COGNITIVE CHANGES AFTER DEEP BRAIN STIMULATION SURGERY FOR PARKINSON'S DISEASE

By

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Our purpose was to investigate the effects of unilateral deep brain stimulation surgery on cognition in patients with Parkinson's disease. We also sought to examine the significance of effects in individual patients as well as the predictors of cognitive changes after surgery.

Deep brain stimulation surgery to the globus pallidus internus (GPi) or subthalamic nucleus (STN) is regarded as an effective treatment for medication-refractory Parkinson's disease. However, research has shown that it may lead to specific cognitive declines in some patients. We compared neuropsychological data from a group of DBS patients before and 1 year after unilateral surgery to data collected from a group of PD patients tested over a 1-year interval who did not undergo surgery. We hypothesized that compared to PD controls, DBS patients would decline on tasks involving dorsolateral prefrontal cortex circuitry (i.e., letter fluency, semantic fluency, and Digit Span Backward) but not on tasks with less involvement of dorsolateral prefrontal cortex (i.e., Vocabulary, Boston Naming Test). We also predicted that a greater proportion of DBS patients would be classified as having declined significantly using Reliable Change Indexes (RCIs). Finally, we hypothesized that age, baseline cognitive status, preoperative depression severity, and left-sided surgery would be associated with cognitive changes in the DBS group.

We used the University of Florida Movement Disorders Center research database to compile data from 20 DBS patients and 19 PD controls of similar age, education and disability level. Cognitive testing was conducted at the University of Florida Psychology Clinic, and motor testing was conducted at the Movement Disorders Center Clinic.

Compared to PD controls, DBS patients declined on both tasks of verbal fluency, but not on Digit Span Backward or the non-dorsolateral prefrontal cortex tasks. RCI analyses revealed that 45% of DBS patients experienced significant declines on at least one verbal fluency measure, as compared to 11% of controls, and this difference was significant. There was a trend for DBS patients who declined significantly on verbal fluency to experience less motor improvement than DBS patients who did not decline. None of the hypothesized predictors were significantly associated with changes on the test of letter fluency. Only side of surgery was significantly associated with changes on the measure of semantic fluency, such that patients who underwent left-sided surgery were more likely to decline.

Our results suggest that unilateral DBS surgery is associated with verbal fluency declines. Further, left-sided surgery appears to be more associated with declines in semantic fluency than right-sided surgery, and fluency changes do not seem to be significantly related to the patient characteristics of age, baseline cognitive status or pre-operative depressive symptomatology. Finally, classification based on Reliable Change highlights the impact of individual variability in outcome and indicates that fluency declines likely reflect significant changes in a subset of DBS patients who may demonstrate a relatively poor surgical outcome in general.

CHAPTER 1
INTRODUCTION

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease. Its prevalence in the elderly population is estimated to be about 160 per 100,000, and it is estimated that 16 to 19 new cases of PD are diagnosed per 100,000 each year (Hirtz et al., 2007; Twelves et al., 2003). Moreover, due to the aging of our population, general incidence is expected to triple over the next 50 years (Tanner, Goldman & Ross, 2002). Most PD patients develop symptoms gradually in the 6^{th} or 7^{th} decade of life, and the mean age at diagnosis is 70.5 (Van Den Eeden et al., 2003). The incidence of PD is significantly greater in men, with a male to female ratio estimated to be between 1.5 and 2, and the average age of onset in men is, on average, 2.2 years younger than in women (Twelves et al., 2003; Haaxma et al., 2006).

In addition to the prominent motor symptoms, namely, resting tremor, bradykinesia, rigidity and postural instability, patients experience a variety of non-motor complications such as autonomic dysfunction, disturbances of mood and cognitive deficits. Increasing attention paid to these non-motor signs has improved the treatment of the whole Parkinson's patient by expanding our understanding of past, present and possible treatments.

Pathophysiology and Treatment

PD is defined by the death of dopamine-containing neurons in the substantia nigra pars compacta, which results in a reduction of dopamine in the nigrostriatal pathway as well as in the mesolimbic and mesocortical pathways. The deficiency in striatal dopamine disrupts activity in the cortico-basal ganglia-thalamocortical circuits, which leads to pronounced motor impairments (Albin, Young, & Penney, 1989). Specifically, reduced striatal input reduces positive feedback via the "direct" pathway and increases negative feedback via the "indirect" pathway, resulting in

the hallmark overall reduction in movement seen in patients with PD (Alexander, DeLong, & Strick, 1986). Dopamine depletion in other pathways may contribute to mood and autonomic dysfunctions.

Historically, treatment of PD has largely sought to enhance dopaminergic activity pharmacologically; however, drug treatments are often associated with adverse side effects such as unpredictable on/off motor fluctuations and dyskinesias, or excessive movement in particular areas of musculature (Marsden, Parkes, & Quinn, 1982). Motor fluctuations and/or dyskinesias occur in approximately 40% of PD patients receiving levodopa therapy for 4-6 years (Ahlskog & Muenter, 2001). The risk of developing these potentially disabling side effects increases with disease duration, and they represent a distinct challenge in the long-term management of PD (Papapetropoulos & Mash, 2007). Adjunct surgical intervention represents an alternative to exclusive pharmacological management of PD and has been shown to reduce the burden of these drug-related side effects. For example, researchers estimate that bilateral Deep Brain Stimulation (DBS) of the globus pallidus internus (GPi) reduces dyskinesia severity 41 to 87%, and DBS of the subthalamic nucleus (STN) reduces dyskinesias by an average of 70% (Fabbrini et al., 2007).

Cognitive Sequelae

Parkinson's disease is associated with specific cognitive deficits due to fronto-striatal neuropathology. Incidence of cognitive impairment in PD increases with age from 2.7% per year at ages 55-64 to 13.7% per year at ages 70-79 (Galvin, 2006). Approximately 25-30% of PD patients will develop a full-blown dementia syndrome (Aarsland, Zaccai, & Brayne, 2005). However, estimates of dementia prevalence in PD is complicated by the fact that most studies have used diagnostic criteria defined by the Diagnostic and Statistical Manual of Mental Disorders IV (American Psychiatric Association [*DSM-IV-TR*], 2000), which includes memory deficits in the definition of dementia, and a memory dysfunction may not be prominent in many

patients with Parkinson's Disease Dementia (Caballol, Martí, & Tolosa, 2007). Even those patients who do not go on to manifest dementia per sé will commonly evidence a pattern of cognitive impairments that resembles that seen in frontal lobe patients. Indeed, there is an increasing recognition that cognitive impairments in PD are not unique to Parkinson's Disease Dementia (PDD) and may occur in the earliest stages of the disease (Cooper et al., 1991; Muslimovic et al., 2005).

The pattern of cognitive deficits commonly seen in PD involves impairments in attentional set shifting, memory retrieval, visuospatial abilities, and directed verbal fluency. The latter ability is tested with tasks requiring patients to rapidly produce words from pre-defined phonemic or semantic categories within a given period of time. The pathophysiology of PD-type deficits may involve extrastriatal dopamine systems or non-dopaminergic pathology (Williams-Gray et al., 2006). Of note, the impairment in verbal fluency is thought to relate to dysfunction of self-generated search strategies due to executive dysfunction rather than a true language dysfunction (Pillon et al., 2001). Given that PD is associated with a variety of cognitive abnormalities that manifest throughout the disease course, studies looking at cognitive deficits associated with DBS surgery must control for deficits related to the underlying disease process.

