spreen & Strauss, 1991). The Trail Making Test B involves attention, ability to switch cognitive sets (switching repeatedly between numbers and letters), mental sequencing, and visuospatial searching skills (Spreen & Strauss, 1991; Lezak, 1995). The Tower of Toronto Test measures procedural learning and involves stacking wooden disks in order to achieve a particular design (Saint-Cyr, Taylor, & Lang, 1988; Lezak, 1995). Some experimental measures of executive functioning were also used in the battery. The tests used were Delayed Responding (DR), Delayed Alternation (DA), Conditional Associative Learning Task (CALT), and the Subject Ordered Pointing Test (SOP). The Delayed Responding Test assesses mediation ability, which has been noted as the ability to use data from the immediate past to make decisions in the present (Oscar-Berman, McNamara, & Freedman, 1991). The Delayed Alternation Test is a delayed-reaction task involving multiple trials that require the examinee to alternate responses, as the correct response from the immediately preceding trial becomes the incorrect response in the next trial, and vice-versa (Oscar-

Berman et al., 1991). The Conditional Associative Learning Task is a task that involves the "learning of arbitrary associations between a set of stimuli and a set of responses" (Petrides, 1985, p. 601). The Subject Ordered Pointing Test is a test that involves being presented with a set of pages, each page displaying the same set of items (e.g., the same words, pictures, or designs), but arranged in a different order on each page. For each page, the subject is required to choose an item, while trying to avoid choosing any item already chosen on any previous page in the set of pages. In essence, this test requires "the organization of a sequence of pointing responses" (Petrides & Milner, 1982, p. 249).

In the domain specifically focusing on **expressive language**, the Controlled Oral Word Association Test was employed. This time-limited test assesses ability to orally produce words that start with a particular letter of the alphabet, without prior notice (Spreen & Strauss, 1991).

In the domain of **visuospatial functioning**, the tests used were the Hooper Visual Organization Test (HVOT) and the Judgment of Line Orientation Test. The HVOT requires the examinee to mentally reorganize pieces of pictures that have been fragmented (Spreen & Strauss, 1991). The task for the examinee is to determine what common objects the pieces represent when organized correctly. The Judgment of Line Orientation Test examines one's capacity to determine relationships between line segments and match them according to their angular orientations (Lezak, 1995).

In the domain of **motor functioning**, as noted previously, assessment measures used were the Grooved Pegboard and the MNO. The Grooved Pegboard, a test of motor dexterity and coordination, assesses the speed at which an examinee can complete a motor task of placing pegs into a pegboard (Spreen & Strauss, 1991; Lezak, 1995). The

MNO Test requires the examinee to repeatedly write "*mno*" in a continuous row across a sheet of paper. This test assesses the examinee's writing ability and evaluates for the presence of perservations, as well as changes in writing size.

The Appendix outlines each test according to domain and provides descriptions of the data collected.

# RESULTS

## Statistical Analysis

Given that each research participant was assessed twice (e.g., baseline and follow-up assessments) using the same tests, data for each variable was analyzed using a repeated measures analysis of variance statistical procedure. Assessment Time (Baseline, Follow-up) was the within-subject factor while Study Group (Control Group, Surgical Group) was the between-subject factor. For both study groups, a time lapse of approximately two months occurred between baseline and follow-up assessments. The test scores of the Surgical Group pre and post surgery were compared with the test scores of the Control Group, who had no surgical intervention between assessments. In the data analysis, the review of Study Group by Assessment Time interaction was particularly important as this term would show the impact of the surgical intervention on the dependent variables of interest. Estimates of effect size are also provided, in terms of partial eta squared ($\eta_p^2$) values. A partial eta squared value denotes the percentage of variance accredited to a particular effect, while partialling out the influence of other factors.

Each time a significant interaction was found, follow-up simple effects analyses were conducted. Simple effects analyses were first done comparing the study groups at baseline assessment and, also, comparing the study groups at follow-up assessment. Further simple effects analyses were done for each group separately, by comparing

baseline and follow-up assessments. For all analyses, an alpha level of 0.05 was established for significance.

Table 3 following outlines how many patients in each of the two study groups were tested at the baseline and follow-up sessions. For each variable, the numbers in parentheses refer to the numbers of patients whose assessment data were part of the data analyses for each study group. Data from patients who did not complete both the baseline and follow-up testing on a particular measure were not included in the data analyses for that measure. Missing data were mainly due to fatigue experienced by patients and/or assessment time constraints.

**Table 3: Numbers of Subjects in the Control and Surgical Groups Who Were Tested on Each of the Study Variables**

| Assessment Measure | Variable | Surgical Group (n = 19) | | Control Group (n = 16) | |
|---|---|---|---|---|---|
| | | A1 | A2 | A1 | A2 |
| Premorbid Intelligence | | | | | |
| North American Adult Reading Test | Total errors made | 17(14) | n/a | 15 | n/a |
| Overall Cognitive Status | | | | | |
| Mattis Dementia Rating Scale | Overall score | 19 | n/a | 16 | n/a |
| Quality of Life | | | | | |
| Medical Outcomes Survey – Short Form (Variables listed are the survey subscales) | Physical Functioning | 19 | 17(17) | 16 | 15(15) |
| | Role-Physical | 19 | 17(17) | 16 | 15(15) |
| | Bodily Pain | 19 | 17(17) | 16 | 15(15) |
| | General Health | 19 | 17(17) | 16 | 15(15) |
| | Vitality | 19 | 17(17) | 16 | 15(15) |
| | Social Functioning | 19 | 17(17) | 16 | 15(15) |
| | Role-Emotional | 19 | 17(17) | 16 | 15(15) |
| | Mental Health | 19 | 17(17) | 16 | 15(15) |
| | Health Transition | 19 | 17(17) | 16 | 15(15) |
| Mood | | | | | |
| Profile of Mood States (Variables listed are the measure subscales) | Tension-anxiety | 19 | 17(17) | 16 | 15(15) |
| | Depression-dejection | 19 | 17(17) | 16 | 15(15) |
| | Anger-hostility | 19 | 17(17) | 16 | 15(15) |
| | Vigor-activity | 19 | 17(17) | 16 | 15(15) |
| | Fatigue-inertia | 19 | 17(17) | 16 | 15(15) |
| | Confusion-bewilderment | 19 | 17(17) | 16 | 15(15) |