Deep Brain Stimulation Surgery

Description

Deep Brain Stimulation is currently considered the "gold standard" surgical treatment for PD and has surpassed ablative surgeries largely because of its reversibility and flexibility, in that one can modify stimulation parameters to achieve optimal clinical benefit (Kopell et al., 2006; Okun et al., 2007). DBS involves implanting a lead with electrodes at the tip into specific brain regions via stereotactic neurosurgery. The most commonly targeted brain regions are GPi and STN, although surgeries involving the ventral intermediate nucleus of the thalamus are also

regularly conducted. An electrical pulse that is generated by a neurostimulator implanted below the clavicle travels through a subcutaneous wire and delivers high frequency stimulation (HFS) to subcortical target areas. Since traditional DBS electrodes have multiple contact points and can be programmed to produce varying frequencies of stimulation, unique stimulator settings can be determined and adjusted for individual patients and changed over time.

The mechanism of action of HFS is not fully understood, although it is generally conceptualized as a reversible functional lesion in that stimulation disrupts the abnormal electrical activity in basal ganglia circuits. Current theories suggest a modulation of patterns of both excitation and inhibition of neural tissue. Within the localized electrical field, stimulation appears to inhibit neurons of the STN and excite other fibers that are exiting, passing through or passing near the structure (Filali et al., 2004; McIntyre et al., 2004; Vitek, 2002; Windels et al., 2003). The underlying physiology of these effects likely involves some combination of events such as jamming of feedback loops, activation of inhibitory structures included in a more complex network, induction of early genes, changes in local blood flow, desynchronization of network oscillations, depression of intrinsic voltage-gated currents, synaptic inhibition and/or synaptic failure (Benabid, Benazzous, & Pollak, 2002; Meissner et al., 2005; Beurrier et al., 2001; Dostrovsky et al., 2000; Urbano & Llinas, 2002).

Efficacy

Motor functioning following optimal DBS programming is markedly improved, on average, as commonly assessed with the Unified Parkinson's Disease Rating Scale (UPDRS). Recent meta-analyses have reported 40-52% reductions in scores on subscale III of the UPDRS, which assesses the cardinal motor symptoms of PD, in patients evaluated in the "off" medication state before and after bilateral GPi or STN surgery (Kleiner-Fisman et al., 2006; Weaver et al.,

2005). PD symptoms most noticeably and consistently responsive to DBS include: tremor, rigidity and limb akinesia (Kumar et al., 1998; Limousin et al., 1998; Vesper et al., 2002).

Cognitive Outcome

Compared to the body of literature devoted to motor outcomes, studies of cognitive effects following DBS surgery are limited. Recently, researchers have increasingly attended to non-motor effects of surgery, which can include both mood and cognitive changes. A recent meta-analysis reported that cognitive problems occurred in approximately 41% of patients who underwent bilateral STN DBS (Temel et al., 2006). There is some data to suggest that stimulation of the STN is more likely to produce non-motor side effects than stimulation of the GPi, perhaps due to a greater risk of electrode misplacement or current spread attributable to the relatively small size of the STN (Walter & Vitek, 2004). Alternatively, this finding may be an artifact of the fact that fewer reports of GPi DBS are available, and limited data suggests that fluency impairments, which represent the most commonly reported cognitive deficit in the STN literature, also occur after GPi DBS (Kern & Kumar, 2007).

Despite the heterogeneity of results, the most robust and consistent finding across studies is a decline in verbal fluency in patients who have undergone DBS (Voon et al. 2006; Funkiewiez et al., 2004; Rothlind et al., 2007; De Gaspari et al., 2006; Smeding et al., 2006; Castelli et al., 2006; Gironell et al., 2003). One meta-analysis calculated Cohen's *d* effect sizes of .51 for letter fluency and .73 for semantic fluency (Parsons et al., 2006). Further parsing verbal fluency tasks into their subcomponents of clustering (generation of contiguous words within a semantic sub-category) and switching (disengaging from a prior sub-category and shifting to another), several groups have reported that only the latter subcomponent declined following STN DBS (Saint-Cyr et al., 2000; De Gaspari et al., 2006). Convergent findings from neuropsychological and neuroimaging studies indicate that clustering relies primarily on

temporal structures, while switching relies on frontal-subcortical circuit integrity (Troyer et al., 1998; Tröster et al., 1998; Frith et al., 1991; Parks et al., 1988; Schlösser et al., 1998). Using ECD-SPECT, researchers have recently associated post-STN DBS fluency declines with perfusion decrements in left dorsolateral prefrontal cortex (Cilia et al., 2007). Thus, it is reasonable to hypothesize that fluency deficits following high frequency stimulation of DBS target structures result from a disruption of frontal-subcortical circuitry.

Aside from verbal fluency, there is little agreement on the other cognitive tasks affected by DBS. A qualitative review of the literature discovered a multitude of disparate findings across studies (Voon et al., 2006). Tasks reported to decline after DBS included: verbal memory, visuospatial memory, Stroop, working memory, conditional associative learning, Trails B, construction and episodic memory. Many studies did not document declines on Digit Span Backward, a specific working memory task; however, most studies either did not administer this test or had small sample sizes. Numerous studies in the literature have reported declines in the working memory domain (Hershey et al., 2004; Saint-Cyr et al., 2000; Morrison et al., 2004).

One meta-analysis attempted to identify specific neurocognitive domains represented by the various tasks used in studies of cognitive outcome following DBS. Aside from large effects for both letter and semantic fluency, the authors reported significant declines on measures of executive and verbal functions; however, effect sizes were small: Cohen's d = .08 & .21, respectively (Parsons et al., 2006). Thus, there is a need to resolve the discrepancies currently existing in the literature in order to determine the true effects of DBS on cognition.

One proposed hypothesis for these cognitive changes following DBS implicates a disruption in the associative basal ganglia-thalamocortical loop due to the spread of electrical current beyond the targeted brain tissue. Although neurosurgeons attempt to target the more

lateral sensorimotor subregions of GPi or STN in order to correct the pathological activity in the motor loop, it is conceivable that electrical current may affect neural activity in the associative subregions, which are directly adjacent to the sensorimotor subregions in both GPi and STN.

Indeed, high frequency stimulation has been found to differentially affect the associative and limbic basal ganglia-thalamocortical loops (Haegelen et al., 2005; Schroeder et al., 2003; Sestini et al., 2002; Hilker et al., 2004). Imaging studies have revealed that high frequency stimulation modifies cerebral blood flow in the cortical areas of these non-motor loops during cognitive tasks (Limousin et al., 1997; Schroeder et al., 2003). Additionally, non-motor subregions of GPi and STN may possess different physiological properties such that different stimulation frequencies may exert different effects on motor behaviors and cognition (Temel et al., 2005). Evidence from human studies supports this idea in that high frequency stimulation leads to motor improvement and concomitant cognitive deterioration, while low frequency stimulation enhances cognitive performance in a context of motor worsening (Wojtecki et al., 2006). Additionally, modifying stimulation parameters may change the extent to which non-motor features are expressed (Francel et al., 2004).

CHAPTER 2
STATEMENT OF THE PROBLEM

In both efficacy and frequency, Deep Brain Stimulation surgery for the treatment of Parkinson's disease has surpassed traditional surgical approaches such as ablative procedures (e.g. pallidotomy), which aim to destroy circumscribed regions of subcortical tissue. FDA approval of and subsequent media attention directed toward DBS procedures have led to their being more regularly offered at a variety of medical facilities, not just tertiary-care specialty centers. This increased accessibility and commonness of DBS surgery in the U.S. is largely attributable to the numerous published reports of the treatment's effectiveness in controlling cardinal motor symptoms and reducing both unpredictable "on-off" fluctuations and drug-induced side effects such as dyskinesias. However, the number of articles aimed at examining cognitive side effects of DBS is relatively meager. Additionally, significant conflict persists, and recently, criticism has been directed toward the imperfect statistical methodologies used in the majority of cognitive studies. Given the unresolved state of the extant literature and the rising incidence of DBS throughout the world, it is important for researchers to work toward identifying the nature, frequency, predictors and causes of cognitive side effects in order to ensure that Parkinson's patients are well-informed and receive the best possible care.