| Assessment Measure | Variable | Surgical Group ( n = 19) | | Control Group ( n = 16) | |
|---|---|---|---|---|---|
| | | A1 | A2 | A1 | A2 |
| Learning and Memory | | | | | |
| Rey Auditory Verbal Learning Test | Total words recalled Trial 1 to Trial 5 | 19 | 19(19) | 16 | 16(16) |
| | List A immediate recall | 19 | 19(19) | 16 | 16(16) |
| | List A delayed recall | 19 | 19(19) | 15 | 16(15) |
| | List A delayed recognition | 19 | 19(19) | 15 | 16(15) |
| Benton Visual Retention Test | Total drawing errors made | 18 | 18(18) | 16 | 15(15) |
| Mental Speed | | | | | |
| Stroop Word Reading | Total correct answers | 17 | 18(17) | 16 | 16(16) |
| Stroop Color Naming | Total correct answers | 17 | 18(17) | 16 | 16(16) |
| Trail Making Test A | Task completion time | 18 | 19(18) | 16 | 16(16) |
| Symbol Digit Modalities Test (90 second oral administration) | Total correct answers | 13 | 12(12) | 11 | 11(10) |
| Attention | | | | | |
| Corsi Blocks (forward) | Total correct | 19 | 19(19) | 16 | 16(16) |
| Digit Span (forward) | Total correct | 19 | 19(19) | 15 | 16(15) |
| Working Memory | | | | | |
| Corsi Blocks (backward) | Total correct | 18 | 19(18) | 16 | 16(16) |
| Digit Span (backward) | Total correct | 19 | 19(19) | 15 | 16(15) |

| Assessment Measure | Variable | Surgical Group (n = 19) | | Control Group (n = 16) | |
|---|---|---|---|---|---|
| | | A1 | A2 | A1 | A2 |
| Executive Functioning | | | | | |
| Tower of Toronto Test | Total moves made | 12 | 11(9) | 12 | 13(12) |
| | Total time taken | 12 | 11(9) | 12 | 13(12) |
| | Total errors made | 12 | 11(9) | 12 | 13(12) |
| Trail Making Test B | Task completion time | 17 | 16(15) | 15 | 14(14) |
| Stroop Color/Word Trial | Number correct | 17 | 18(17) | 16 | 16(16) |
| Conditional Associative Learning Task | Total errors made | 15 | 16(15) | 12 | 13(12) |
| Subject Ordered Pointing | Total word errors | 17 | 17(17) | 15 | 15(15) |
| | Total drawing errors | 17 | 17(17) | 15 | 15(15) |
| | Total design errors | 17 | 17(17) | 15 | 15(15) |
| Delayed Responding | Total errors made | 6 | 12(5) | 12 | 6(6) |
| Delayed Alternation | Total errors made | 7 | 12(6) | 12 | 7(7) |
| Expressive Language | | | | | |
| Controlled Oral Word Association Test | Total correct words | 19 | 19(19) | 16 | 16(16) |
| Visuospatial Functioning | | | | | |
| Hooper Visual Organization Test | Total correct responses | 19 | 19(19) | 16 | 16(16) |
| Judgment of Line Orientation | Total correct responses | 18 | 18(18) | 15 | 15(15) |
| Motor Functioning | | | | | |
| Grooved Pegboard | Dominant hand time | 19 | 17(17) | 16 | 15(15) |
| | Non-dominant hand time | 18 | 15(14) | 16 | 14(14) |
| MNO | Change in writing height | 18 | 17(17) | 15 | 13(13) |
| | Total perseverations | 18 | 16(16) | 14 | 13(13) |

Note: A1 = Initial assessment. A2 = Follow-up assessment. In the A2 column, numbers in parentheses refer the numbers of patients whose assessment data were part of the data analyses. N/A = not applicable because this test was completed only at the initial assessment.

The results are presented below according to the different domains of interest.

## Mood

For the mood variables, no significant interactions were found.

## Quality of Life

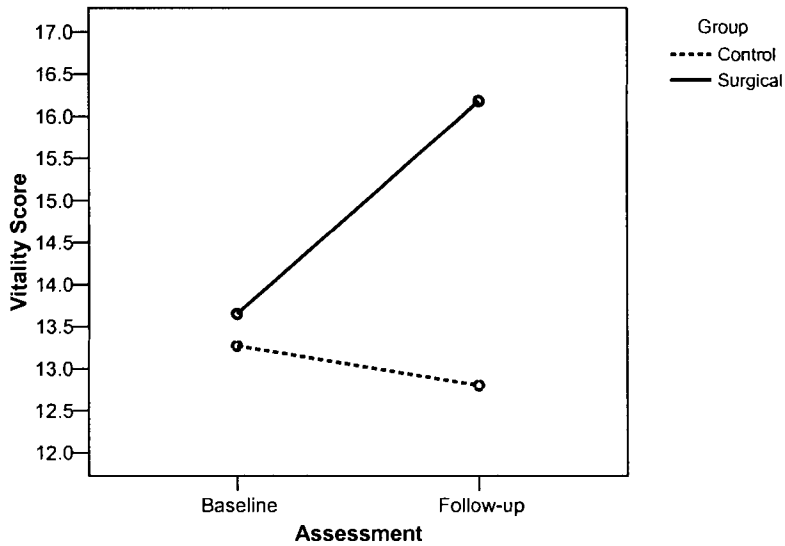
For the Medical Outcomes Survey Short Form (SF-36) subscales (except the Health Transition subscale), higher scores reflect better functioning.

There were significant effects of STN (group by time interactions) on several subscales of the SF-36, as follows:

### SF-36 Vitality

A significant Group by Time interaction was found for the Vitality subscale of the SF-36 [$F(1,30) = 8.796$, $p = 0.006$, $\eta_p^2 = 0.227$] (medium effect size). The difference between the two groups at Baseline was not significant [$F(1,30) = 0.085$, $p = 0.773$]. At the Follow-up assessment, the two groups were significantly different [$F(1,30) = 7.429$, $p = 0.011$]. For the Control Group, there was no significant difference between pre- and post-surgical SF-36 vitality scores [$F(1,30) = 0.40$, $p = 0.531$]. The Surgical Group, however, showed a significant increase from pre- to post-surgical SF-36 Vitality scores [$F(1,30) = 13.37$, $p = 0.001$].

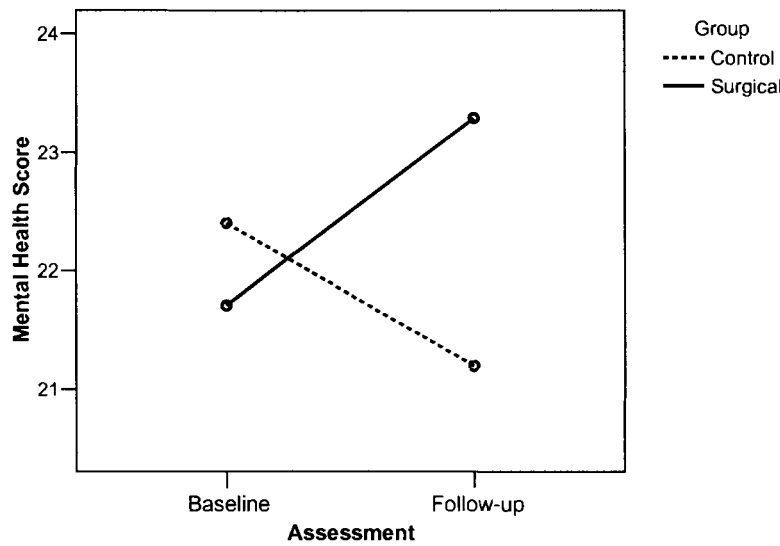
**Figure 2: SF-36 Vitality**



**SF-36 Mental Health**

There was a significant Group by Time interaction on the Mental Health subscale [$F(1,30) = 6.487, p = 0.016, \eta_p^2 = 0.178$] (medium effect size). The two groups did not differ significantly at Baseline [$F(1,30) = 0.301, p = 0.588$], nor at Follow-up [$F(1,30) = 2.009, p = 0.167$]. However, while the Control Group did not show a significant difference in pre- and post-surgical SF-36 Mental Health test scores [$F(1,30) = 2.26, p = 0.143$], there was a significant increase for the Surgical Group [$F(1,30) = 4.49, p = 0.042$].

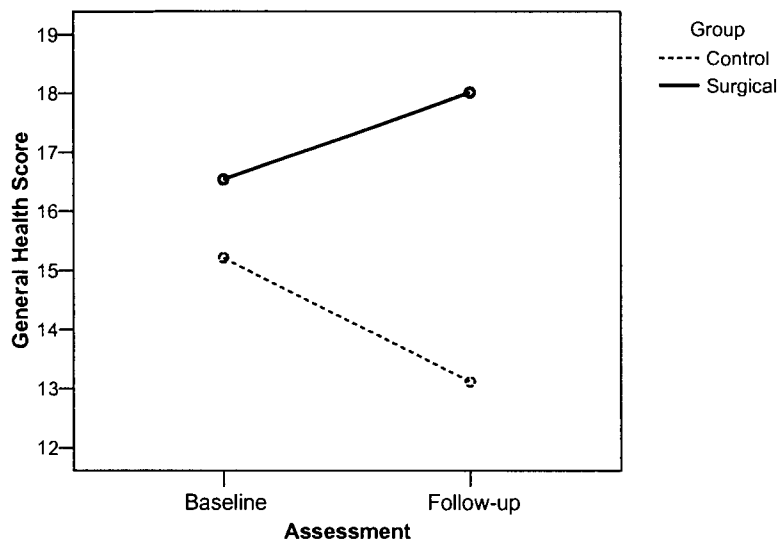
**Figure 3: SF-36 Mental Health**



**SF-36 General Health**

There was a significant Group by Time interaction on the General Health subscale [$F(1,30) = 8.290, p = 0.007, \eta_p^2 = 0.217$] (medium effect size). Though the two groups showed no statistically significant difference at Baseline [$F(1,30) = 0.747, p = 0.394$], they were significantly different at Follow-up [$F(1,30) = 13.323, p = 0.001$]. Though there was a significant decline in pre- and post-surgical SF-36 General Health scores for the Control Group [$F(1,30) = 5.35, p = 0.028$], there was no significant difference for the Surgical Group [$F(1,30) = 3.04, p = 0.092$].

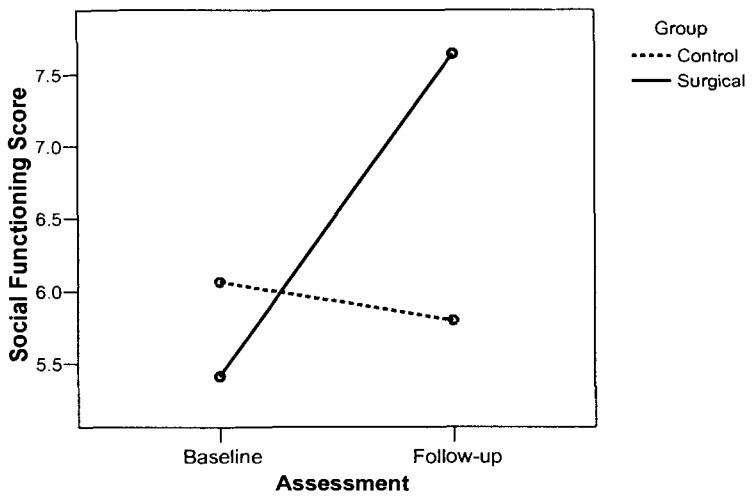
**Figure 4: SF-36 General Health**



### SF-36 Social Functioning

There was a significant Group by Time interaction on the Social Functioning subscale [$F(1,30) = 9.718, p = 0.004, \eta_p^2 = 0.245$] (medium effect size). The two groups showed no significant difference at Baseline [$F(1,30) = 0.486, p = 0.491$], but were significantly different at Follow-up [$F(1,30) = 6.458, p = 0.016$]. Although there was no significant difference in pre- and post-surgical SF-36 Social Functioning scores for the Control Group [$F(1,30) = 0.21, p = 0.652$], there was a significant improvement for the Surgical Group [$F(1,30) = 16.55, p = 0.000$].

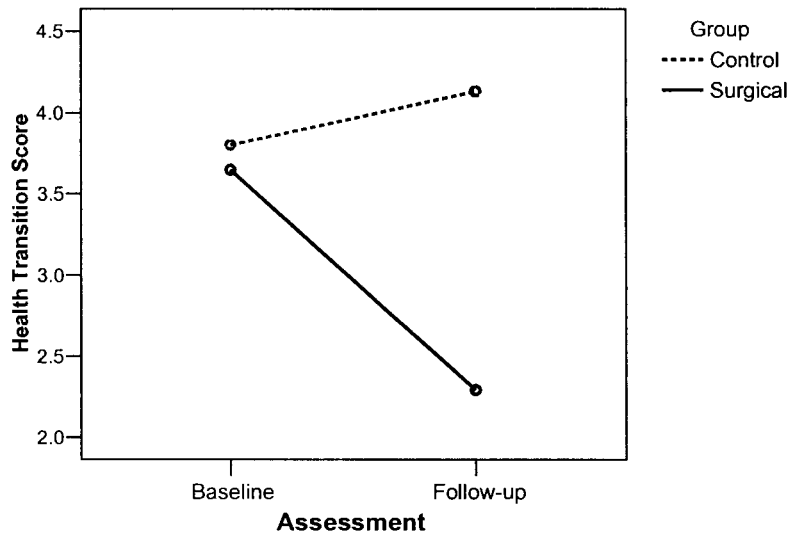
**Figure 5: SF-36 Social Functioning**



### SF-36 Health Transition

There was a significant Group by Time interaction on the Health Transition subscale [$F(1,30) = 21.777, p = 0.000, \eta_p^2 = 0.421$] (large effect size). For this subscale, a subscale in which higher scores reflect poorer health, the two groups were not significantly different at Baseline [$F(1,30) = 0.230, p = 0.635$], but were at Follow-up [$F(1,30) = 14.633, p = 0.001$]. While there was not a significant difference in pre- and post-surgical SF-36 Health Transition scores for the Control Group [$F(1,30) = 1.60, p = 0.215$], there was a significant improvement for the Surgical Group [$F(1,30) = 29.91, p = 0.000$].