It is difficult to synthesize findings from the literature on cognitive changes after DBS due to differences in neuropsychological testing batteries, variation in time to follow-up, non-routine reporting of stimulation parameters and lack of post-operative target confirmation. Additionally, most previously-published studies suffer from major methodological limitations, including small sample sizes, an exclusive focus on group mean differences and a failure to include a non-surgical control group. Unlike most previous research on cognitive outcome

following DBS surgery that analyzed large neuropsychological datasets using an exploratory approach, the present study reflects a theory-driven method of task selection.

A recent article that reviewed 30 studies examining cognitive effects of DBS to the STN in PD patients revealed that due to insufficient sample sizes, the majority of these studies possessed adequate power to detect only those effect sizes that are very large according to Cohen's conventions (Woods et al., 2006). These studies suffered from Type II error risk in that they possessed surprisingly low estimated power to detect changes associated with small, medium and large effect sizes. The authors of the review concluded that future efforts be directed toward examining the significance of effects at the individual level, not just group differences. One recommended method for characterizing individual changes in performance over time uses a Reliable Change Index (RCI), which takes into account the imprecision of a measurement instrument and places a confidence interval around post-test scores that could be obtained due to chance. Unlike traditional statistical approaches that examine mean scores to determine the statistical rarity of post-test scores, the RCI method determines the statistical significance of individual changes in performance, thereby allowing for the differentiation of group differences resulting from small changes in the majority of a sample versus those due to relatively large changes in a subset of a sample.

We chose to include a control group of PD patients who did not undergo surgery because we believe it to be essential in this type of research for two primary reasons. First, the neurodegenerative process of Parkinson's disease itself leads to cognitive changes that may not be attributable to the surgical intervention. Second, virtually all serial neuropsychological research can be influenced by practice effects, or the tendency for patients to perform better on a measure simply as a result of their taking it twice. Comparisons with a control group reduce the

influence of these confounds on the interpretation of results. The overall aim of the present study is to advance our understanding of the cognitive effects of Deep Brain Stimulation surgery for the treatment of Parkinson's disease. The specific aims and hypotheses are outlined below.

Specific Aim I

To test the hypothesis that cognitive declines associated with Deep Brain Stimulation surgery manifest in diminished performance on neuropsychological tasks shown to involve the dorsolateral prefrontal cortex (DLPFC). To investigate this hypothesis, we chose to examine performance changes on three tasks, two involving directed fluency and one involving working memory. Tasks included: the Controlled Oral Word Association Test (COWAT), the Animal Fluency Test and Digit Span Backward from the Wechsler Adult Intelligence Scale (WAIS-III). Each of these tasks has been shown, in lesion and/or functional neuroimaging studies, to involve participation of dorsolateral prefrontal regions of the brain. In addition, we analyzed performance on tasks that do not predominately involve the dorsolateral prefrontal cortex, namely, the Boston Naming Test (BNT) and the Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI). We included these tasks in order to rule out the possibility that cognitive declines seen after DBS represent arbitrary or more wide-spread cognitive dysfunction.

Unlike previous studies of cognitive outcome following DBS that have analyzed large and disparate cognitive batteries in an exploratory manner, the present study involved tasks selected in a hypothesis-driven manner, based on evidence for their activation of dorsolateral prefrontal cortex circuitry. Furthermore, we compared data from pre-operative and post-operative (1-year) neuropsychological assessments to data from patients with PD who did not undergo surgery in order to control for possible practice effects or disease-related cognitive decline. We predicted that performance on the three cognitive tasks shown to involve dorsolateral prefrontal cortex would decline in the DBS group as compared to controls, while

performance on tasks requiring less involvement of dorsolateral prefrontal cortex would be similar in DBS and control subjects at both time points.

Specific Aim II

To determine the significance of changes in performance on tasks shown to decline in the DBS group using Reliable Change Indexes (RCIs). The heterogeneity of results in the extant literature on cognitive decline subsequent to DBS surgery may be at least partially explainable by the extensive variability of outcome amongst patients. That is, while many patients do not shown cognitive dysfunction after surgery, a subset of patients seems to experience pronounced impairments. The traditional inferential statistical procedures employed by the vast majority of studies published to date examine mean scores in order to determine the statistical rarity of post-test scores. These methods provide limited information about the individual variability within a sample and no information about the significance of individual changes in performance. In order to address these potentially useful clinical questions, we used the method of Reliable Change, first described by Jacobson & Truax (1991) and later modified by Chelune et al. (1993) to additionally control for practice effects. We hypothesized that compared to the control group, a greater proportion of patients undergoing DBS surgery would fall below the confidence intervals defined by Reliable Change.

Specific Aim III

To identify risk factors for the development of post-operative cognitive dysfunction. The discovery of factors that predict which patients are more likely to experience adverse cognitive side effects as a result of DBS surgery is imperative, and current research has failed to demonstrate consistent findings (Temel et al., 2006). Studies have implicated a handful of disparate factors that may predict post-surgical declines in cognitive performance, including age, side of surgery, and a variety of pre-operative patient attributes such as poor cognitive status,

depressive symptomatology, apathy, neuropsychiatric conditions, disease duration and/or severity, and dopaminergic psychosis (Smeding et al., 2006; Funkiewiez et al., 2004; De Gaspari et al., 2006; Perriol et al., 2006). However, predictors vary across studies, and many studies have not identified any factors, pre-operative, surgery-related or post-operative, that significantly predict cognitive outcome. We hypothesized that age, baseline cognitive status, side of surgery (i.e., left) and pre-operative depressive symptomatology would be associated with adverse cognitive outcome.

CHAPTER 3
METHODS

Participants and Procedures

Recruitment

Participants included thirty-nine patients with idiopathic Parkinson's disease who are being followed by the Movement Disorders Center (MDC) at the University of Florida (UF) and who signed informed consent for their data to be included in the UF MDC research database. Motor, neuropsychological and demographic data were obtained from this IRB-approved database. All patients underwent neuropsychological evaluation through the University of Florida Psychology Clinic and were taking their normal "dopa" medications at the time of assessment. The PD DBS group comprised 20 individuals who underwent unilateral DBS surgery to either the right (N=7) or left (N=13) brain. Surgical targets included GPi (N=11) or STN (N=9). The PD control group comprised 19 individuals who were followed over time without undergoing DBS surgery.

Parkinson's Disease Diagnosis

All patients included in this study underwent extensive neurological screening in order to establish a definitive diagnosis of idiopathic Parkinson's disease. Consistent with the UK Brain Bank criteria (Hughes et al., 1992), the presence of bradykinesia as well as at least one other motor sign (i.e., rigidity, resting tremor or postural instability) were required for diagnosis. The diagnosis was ruled out if patients met any of the UK Brain Bank exclusion criteria (e.g., history of repeated head injury, history of definite encephalitis, supranuclear gaze palsy, cerebellar signs, etc). Also consistent with the UK Brain Bank criteria, Dr. Okun and his team required a demonstrated good response to levodopa therapy in order to exclude patients with Parkinson plus syndromes (e.g., progressive supranuclear palsy, multiple systems atrophy, corticobasal

degeneration, Lewy body disease, etc.). Other "supportive prospective positive criteria" from the UK Brain Bank list, including unilateral onset, persistent asymmetry and levodopa-induced chorea, were taken into account as well.