**Figure 6: SF-36 Health Transition**

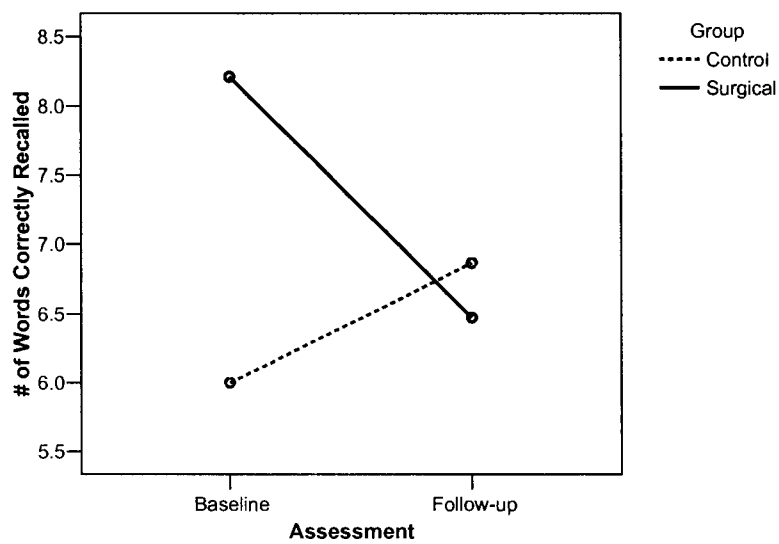


## Learning and Memory

### Rey Auditory Verbal Learning Test (Delayed Recall)

In this domain, there was a significant Group by Time interaction on the Delayed Recall trial on the Rey Auditory Verbal Learning Test [$F(1,32) = 6.197, p = 0.018, \eta_p^2 = 0.162$] (medium effect size). The two groups showed no statistically significant differences at Baseline [$F(1,32) = 2.59, p = 0.117$] or Follow-up [$F(1,32) = 0.090, p = 0.766$]. However, while there was no significant difference in pre- and post-surgical RAVLT Delayed Recall scores for the Control Group [$F(1,32) = 1.23, p = 0.276$], there was a significant decline for the Surgical Group [$F(1,32) = 6.25, p = 0.018$].

**Figure 7: RAVLT Delayed Recall**



## Mental Speed

In this domain, there were no significant Group by Time interactions.

## Attention

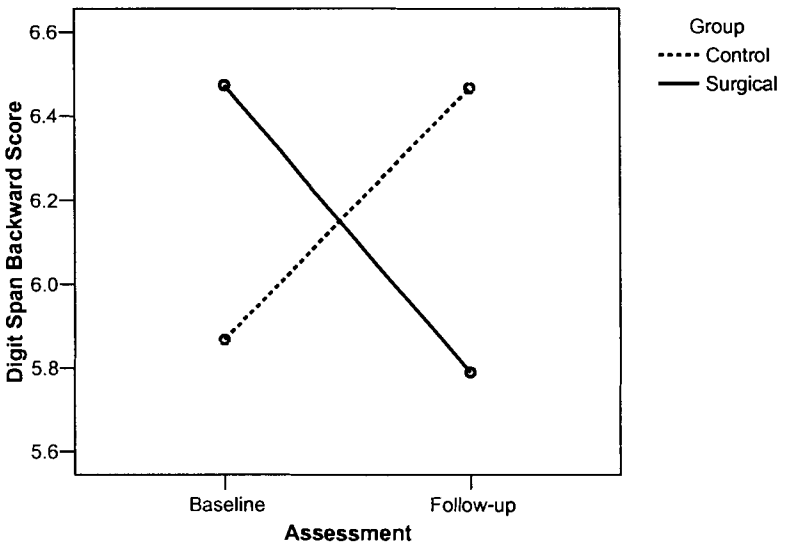
No significant Group by Time interactions were found in this domain.

## Working Memory

### Digit Span Backward

A significant Group by Time interaction was obtained on the Digit Span Backward score [$F(1,32) = 7.666, p = 0.009, \eta_p^2 = 0.193$] (medium effect size). The two groups were not significantly different at Baseline [$F(1,32) = 0.694, p = 0.411$] or Follow-up [$F(1,32) = 0.940, p = 0.340$]. Though there was no significant difference in pre- and post-surgical Digit Span Backward scores for the Control Group [$F(1,32) = 2.99, p = 0.093$], there was a significant decline for the Surgical Group [$F(1,32) = 4.93, p = 0.034$].

**Figure 8: Digit Span Backward**

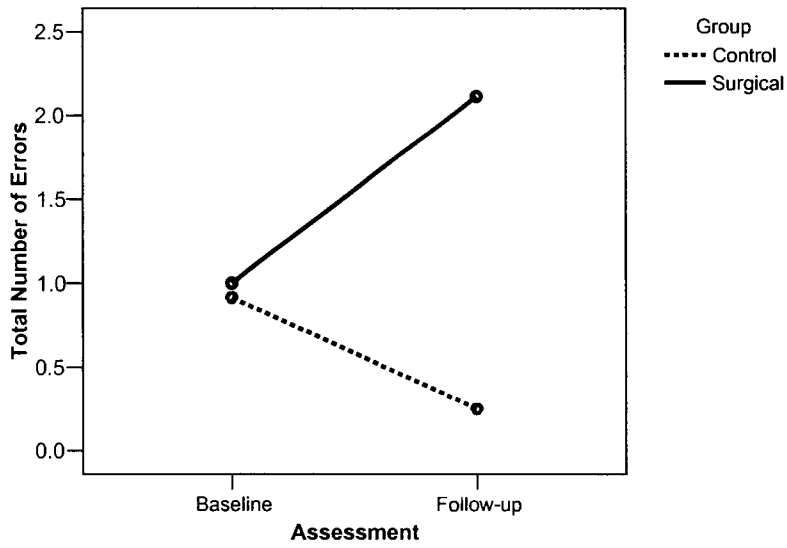


## Executive Functioning

### Tower of Toronto Test (Total Errors Made Across Trials)

There was a significant Time by Group interaction on errors made in completing the 3-disk trials of the Tower of Toronto Test [$F(1,19) = 7.090, p = 0.015, \eta_p^2 = 0.272$] (medium effect size). The two groups were not significantly different at Baseline [$F(1,19) = 0.019, p = 0.891$], but were at Follow-up [$F(1,19) = 5.923, p = 0.025$]. For the Control Group, there was not a significant difference in pre- and post-surgical Tower of Toronto Test total errors made [$F(1,19) = 2.33, p = 0.144$], but there was a significant decline (more errors made) for the Surgical Group [$F(1,19) = 4.85, p = 0.040$].