Inclusion and Exclusion Criteria

All patients included in this study were required to be between the ages of 50 to 75. Of the 23 patients identified as meeting inclusion criteria for the DBS group, 3 were excluded from the present analyses in order to render the DBS and control groups more comparable on age. On average, these excluded patients were 51.67 years old (range 51 to 52), and they did not significantly differ from the remaining 20 DBS patients with regard to their level of education, severity of motor symptoms or disease stage. Patients were excluded from either group if they: evidenced dementia (MMSE < 25; DRS-2 < 130), had undergone previous DBS or ablative procedures, or received bilateral DBS surgery.

Motor Testing Instruments

Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-III)

The UPDRS-III (Fahn, Elton, & Committee, 1987) quantifies the type, number and severity of motor symptoms common to Parkinson's disease. It takes approximately 15 minutes to administer and was conducted by a MDC neurologist or physician's assistant. The UPDRS is routinely administered in the UF MDC both in PD clinical trials and as part of patients' normal clinical care. This assessment was carried out when patients were "on" and "off" medications.

Hoehn and Yahr Stage Scale

The Hoehn & Yahr Scale (Hoehn & Yahr, 1967) is a clinician-rated scale of disease-related disability that allocates a stage (0-5) and is a ubiquitous measure of disease severity.

Neuropsychological/Mood Testing Instruments

Dementia Screening

Mini-Mental State Examination (MMSE)

The MMSE (Folstein, Folstein, & McHugh, 1975) is routinely administered as a rapid screen for dementia in a variety of clinical and research settings. The maximum score on the MMSE is 30 points, and it assesses several domains of functioning: memory, attention, formation, orientation, figure copying, reading and writing. Consistent with previous research, we included only patients obtaining a score of 25 or above in order to minimize the possibility that patients evidenced probable dementia.

Dementia Rating Scale 2 (DRS-2)

The DRS-2 (Mattis, 2001) is a widely-used screening measure for dementia. It takes about 20-30 minutes to administer and assesses domains of memory, attention, initiation, language and visuoconstruction. The maximum score on the DRS-2 is 144, and we employed a cut-off score of 130, considering scores below 130 as indicative of probable dementia. Total, raw DRS-2 scores were used in analyses for Aim 3.

Dorsolateral Prefrontal Cognitive Tests

Controlled Oral Word Association Test (COWAT)

The COWAT (Benton, Hamsher, & Sivan, 1994) is the most commonly-used measure of letter fluency in a variety of patient populations. The test allows patients 60 seconds to generate words beginning with a particular letter. The form employed in the present study used the letters F, A and S, and the instructions given to patients were those described by Spreen and Benton (1977). Patients were told not to provide proper nouns or multiple words containing the same stem. Convergent evidence from lesion and functional imaging studies suggests that this type of intrinsic word generation to letters involves several prefrontal subregions, including Brodmann's

areas (BA) 4, 6, 44 and 45 (Baldo et al., 2006; Costafreda et al., 2006; Amunts et al., 2004; Friston et al., 1991). The total number of words generated for each of the three letters was converted to T-scores based on age, education, and gender norms (Heaton et al, 2004).

The Animal Fluency Test

The Animal Fluency Test, a measure of semantic fluency, asks patients to generate names of animals for 60 seconds. The instructions given to patients were those described by Rosen (1980). In addition to engaging left dorsolateral prefrontal cortex, semantic fluency may also rely on its right homologue (Szatkowska, Grabowska, & Szymanska, 2000). The total number of words generated was converted to T-scores based on age, education, and gender norms (Heaton et al, 2004).

Digit Span Backward

The Digit Span task is one subtest from the Wechsler Adult Intelligence Scale-3rd edition (WAIS-III; Wechsler, 1997) and is widely regarded as a conventional measure of auditory working memory. The backward portion is thought to measure brief storage, mental tracking and mental manipulation (Lezak, 1995). It takes about 5 minutes to administer and requires patients to first listen to a string of numbers verbally presented by an experimenter and to then repeat the string aloud with the numbers in the reverse order. The first two trials contain 2 digits, and subsequent trials include increasing numbers of digits, with two trials of each difficulty level. Testing is discontinued when patients fail to correctly complete two trials of the same difficulty level. Imaging studies using this working memory task have reported activations in several prefrontal areas, including BA 6, 9, 44 and 46 (Owen, 2000; Tsukiura et al., 2001). Compared with the forward portion, Digit Span Backward selectively activates dorsolateral prefrontal cortex in younger adults (Hoshi et al., 2000). The total number of correct trials was converted to scaled scores based on age-based norms (Wechsler, 1997) and then to T-Scores.

Other Cognitive Tests

Boston Naming Test (BNT)

The BNT is a 60-item test of visual confrontation naming (Kaplan, Goodglass, & Weintraub, 1983). In this test, patients are asked to name visually-presented images. Scores representing the total number of correct namings were converted to T-scores based on age, education, and gender norms (Heaton et al, 2004).

Vocabulary

Vocabulary is one subtest from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and requires patients to provide verbal definitions of a series of words that increase in difficulty. Patients can obtain 0, 1 or 2 points on each trial, depending on the depth and accuracy of the response. Administration is discontinued when the patient obtains a score of "0" on five consecutive trials. Scores representing total points obtained were converted to scaled scores based on age-based norms (Wechsler, 1999) and then to T-Scores.

Mood Measure: Beck Depression Inventory 2nd Edition (BDI-II)

The BDI-II (Beck, Steer, & Brown, 1996) is a self-report measure of depressive symptomatology that is routinely given to patients at the UF MDC and UF Psychology Clinic. For each of the 21 items representing different depressive symptoms, patients choose one statement that best describes how they have felt over the past week. For each item, statements correspond to 0, 1, 2 or 3 points, and total scores can range from 0 to 63. Raw scores were used in analyses for Aim 3.

Statistical Analyses

The first prediction was that compared to a control group, DBS patients would decline only on those neuropsychological tasks with greater dorsolateral prefrontal cortex involvement. To test this prediction, repeated-measures analyses of variance (ANOVAs) were conducted on

the dependent variables (T-scores) in each of the five cognitive tests (COWAT, Animal Fluency, Digit Span Backward, Vocabulary and BNT). For each ANOVA, the between-subjects variable was group membership (DBS vs. PD control) and the within-subjects variable was time. Bonferroni-corrected follow-up t-tests were conducted in order to explicate specific group differences when a significant Group X Time interaction was detected. To ensure that the assumptions required for General Linear Model analyses were met, data were screened for homogeneity of variance and normality through examination of descriptive statistics and graphical distributions. For all group comparisons, Levene's tests for the homogeneity of variance were conducted before analyses were performed, and appropriate statistics were used when this test indicated non-homogeneity of variance.

The second aim was to examine the significance of individual changes in performance on tasks shown to decline in the DBS group. To test this aim, Reliable Change Indexes (RCIs) corrected for practice effects were calculated using formulas described by Jacobson & Truax (1991) and modified by Chelune, et al. (1993). Consistent with the majority of previous literature using RCIs, 90% confidence intervals were chosen. Patients were then classified as "*decliners*" if the difference between their obtained post-test score and their individualized expected score fell outside of the RCI for the specific cognitive test. Pearson chi square tests were then conducted in order to assess the significance of proportional differences between the numbers of decliners in the two groups. In addition, phi values were obtained to index effect sizes, and odds ratios were calculated to facilitate interpretation.

The third prediction was that age, side of surgery, cognitive impairment and depressive symptomatology would correlate with cognitive decline in the DBS group. To test this prediction, independent linear regressions were conducted in which the dependent variable in

each analysis was performance change (post-test T-scores minus pre-test T-scores) on each of the cognitive tests identified by significant Group X Time interactions in Aim 1 repeated-measures ANOVAs. Independent variables (i.e., predictors) in each regression were: baseline age, total baseline DRS-2 scores, total baseline BDI-II scores and side of surgery. Overall significance of the model and, when appropriate, the relative contribution of each predictor were reported.

To further explicate the role of the above-mentioned predictors, follow-up t-tests were conducted comparing DBS patients classified as decliners and non-decliners. Additionally, a selection of decliners' and non-decliners' baseline disease variables (i.e., UPDRS "*on*" and "*off*" and disease duration) as well as change (post minus pre) variables (i.e., Hoehn & Yahr stage, UPDRS "*on*" and "*off*", levodopa equivalent dose and BDI-II) were statistically compared using independent samples t-tests.

CHAPTER 4
RESULTS

Demographic and Disease Variables: DBS vs. Controls

Table 4-1 compares demographic and disease-related data on the two groups. DBS patients included 16 men and 4 women who ranged in age from 53 to 70 years (M = 61.3, SD = 5.2). These patients had obtained an average of 14 years of education (SD = 2.3, range 7 to 16 years). On average, the DBS patients' motor symptoms were moderately severe when they were assessed "*on*" medications with the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS-III = 23.0, SD = 8.5, range 8 to 41), and they were in the middle stage of PD as defined by the Hoehn & Yahr staging system (M = 2.2, SD = 0.4, range 2 to 3). PD control patients included 12 men and 7 women who ranged in age from 54 to 74 years (M = 64.7, SD = 6.6). These patients had obtained an average of 15.4 years of education (SD = 3.0, range = 12 to 20 years). Like those of DBS patients, the motor symptoms of the PD controls were moderately severe when patients were assessed "*on*" medications (UPDRS-III = 25.3, SD = 8.5, range 14 to 43), and they were in the middle stage of PD, as defined by the Hoehn & Yahr staging system (M = 2.4, SD = 0.4, range 2 to 3). As shown in Table 4-1, there were no significant differences between groups on any of these variables. Moreover, there were no significant differences at baseline between the DBS and PD controls on the two cognitive screening measures (i.e., DRS-2 and MMSE) or on a self-report measure of depressive severity (i.e., BDI-2).

Duration of parkinsonian symptoms, per patient self-report, was approximately 147.3 months for the DBS group (SD = 64.6, range 52 to 319 months) and approximately 76.5 months for the PD controls (SD = 69.1, range 21 to 310 months). This difference in symptom duration (i.e., 70.7 months) was significant ($t(37) = -3.30$, $p = .002$, $r = .48$). In addition, DBS patients' motor symptoms were more severe than those of PD controls when patients were assessed "*off*"

medications with the UPDRS-III (DBS group M = 45.2 vs. PD control M = 30.8; $t(37) = -4.38$, $p < .001$, $r = .58$).

Aim 1: Group Differences in Cognitive Performance over Time

Mean scores of the DBS and PD control patients tested at baseline (Time 1) and again at Time 2 across each of the five cognitive tests are shown in Table 4.2. Two of these tasks were predicted not to be affected by DBS (i.e., WASI Vocabulary, Boston Naming Test), whereas three tasks were predicted to decline following DBS (i.e., Digit Span Backward, COWAT and Animal Fluency Test). Results from five separate repeated-measures ANOVAs are presented in Table 4.3. As shown, there were no significant main effects of Group or Time for any of the cognitive tests. However, significant Group X Time interactions were detected for the two fluency tasks: COWAT ($F[1, 37] = 10.83$; $p = .002$; $\eta_p^2 = .23$) and Animal Fluency Test ($F[1, 37] = 4.45$; $p = .04$; $\eta_p^2 = .11$). These interactions are displayed graphically in Figures 4-1 and 4-2.

Decomposition of these interactions using Bonferroni-corrected t-tests revealed the following. For letter fluency (COWAT), DBS and PD control patients did not differ at baseline testing (Control M = 48.4 vs. DBS M = 47.7; $t(37) = 0.2$; $p = .84$; $r = .03$); however, the DBS patients produced significantly fewer words than PD controls at follow-up testing (Control M = 50.5 vs. DBS M = 41.4; $t(37) = 2.23$; $p = .03$; $r = .34$). Furthermore, DBS patients' post-surgery scores were significantly lower than their baseline scores (Pre M = 47.7 vs. Post M = 41.4; $t(19) = 3.55$; $p = .001$; $r = .63$), while control patients' pre- and post-test scores did not differ significantly (Pre M = 48.4 vs. Post M = 50.5; $t(18) = 1.14$; $p = .26$; $r = .24$). For semantic fluency (Animal Fluency Test), DBS and PD control patients did not differ at baseline (Control M = 47.7 vs. DBS M = 51.5; $t(37) = 0.99$; $p = .33$; $r = .16$) or at follow-up testing (Control M = 48.4 vs. DBS M = 44.5; $t(37) = 0.90$; $p = .37$; $r = .15$). However, DBS patients produced significantly fewer animal names at post testing than at baseline (Pre M = 51.5 vs. Post M = 41.4;

$t(19) = 2.74$; $p = .009$; $r = .53$), while control patients' pre- and post-test scores did not differ significantly (Pre $M = 47.8$ vs. Post $M = 48.4$; $t(18) = 0.28$; $p = .63$; $r = .07$).

Because DBS patients and PD controls differed significantly on two key disease variables (i.e., disease duration and UPDRS-III "*off*"), analyses of variance were re-run using these variables as covariates (ANCOVAs). Results revealed a trend for the Group X Time interaction to persist for letter fluency ($F(1, 32) = 4.05$, $p = .053$, $\eta_p^2 = .11$); however, the interaction was no longer significant for semantic fluency ($F(1, 32) = 0.4$, $p = .53$, $\eta_p^2 = .01$). No other main effects or interactions approached significance in either of the ANCOVAs.

Aim 2: Reliable Change Results

Reliable Change Indexes (RCIs) corrected for practice effects were calculated in order to determine the statistical significance of individual changes on the two cognitive tests for which Group X Time interactions were identified, namely, letter and semantic fluency. Test-retest correlations and standard deviations used to calculate standard errors of the measures using Equation 4-1 were obtained by examining data from the PD control group. RCIs for each measure were calculated separately using the standard error of the difference in the PD control group (Equation 4-2). The sizes of the 90% confidence intervals were defined using Equation 4-3 (Jacobson & Truax, 1991). Practice effects were calculated separately for each cognitive test by subtracting mean pre-test scores from mean post-test scores obtained by the PD controls. For each test, each individual patient's predicted score was estimated by adding the expected practice effect to the patient's baseline score on the test (Chelune et al., 1993). Patients were classified as "*decliners*" on a measure if they obtained a lower post-test score than could be expected due to chance, that is, if the difference between their obtained and predicted scores exceeded the RCI for the particular cognitive test.