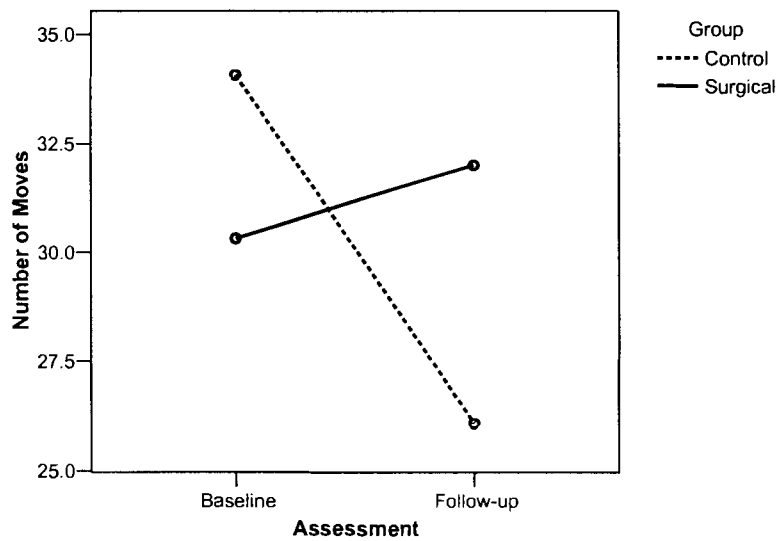
**Figure 9: Number of Errors Made on the Tower of Toronto Test**



**Tower of Toronto Test (Total Moves Across Trials)**

There was a significant Time by Group interaction on the number of moves needed to complete the Tower of Toronto Test [$F(1,19) = 5.960, p = 0.025, \eta_p^2 = 0.239$] (medium effect size). Though there was no significant difference between the two groups at Baseline [$F(1,19) = 1.162, p = 0.295$], there was one at Follow-up [$F(1,19) = 6.232, p = 0.022$]. For the Control Group, there was a significant decrease in the pre- and post-surgical Tower of Toronto moves [$F(1,19) = 9.52, p = 0.006$], but for the Surgical Group, there was no significant difference [$F(1,19) = 0.31, p = 0.584$].

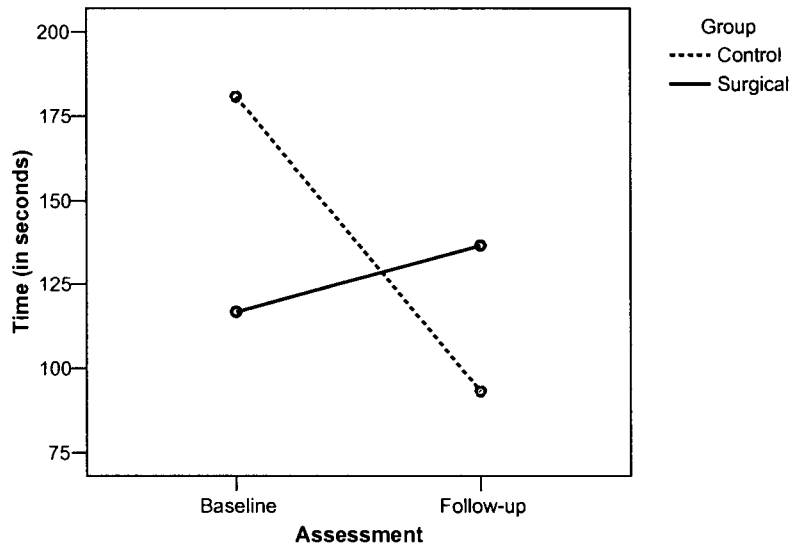
**Figure 10: Number of Moves Needed to Complete the Tower of Toronto Test**



**Tower of Toronto Test (Total Time Across Trials)**

There was a significant Time by Group interaction on time needed to complete the Tower of Toronto Test [$F(1,19) = 14.958, p = 0.001, \eta_p^2 = 0.440$] (large effect size). There was no significant difference between the groups at Baseline [$F(1,19) = 3.147, p = 0.092$] or at Follow-up [$F(1,19) = 2.339, p = 0.143$]. For the Control Group, there was a significant decrease (improved performance) in pre- and post-surgical Tower of Toronto time [$F(1,19) = 23.19, p = 0.000$], but there was no significant difference for the Surgical Group [$F(1,19) = 0.89, p = 0.356$].

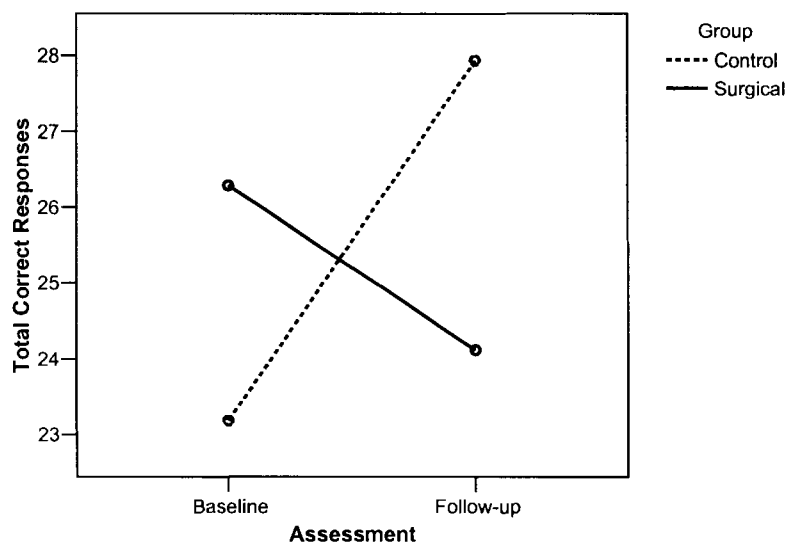
**Figure 11: Time Needed to Complete the Tower of Toronto Test**



**Stroop Color-Word Interference Trial (# Correct Responses)**

There was a significant Time by Group interaction on speed of color-word naming on the Stroop Test [$F(1,31) = 8.19, p = 0.007, \eta_p^2 = 0.209$] (medium effect size). The two groups did not differ significantly at Baseline [$F(1,31) = 0.707, p = 0.407$] or at Follow-up [$F(1,31) = 0.835, p = 0.368$]. Though there was a significant improvement in pre- and post-surgical speed of color-word naming for the Control Group [$F(1,31) = 7.47, p = 0.010$], no significant difference was found for the Surgical Group [$F(1,31) = 1.67, p = 0.206$].