$$SE_M = SD * \sqrt{(1-r_{xx})} \qquad (4\text{-}1)$$

$$SE_{DIFF} = \sqrt{(SE_M(\text{Time 1})^2 + SE_M(\text{Time 2})^2)} \quad (4\text{-}2)$$

$$RCI = \pm 1.645 * SE_{DIFF} \quad (4\text{-}3)$$

As shown in Table 4-4, two (11%) of the PD control patients showed significant decline on one fluency measure, and none showed decline on both measures. In contrast, 9 (45%) DBS patients evidenced significant decline on one or both fluency measures. Specifically, 5 DBS patients declined on only one measure (3 on Letter Fluency and 2 on Semantic Fluency) and 4 DBS patients declined on both. There was a significant and moderate association between having surgery and declining on at least one verbal fluency measure ($\chi^2(1) = 5.72$, $p = .02$, Phi = .38). Using Equation 4-4, the odds of declining were calculated separately for DBS patients and PD controls. Next, odds ratios were calculated using Equation 4-5. Compared to patients who did not undergo surgery, DBS patients had 7 times greater odds of experiencing significant decline on at least one measure of verbal fluency. Looking at letter and semantic fluency individually, DBS patients had 10 times greater odds of declining on letter fluency and 7.7 times greater odds of declining on semantic fluency, as compared to PD controls.

$$odds_{declining} = (\#\text{ of decliners}) / (\#\text{ of non-decliners}) \quad (4\text{-}4)$$

$$\text{odds ratio} = odds_{\text{declining after DBS}} / odds_{\text{declining as PD control}} \quad (4\text{-}5)$$

Aim 3: Predictors of Cognitive Change

Regression Results

To determine which factors (i.e., age, baseline cognitive status, baseline depression status, side of DBS surgery) were significantly related to changes in performance on the verbal fluency tasks, two linear regressions were conducted. For both regressions, these four variables were regressed on change (T-score) in letter fluency or semantic fluency, respectively. The model was not significant in predicting change in performance on letter fluency ($R^2 = .14$; $p =$

.74); however, the model *was* significant in predicting change in performance on semantic fluency (R^2 = .69; p = .005).

Table 4-5 displays the unstandardized and standardized beta weights for the predictors in the semantic fluency model. Importantly, only the predictor *side* was significantly related to change in semantic fluency performance (β = -.80; p < .001). On average, patients who underwent surgery to their *right* brain experienced an increase in performance of 5.1 points, while patients who underwent surgery to their *left* brain experienced a decrease in performance of 13.5 points; this difference was large and significant (t[18] = 4.88; p < .001; r = .75).

Of the 7 patients who underwent surgery to their right brain, none experienced a significant decline on the measure of semantic fluency, according to the RCI analyses. In contrast, 6 out of the 13 patients who underwent left-sided surgery experienced significant decline on this measure. There was a significant association between side of surgery and semantic fluency decline (χ^2(1) = 4.62; p = .03; Phi = .48).

Exploratory Group Comparisons

In order to investigate other possible differences between DBS patients who experienced significant declines in verbal fluency and those who did not, a series of exploratory t-tests were conducted. These tests compared decliners and non-decliners on a variety of baseline factors as well as on variables reflecting changes after surgery. As shown in Table 4-6, none of the baseline characteristics examined (i.e., age, BDI-II, DRS-2, months with symptoms, UPDRS-III "*on*" or "*off*") were significantly different between the groups. However, the groups *did* significantly differ on side of surgery. Namely, 8 out of the 9 decliners had undergone surgery to their left brain (t(17.13) = -2.25; p = .038; r = .48).

With regard to patients' motor changes, there were trends for decliners and non-decliners to evidence moderately-sized differences on changes in their UPDRS scores when they were

assessed both "*on*" ($t(17) = -2.08$; $p = .054$; $r = .45$) and "*off*" medications ($t(17) = -1.89$; $p = .079$; $r = .42$). Note that lower scores indicate better motor performance. On average, non-decliners experienced a reduction of 4.8 points when assessed "*on*" medications and a reduction of 14.2 points when assessed "*off*" medications. In contrast, decliners experienced an increase of 3.8 points when assessed "*on*" medications and a reduction of only 5.4 points when assessed "*off*" medications.

Table 4-1. Comparisons between DBS and PD controls at baseline

	Controls	DBS	t	df	p
Age (years)	64.6 (6.6)	61.3 (5.2)	1.80	37	.08
Education (years)	15.4 (3.0)	14.1 (2.3)	1.56	37	.13
Male/Female	12/7	16/4	1.15	35.01	.26
Months with symptoms	76.5 (69.1)	147.3 (64.6)	-3.30	37	.002
Hoehn & Yahr stage	2.4 (0.4)	2.2 (0.4)	1.12	35	.27
UPDRS "*on*"	25.3 (8.5)	23.0 (8.5)	0.83	34	.41
UPDRS "*off*"	30.8 (8.3)	45.2 (11.2)	-4.38	34	<.001
BDI-II	9.2 (8.6)	9.9 (8.4)	-0.22	32	.83
MMSE (raw)	28.3 (1.9)	28.7 (1.5)	-0.71	37	.48
DRS-2 (raw)	138.6 (3.5)	138.0 (4.4)	0.46	37	.65

Table 4-2. Performance (T-scores) on specific cognitive tests at Times 1 & 2

	Controls	DBS	t	df	p
Vocabulary					
Time 1	58.0 (7.9)	55.0 (6.8)	1.24	37	.22
Time 2	57.1 (13.1)	54.3 (8.3)	0.80	35	.43
BNT					
Time 1	55.5 (10.8)	55.1 (11.5)	0.15	37	.88
Time 2	55.8 (11.9)	53.9 (12.9)	0.49	37	.63
Digit Span Backward					
Time 1	51.9 (13.5)	52.8 (6.8)	-0.25	37	.80
Time 2	50.1 (8.6)	50.0 (6.2)	0.05	36	.96
COWAT					
Time 1	48.4 (10.4)	47.7 (13.5)	0.20	37	.84
Time 2	50.5 (11.7)	41.4 (13.6)	2.23	37	.03
Animal Fluency					
Time 1	47.7 (11.0)	51.5 (12.7)	-0.99	37	.33
Time 2	48.4 (12.7)	44.5 (14.6)	0.90	37	.37

Table 4-3. Repeated-measures analyses of variance

	SS	MS	F	p	Effect Size (η_p^2)	Power
Vocabulary						
Group	184.95	184.94	1.36	.25	.04	.21
Error (between)	4744.99	135.57				
Time	23.58	23.58	0.64	.43	.02	.12
Group x Time	1.53	1.53	0.04	.84	.00	.06
Error (within)	1281.33	36.61				
BNT						
Group	29.56	29.56	0.11	.74	.00	.06
Error (between)	9613.44	259.82				
Time	2.996	2.996	0.15	.69	.00	.07
Group x Time	9.77	9.77	0.52	.48	.01	.11
Error (within)	693.95	18.76				
Digit Span Backward						
Group	5.26	5.26	0.04	.84	.00	.06
Error (between)	4579.72	127.22				
Time	113.80	113.80	2.63	.11	.07	.35
Group x Time	8.22	8.22	0.19	.67	.01	.07
Error (within)	1558.22	43.28				
COWAT						
Group	472.17	472.17	1.70	.20	.04	.25
Error (between)	10261.37	277.33				
Time	85.83	85.83	2.77	.11	.07	.37
Group x Time	335.83	335.83	10.83	.002	.23	.89
Error (within)	1147.35	31.01				
Animal Fluency						
Group	0.21	0.21	0.001	.98	.00	.05
Error (between)	9803.8	264.97				
Time	191.11	191.11	2.91	.10	.07	.38
Group x Time	291.62	291.62	4.45	.04	.11	.54
Error (within)	2426.84	65.59				