**Figure 12: Number of Correct Responses on the Stroop Test (Interference Trial)**

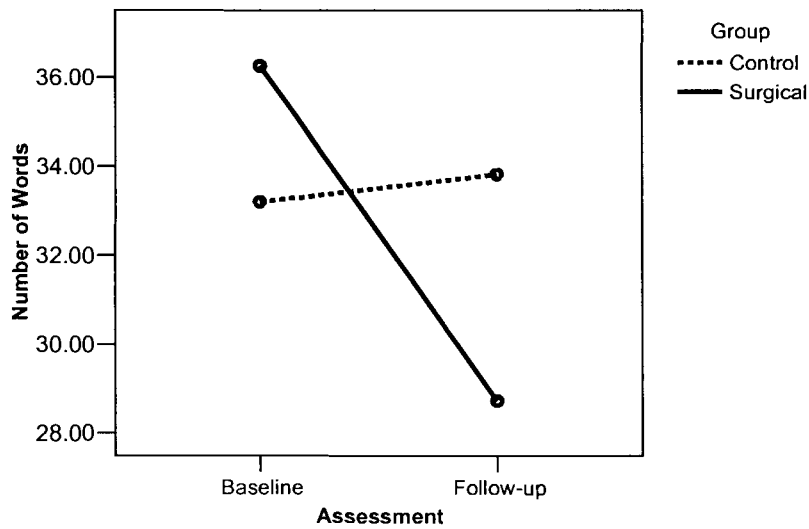


## Expressive Language

### COWA (Total Words)

There was a significant Time by Group interaction for verbal fluency [COWA, $F(1,33) = 6.864, p = 0.013, \eta_p^2 = 0.172$] (medium effect size). The two groups were not significantly different at Baseline [$F(1,33) = 0.259, p = 0.614$] or at Follow-up [$F(1,33) = 0.823, p = 0.371$]. However, while there was no significant difference in pre- and post-surgical verbal fluency scores (total words) for the Control Group [$F(1,33) = 0.07, p = 0.787$], there was a significant decline for the Surgical Group [$F(1,33) = 12.80, p = 0.001$].

**Figure 13: Controlled Oral Word Association Test (Number of Words)**



## Visuospatial Functioning

For this domain, all Time by Group interactions were non-significant.

## Motor Functioning

No statistically significant Time by Group interactions were found in this domain.

# DISCUSSION

## Cognitive Effects

Study participants in the Surgical Group showed declines on measures of executive functioning, verbal delayed memory, verbal working memory, and verbal fluency, in comparison to study participants in the Control Group. In an earlier section of this thesis, many previous studies on neurobehavioral outcome of STN DBS were reviewed. Of all these studies, only one found as broad a range of cognitive consequences of STN DBS in Parkinson's Disease as the present study (Saint-Cyr et al., 2000). Thus, it appears that this study, which is one of the very few pre-post studies done in this area that has included a Control Group, presents a more sobering picture of the cognitive decline with STN DBS than has previously been reported. However, although patients in the Surgical Group showed significant decline in absolute test scores, their performance on these tests was not at an impaired level.

### Cognitive Declines and Neurocircuitry

Research has identified frontal-subcortical circuitry and disruptions to this circuitry are associated with deterioration in executive functioning. Declines in **executive functioning** have been noted in clinical studies, though improvements in executive functioning have also been shown. The domain of executive functioning can involve reliance on many executive tasks including set shifting, selective responding, planning, and mental ordering, to name a few. Executive functioning skills depending on

the integrity of frontal-subcortical circuitry are compromised when disruption and disconnection occurs to this circuitry. Though the aim of STN DBS is to stimulate only the motor pathways of this circuitry, it is likely that other nearby pathways, such as the dorsolateral prefrontal (DLPC) circuitry, were unintentionally stimulated. This stimulation likely disrupted the DLPC circuitry, which, in turn, gave rise to executive dysfunction.

The **verbal fluency** results of the present study are concordant with the results of all previous findings noted (see Table 1). The **verbal working memory** findings are supportive of the results of some previous studies, but not exclusively, as improvement in working memory has also been shown in some other studies (see Table 1). Interestingly, verbal fluency, verbal working memory and executive functioning (e.g., Stroop Test interference trial) share a common attribute: reliance on executive skill. Verbal fluency requires executive search skills such as the ability to respond in a selective, strategic, and systematic manner. Verbal working memory relies on executive skills including mental ordering, strategy, and planning. Given that verbal working memory, executive functioning, and verbal fluency all involve executive components, it is probable that disruption to DLPC pathways would compromise performance in all three of these domains.

The **verbal delayed recall** results are consistent with the results of many other studies (see Table 1). Several assessment tasks, namely RAVLT, COWA, and Stroop Test (Interference trial), require verbal output. It could be that the deteriorated performance may be more due to declines in speech or motor speed. However, if this was the case, then deteriorated performance should have also been observed on other

tasks relying on these abilities, such as the Reading and Color Naming trials of the Stroop Test. However, in the current study, deterioration on these latter two tasks was not seen. As noted earlier, STN DBS may impinge on circuits in the STN that are in close proximity to the motor circuit (i.e., the dorsolateral prefrontal circuit), likely interfering with processes related to this circuitry. It is possible that the verbal delayed recall may also be tied into dysfunction of the dorsolateral prefrontal cortex circuit. Bronstein and Cummings (2001) note that disruption in the prefrontal-subcortical circuit produces a retrieval deficit syndrome characterized by poor recall. Furthermore, Lezak (1995) notes that memory disorders are often linked to prefrontal dysfunction. Individuals with prefrontal dysfunction may fail to spontaneously utilize an organization or framework by which to aid in recall tasks (Lezak, 1995). This, in turn, would likely impact performance on tasks involving verbal delayed recall.

## Quality of Life

In terms of **Quality of Life**, contrary to predictions, the Surgical Group did not report significant improvement in areas to do with motor and physical functioning post-surgery. This absence was surprising because motor functioning is expected to improve after surgery and it was hypothesized that patients, in turn, would report improved physical functioning. This lack of reported improvement in physical functioning may be related to the timing of the follow-up assessments. For instance, patients often receive a number of post-operative adjustments to their deep brain stimulation settings before the optimal setting is reached. Typically, a patient in the study needed at least one more stimulator adjustment beyond the timeline of the study. Thus, it is possible that optimal stimulation settings may not have been reached by the time post-operative SF-36

questionnaires were completed. In turn, patients may not have been enjoying much physical improvement at the time of the follow-up assessment. Another factor that may be reducing perceived improvement in physical functioning may be comorbidity with other physical illnesses. Other physical illnesses suffered by patients may interfere with patients enjoying the full potential of motor benefit that STN DBS could have provided.

Study participants in the Surgical Group reported better **general health** post-surgery and **better health** than they had over the previous year, even though Parkinson's Disease is a progressive disorder. Reports of improved general health post STN DBS have also been noted in other studies (Gronchi-Perrin et al., in press).

Patients in the Surgical Group also noted improved **social functioning** after surgery. This type of improvement post STN DBS has also been described by other researchers (Martinez-Martin et al., 2002; Lagrange et al., 2002). It is quite possible that the visible physical symptoms of Parkinson's Disease can be very embarrassing, especially in social situations. It is likely that people with Parkinson's Disease may feel self-conscious or interpersonally uncomfortable when their symptoms are displayed to others and thus, may be likely to reduce the quantity and quality of social interaction. With decreased symptoms after surgery, PD features should be less visible, thus allowing patients to more easily and comfortably participate in social events and engage socially with others. Most patients also have reductions in dopaminergic agents after surgery (Eskandar, Cosgrove, & Shinobu, 2001; Just & Ostergaard, 2002; Charles et al., 2004). As noted previously, chronic use of these agents is associated with side effects, such as dyskinesia, which may interfere with social functioning (Israel & Hassin-Baer, 2005). Thus, it is conceivable that post-surgical reductions in anti-parkinsonian medications

would likely reduce side effects, increase interpersonal comfort and confidence, and post-surgical reports of improved social functioning.

After surgery, patients also report improved **mental health**. Being in the advanced stages of a progressive disorder is often a very stressful stage of life, especially when treatment options have either been exhausted or compounded by debilitating side effects. Moreover, the thought of undergoing delicate surgery that has inherent surgical risks, including the possibility of death, may add to pre-surgical anxiety. Thus, it would be reasonable to feel pre-surgical mental strain, which would dissipate post-surgically and may be alleviated by improvements in motor functioning and, perhaps, a renewed sense of hope and optimism for a better life.

After surgery, patients also report an increase in **vitality**. This has also been found in other studies (Siderowf et al., 2006). Patients with Parkinson's Disease often have much undesired movement in the form of tremors. This can be very physically draining. By having surgery, which is known to reduce all three cardinal symptoms of Parkinson's Disease including tremor, unwanted movement and use of energy may be reduced post-surgically. Moreover, improvement in the other two cardinal symptoms of Parkinson's Disease, namely rigidity and slowness of movement, likely also contribute to patients' post-surgical report of feeling energetic more often. This outcome may be especially true as DBS surgery is known to increase the amount of time in so-called "on" periods, during which patients feel more active, are more flexible in their movements, and are able to move around more quickly.

Interestingly, even though STN DBS patients reported improved quality of life, study findings suggest that they did not report changes in mood. How might this be

explained? Following STN DBS, patients typically experience a reduction in dopaminergic medication (e.g., levodopa) use. Levodopa is believed to have mood-elevating effect (Maricle, Nutt, Valentine, & Carter, 1995). Thus, it is possible that post-surgical reduction in levodopa may lead to a slight mood dampening, even though patients are reporting improved quality of life.

**Reported QoL Improvement Despite No Observed Motor Change**

Prior to surgery, patients often experience levodopa-induced dyskinesia. Thus, a post-surgical reduction in anti-parkinsonian medication typically reduces dyskinesia in these patients. Reduction in dyskinesia may have contributed to surgical patients' reported improvement in several important aspects of quality of life, such as social functioning, health, vitality, and mental health. The reported improvement in several areas of quality of life may also be attributed to placebo effects. As reported by de la Fuente-Fernandez and Stoessl (2002), a placebo effect may be activated in patients with Parkinson's Disease when they are given a non-therapeutic intervention which the patients believe will lead to clinical improvement. As noted by these researchers, a symptom particularly susceptible to this effect is bradykinesia, which tends to be the predominant motor symptom for patients selected for STN DBS.

It is also conceivable that reported quality of life improvements may be related to the possible impact that the STN DBS may have on limbic frontal-subcortical circuitry. As noted previously, the effects of stimulation may extend beyond the motor circuitry.

It must also be noted that both pre- and post-surgery, patients are tested in their optimal "on" motor state, with test focus on their absolute level of motor functioning.

This knowledge may aid in understanding why no significant changes are observed in motor functioning. Even though patients' absolute level of motor functioning test performance has not changed significantly, they may actually be enjoying a greater amount of time (i.e., amount of time over the course of a day) in an optimal motor state. Future studies may benefit in posing questions that not only focus on absolute levels of motor functioning, but also on how much time in a given day patients are in an optimal state. It is conceivable that patients enjoying longer periods in "on" motor states may also be experiencing an improved quality of life.

It is also possible that a lack of accurate monitoring of self may be underlying not only deteriorated performance noted in several executive functioning tasks, but also reported quality of life post-surgery, which also relies on accurate self-monitoring. Given the potential for this situation to arise, it would be useful to attain the viewpoint of a third-party who may have the opportunity, perhaps on a daily basis, to observe the patient's functioning. If possible, an ideal study may require each patient's family members and/or caregivers to complete questionnaires based on their perspectives of the patient's level of motor, cognitive, and social functioning. This would be a useful way to gain corroborative information from a third party and may also highlight potential limitations or areas of concern that may be detected by caregivers, but not directly reported or noticed by patients.

## Clinical Implications

Despite STN DBS improving motor functioning, as noted in many previous studies, results of this study suggest that STN DBS has cognitive consequences. Patients with advanced Parkinson's Disease who undergo STN DBS experience declines in

several areas of cognitive functioning and this information should be shared with patients considering this surgical intervention.

Interestingly, amongst the current findings, whenever a significant interaction was found for a cognitive variable, it was invariably the Surgical Group that consistently performed worse. So, for these cognitive variables, not only did the Surgical Group not show any significant benefit of practice, but rather their performance declined. This finding is particularly interesting, given that of the two groups, the Surgical Group had a lower percentage of group members with scores on the Mattis Dementia Rating Scale (MDRS) suggestive of dementia. However, patients referred to the SCMD for STN DBS typically do not appear overtly demented. This may possibly reflect some sort of pre-selection process used by referring physicians, given the known post-surgical demands placed on STN DBS patients (e.g., the need to understand how to properly use the DBS system and, also, to complete a series of follow-up visits to the SCMD).

With the information noted above that the Surgical Group had a lower percentage of participants with MDRS scores suggestive of dementia, it may have been expected that the Surgical Group would show less decline at follow-up compared to the Control Group. Based on the findings of this study, however, the opposite appeared to be true. How might this be explained? First, perhaps the Surgical Group may have shown larger declines because the surgery may have negatively impacted performance on these cognitive measures. Second, it is also possible however, that the Control Group, which had worse (though non-significantly) mean performance for all these variables (except for Tower of Toronto errors) at Baseline, may have shown less of a decline at Follow-up because of floor effects. This argument would be more persuasive if the Control Group's

performance had not improved. However, for some of the variables, the Control Group is actually showing *improved* test performance at the follow-up assessment, relative to their baseline assessment. Moreover, sometimes the Surgical Group, post-surgically, scores *below* the baseline performance levels of the Control Group. These two factors suggest that floor effects do not provide the full explanation for the results seen. As well, the improved test performance on some variables (e.g., Tower of Toronto Test) for the Control Group may actually suggest that despite PD being a progressive disorder, patients may actually be showing practice effects and have an intact ability to learn and benefit from practice. This, in turn, may have implications for strategies pertaining to independent functioning and living issues. Past studies not utilizing control groups have missed the opportunity to observe this phenomenon.

As noted earlier, despite the cognitive declines of study participants who underwent STN DBS, they reported improved quality of life in several important aspects of functioning. Some may argue, from a client-centred perspective, improved quality of life is the ultimate goal of medical intervention. Even if patients experience cognitive declines following STN DBS, they still feel that their lives have improved. This provides evidence that STN DBS should remain a viable option for patients with advanced Parkinson's Disease, even if some cognitive decline may be experienced. Overall, the present study's findings regarding the neurobehavioral effects of STN DBS may contribute to efforts to predict outcome following surgery and, in turn, may assist in selecting appropriate patients for this surgical intervention.