Table 4-4. Proportion of DBS patients vs. controls evidencing decline

	Controls	DBS patients	Odds ratio	Pearson chi-square	p	Phi
Letter fluency	1	7	10	5.28	.022	.37
Semantic fluency	1	6	7.7	4.05	.044	.32
Either measure	2 (11%)	9 (45%)	7	5.72	.017	.38

Note, 2 cells had expected count less than 5 in chi-square tests for individual fluency measures

Table 4-5. Predictor variables regressed on semantic fluency change scores

	B (std error)	Beta	t	p
Age	0.08 (0.44)	.03	0.18	.86
DRS-2	-0.45 (0.46)	-.17	-0.97	.35
BDI	0.20 (0.28)	.13	0.72	.49
Side of surgery	-20.39 (4.23)	-.80	-4.83	<.001

R square = .69; p = .005

Table 4-6. Baseline and change score comparisons in decliners vs. non-decliners

	Decliners	Non-decliners	t	df	p	r
Age	61.8 (5.6)	60.8 (5.1)	-0.40	18	.69	.01
BDI-II	11.1 (10)	8.5 (6.6)	-0.63	15	.54	.16
DRS-2	137.8 (5)	138.2 (4)	0.20	18	.84	.05
UPDRS "*on*"	23.8 (7.1)	22.3 (9.8)	-0.39	18	.71	.09
UPDRS "*off*"	42.4 (10.7)	47.4 (11.6)	0.95	16	.36	.23
Disease duration (months)	150.9 (72.3)	144.3 (61)	-0.22	18	.83	.05
Left/Right	8/1	5/6	-2.25	17.13	.038	.48
Hoehn & Yahr change	0.4 (0.7)	-0.1 (0.5)	-1.71	14	.11	.42
UPDRS "*on*" change	3.8 (6.7)	-4.8 (10.2)	-2.08	17	.05	.45
UPDRS "*off*" change	-5.4 (12.3)	-14.2 (6.9)	-1.89	15	.08	.42
BDI-II change	4.9 (8.7)	0.1 (6.2)	-1.29	15	.22	.32
DRS-2 change	-5.6 (5.9)	-3.7 (6.8)	0.64	18	.53	.15