## Study Limitations

### Limited Assessment of Motor Functioning

Although two tests were incorporated into the battery to assess motor functioning, they are limited, brief tests and may not fully capture the many and complex aspects of motor functioning that are of concern to patients in the study. The STN surgery is done mainly to address bradykinesia (slowness of movement). However, the motor tests used in this study are not sensitive measures of bradykinesia. Thus, these measures may fail to capture the most likely area of motor improvement following surgery. A more detailed and extensive evaluation of motor functioning might evaluate study participants with the Unified Parkinson's Disease Rating Scale, which has four parts, including one that focuses on motor functioning (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). This testing could be done at baseline and follow-up assessments, preferably by a trained health professional blind to the study objectives and group membership.

### Motor Improvement within Study Time Frame?

Patients in the Surgical Group are typically seen within a few weeks of getting their first stimulation adjustments. Given that some patients have their stimulation adjusted for several months in order to find an optimal setting, patients were typically assessed while they were still in the process of getting their stimulators fine-tuned. It is not inconceivable that if more optimal parameter settings were achieved, more improvement may have been captured by the motor functioning tests. By incorporating longer-term follow-up assessments into the study design, patients could be tested once the vast majority of parameter adjustments are made.

**Effect of Stimulation versus Effect of Surgery**

This study has not separated the impact of the actual surgery from the impact of the electrical stimulation. It is plausible that events related to the surgery may also impact post-surgical performance. During surgery, microlesioning occurs as electrodes pass though brain tissue in order to reach the subthalamic nucleus. Further, microlesioning may also occur as intraoperative testing and electrode adjustments are done in order to determine the optimal location for permanent electrodes. The design of this study does not permit the separation of the surgical impact from the stimulation impact as patients are tested post-surgically only on stimulation, never off stimulation. To address this, a potential area for further study would involve testing patients twice after surgery, once while the stimulator is on and once while the stimulator is off.

**Differences in Post-surgical Adjustments**

As each patient receives post-surgical stimulator adjustments, several parameters can be adjusted, such as voltage and pulse. The degree and type of adjustments vary from patient to patient, as these adjustments are customized for the best fit for each patient, in order to reach the optimal setting for clinical improvement (i.e., improved motor functioning). Arguably, different degrees of and adjustments to the STN stimulation may also potentially contribute to the variability in change in cognitive functioning post-surgery. An ideal study may involve keeping records of the degree and type of stimulation after surgery in order to observe how these parameters might be related not only to change in motor functioning, but also to changes in cognitive functioning.

# CONCLUSION

In conclusion, STN DBS appears to have a neurobehavioral impact on PD patients. Analyses suggest that STN DBS is associated with significant declines in several areas of cognitive functioning, including executive functioning, verbal working memory, verbal delayed recall, and verbal fluency. Nevertheless, study participants who underwent STN DBS also reported significant improvement in health and several areas of quality of life including vitality, general health, social functioning, and mental health. Thus, this study revealed that not only is STN DBS associated with significant declines on several cognitive measures, it is also associated with significantly improved reported quality of life. Results address the potential involvement of subthalamic nulcei within fronto-striatal circuits relevant to cognitive (especially executive) functioning. It is hoped that the characterization of the neurobehavioral effects of STN DBS may assist health professionals in selecting appropriate candidates for this intervention, as well as increase the precision of information shared with patients regarding potential outcomes as they consider treatment options.

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# APPENDIX:
# TESTS EMPLOYED
# DURING NEUROBEHAVIORAL ASSESSMENTS

| Tests | Description of Data Collected |
|---|---|
| **Premorbid Level of Intelligence** | |
| North American Adult Reading Test | • Total number of pronunciation errors made |
| **Premorbid Cognitive Functioning** | |
| Mattis Dementia Rating Scale | • Total score based on sum of scores on subscales: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory use |
| **Quality of Life** | |
| SF-36<br>(Medical Outcomes Survey – Short Form) | • Scores on several subscales: Physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, and health transition. |
| **Mood** | |
| Profile of Mood States (POMS) | • Total score and subscales: Tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment |
| Affect/Arousal Scale | • Average mood rating |
| **Learning and Memory** | |
| Rey Auditory Verbal Learning Test (RAVLT) | • Sum total of the number of words recalled on the initial five List A trials; number of words recalled during a distractor list trial; number of words recalled during the List A immediate recall trial; number of words recalled on the List A delayed recall trial; difference between the number of true positives and false positives made on the delayed recognition trial |
| Benton Visual Retention Test | • Total number correct and the total number of drawing errors made |
| **Mental Speed** | |
| Stroop Word Reading (45 second trial) | • Total number of test items correctly completed within a 45-second time limit |
| Stroop Color Naming (45 second trial) | • Total number of test items correctly completed within a 45-second time limit |
| Trails Making Test A (Trails A) | • Total time needed to finish the task |
| Symbol Digit Modalities Test (SDMT)- 90 second, oral trial | • Total number of items correctly done within a 90-second time limit |

| Tests | Description of Data Collected |
|---|---|
| **Attention** | |
| Corsi Blocks (forward) | • Total number of test items correctly done |
| Digit Span (forward) | • Total number of test items correctly done |
| **Working Memory** | |
| Corsi Blocks (backward) | • Total number of test items correctly done |
| Digit Span (backward) | • Total number of test items correctly done |
| **Executive Functioning** | |
| Tower of Toronto Test (3-disk) | • Total time needed to complete the three trials, total number of moves made, and total number of errors made in completing the task |
| Trail Making Test B (Trails B) | • Total time needed to finish the task |
| Stroop Color/Word Trial (45 second trial) | • Total number of test items accurately completed within a 45-second time limit |
| Conditional Associative Learning Task (CALT) | • Total number of mistakes made across the six test trials |
| Subject Ordered Pointing (SOP) | • Number of mistakes made during each of the word, drawing, and design trials of the task |
| Delayed Responding | • Number of incorrect responses made during the task |
| Delayed Alternation | • Number of incorrect responses made during the task |
| **Expressive Language** | |
| Controlled Oral Word Association Test (COWA) – 60 seconds per trial | • Total sum of correct words vocalized across the three test trials |
| **Visuospatial Functioning** | |
| Hooper Visual Organization Test (HVOT) | • Total number of drawings correctly described |
| Judgment of Line Orientation (JLO) Test | • Total number of test items correctly answered |
| **Motor Functioning** | |
| Grooved Pegboard | • Total time needed to place pegs into two adjacent rows of the grooved pegboard; two trials are done: one dominant hand trial and one non-dominant hand trial |
| MNO | • Micrographia is measured by calculating the change in writing height (mm) between the first and final MNO of the rows. Incorrect repetitions in the writing are noted as perseverations. |