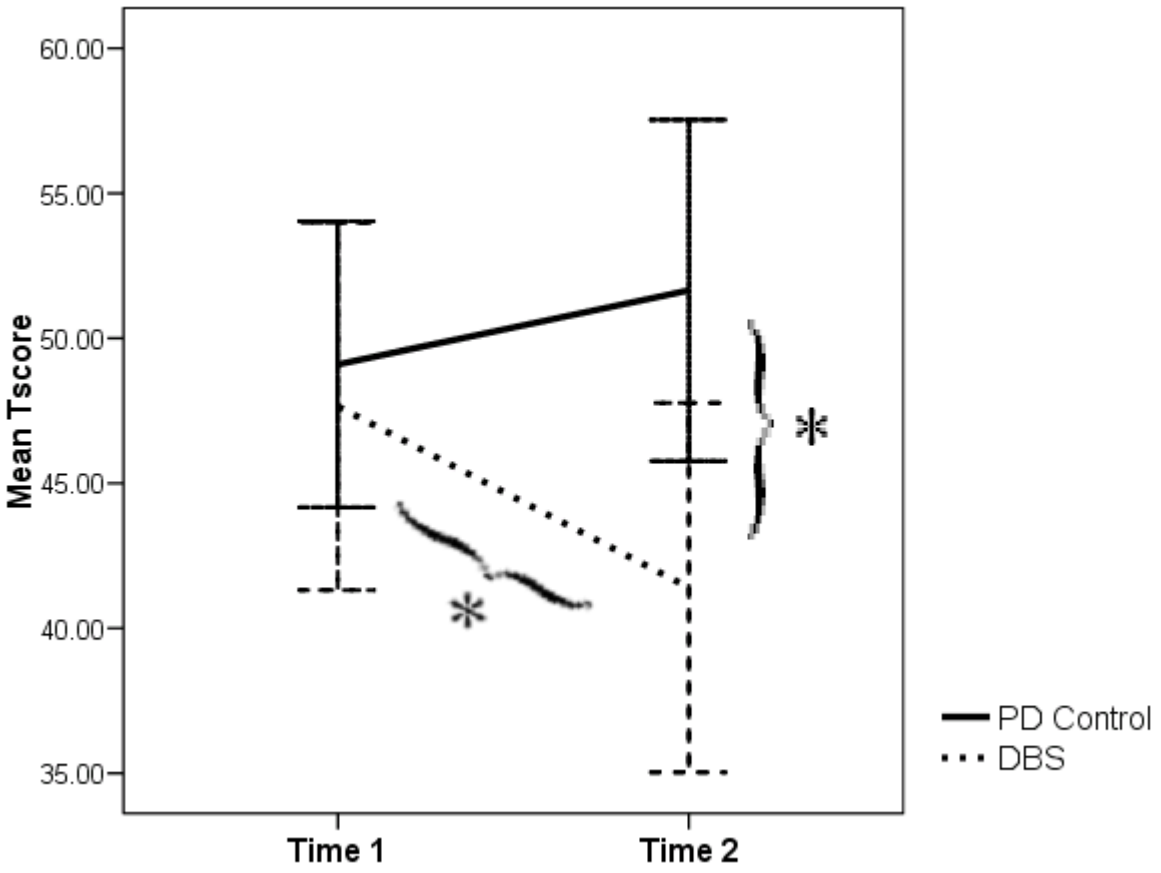

Figure 4-1. Letter fluency interaction

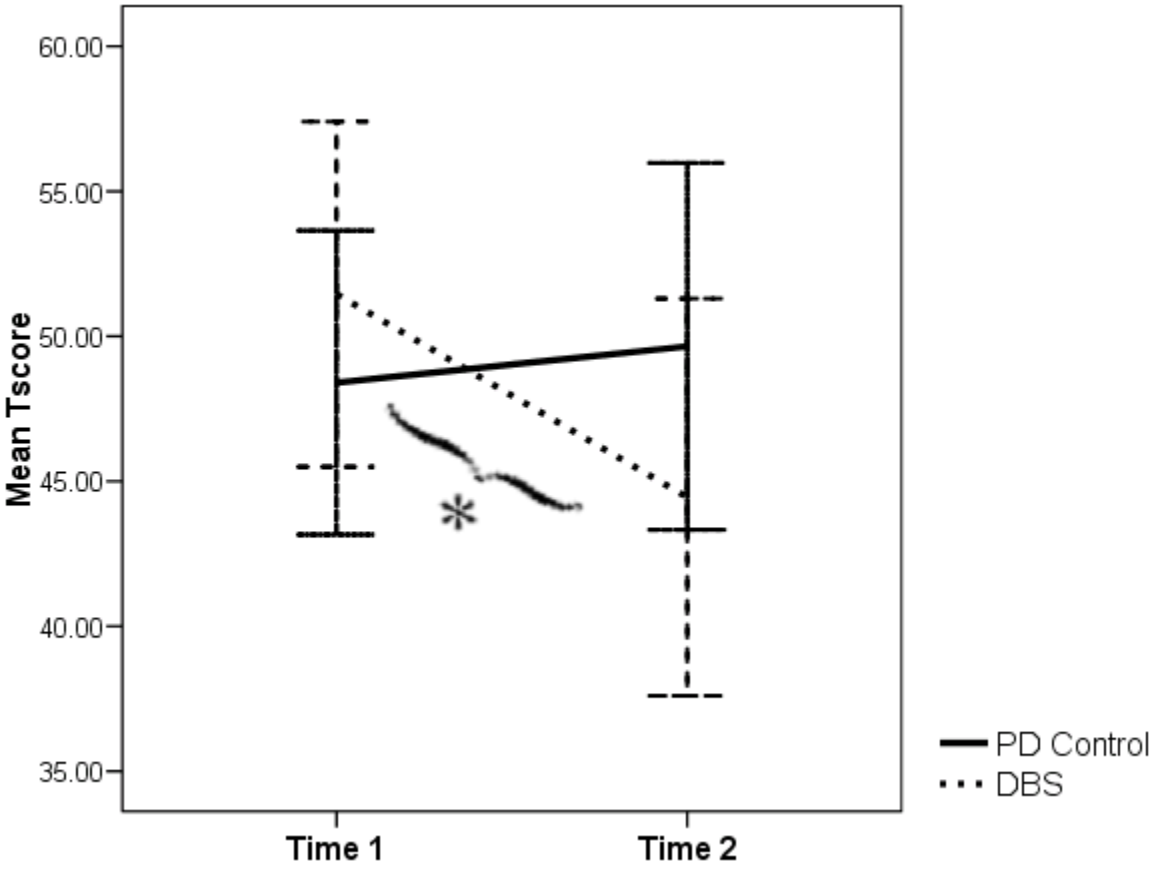

Figure 4-2. Semantic fluency interaction

CHAPTER 5
DISCUSSION

The present study investigated three major aims. First, we hypothesized that compared to PD patients who did not undergo surgery, DBS patients would experience worsened performance on cognitive tests thought to involve the dorsolateral prefrontal cortex. This prediction was based on the supposition that cognitive effects of DBS surgery result from the spread of electrical current from the sensorimotor subregions of subcortical target structures into subregions identified as being involved in the associative basal ganglia-thalamocortical loop, the cortical target of which is the dorsolateral prefrontal cortex. Indeed, previous research has documented declines within cognitive domains commonly associated with dorsolateral prefrontal cortex circuitry.

The second aim sought to assess the significance of individual changes in cognitive performance. The first aim employed inferential statistical procedures in order to infer the statistical rarity of group differences; however, these strategies offer little to no information regarding individual variability in outcome or the significance of individual changes. For this second aim, Reliable Change Indexes (RCIs) corrected for practice effects were calculated based on data from the PD control group in order to identify the magnitude of change that could be expected to occur by chance in an individual patient. Patients whose obtained post-test scores exceeded these 90% confidence intervals were classified as "decliners," and we hypothesized that compared to patients who did not undergo surgery, a greater proportion of DBS patients would evidence significant decline, as assessed by chi square tests.

A final, more exploratory aim of this study attempted to identify factors that differentiate patients who experience cognitive declines after DBS from those who do not. Linear regressions were conducted in order to assess the relative abilities of pre-selected variables identified as

being possibly related to cognitive declines in previous studies (i.e., age, baseline cognitive status, pre-operative depressive symptomatology and side of surgery) to explain variance in cognitive changes. Also, independent samples t-tests were conducted to compare DBS decliners and non-decliners (defined via RCI classification) on a variety of baseline and change variables.

Summary and Interpretation of Findings

The first hypothesis was partially supported by the data. That is, patients who underwent DBS surgery experienced greater declines than controls on the two verbal fluency measures, as predicted, but not on the working memory task (Digit Span Backward) as predicted. The prediction that no significant differences between DBS and control patients would be found on the control tasks of Vocabulary and the Boston Naming Test was supported. Thus, it seems that PD patients *were* more likely to experience selective cognitive decline after undergoing DBS surgery, and these declines were not general across cognitive domains. The declines observed in the present study related to tasks of speeded verbal fluency, which have long been associated with frontal lobe dysfunction. However, evidence for the extent to which declines are observable on all tasks engaging dorsolateral prefrontal cortex circuitry is limited in the present study.

An important contribution of the present study to the literature on DBS-related cognitive changes lies in its use of Reliable Change, a well-established method for defining true, functional change within an individual. Since group comparisons rely on mean performance, it is not possible to fully interpret the meaning of significant group differences without examining individual variability. Significant differences may result from either the majority of a sample performing slightly worse or a subset of a sample performing extremely worse at post-testing. As such, one cannot draw definitive conclusions about the ubiquity of an effect using an exclusively inferential approach. To date, only one published study using RCIs to analyze cognitive effects of DBS surgery for PD exists, and this report featured a shorter (six months) follow-up period,

and the authors only studied patients undergoing bilateral implantation in the subthalamic nucleus (York et al., 2007).

The second hypothesis was supported by the data. The present study documented significant cognitive declines in 45% of the DBS patient group, as compared to only 11% in the control group. This finding supports the view that group-specific cognitive declines likely reflect large and meaningful declines in a subset of patients rather than negligible effects in most or all patients. Individual variability in outcome and the meaningfulness of individual changes may represent the most important information for the clinician, and communicating the incidence of cognitive side effects following DBS surgery to prospective surgical candidates may be more effective with this type of terminology.

The third hypothesis was not fully supported by the data. None of the hypothesized variables (i.e., age, baseline cognitive status, baseline depression score, surgery side) was found to be significantly associated with performance changes on the measure of letter fluency. Moreover, only side of surgery predicted a significant amount of the variance in performance changes on the measure of semantic fluency. It should be noted that the regression analyses used to address this aim were underpowered. The hypothesis that patients undergoing left-sided surgery would experience greater cognitive declines was supported in that significantly more patients who declined had undergone surgery to their left brain. Further comparisons between decliners and non-decliners on a variety of other variables revealed that while these patients did not differ on any baseline measures, there was a trend for decliners to fail to show the degree of motor improvement experienced by non-decliners. Specifically, scores on the UPDRS motor examination, which quantifies the severity of PD-specific motor symptoms, improved moreso in those DBS patients who did not show cognitive decline. This finding could be interpreted as

suggesting that patients who decline cognitively after DBS surgery are those who show a poorer response to surgery in general, perhaps due to variables such as electrode misplacement (Smeding et al., 2007) or the extent of intra-operative complications.

Interpretation and Relationship to the Literature

The majority of studies examining cognitive changes after Deep Brain Stimulation surgery for the treatment of Parkinson's disease document verbal fluency declines; however, reports of working memory changes after surgery, which were not identified in the present study, have been conflicting. The absence of a working memory deficit in this and some previous studies may be at least partially explainable by the fact that verbal fluency tasks and Digit Span Backward engage different neural networks. While research strongly suggests that both verbal fluency and working memory engage the dorsolateral prefrontal cortex, these two types of cognitive tasks involve their own unique and complex neural circuits. Word generation activates a network of frontal, thalamic and basal ganglia structures (Crosson et al., 2003; Friston et al., 1991), while manipulation of auditory material stored in working memory depends on connected areas of various frontal and parietal structures (Jonides et al., 1998). Furthermore, both Digit Span Backward and verbal fluency are composite tasks, comprising multiple subcomponents that seem to differentially employ different areas within these networks (Champod & Petrides, 2007; Tröster et al., 1998).

Aside from differences in the neural circuitry engaged, these two types of neuropsychological tasks differ in the nature of the cognitive abilities they assess. For example, the fluency measures are timed tasks. In contrast, patients are allowed to respond at their own pace in the Digit Span task. Thus, the former tasks are more sensitive to parkinsonian bradyphrenia, or an overall slowing of information processing, which affects patients' response output. Furthermore, the fluency measures require patients to generate endogenous words. In

contrast, patients hear and manipulate exogenous stimuli during the Digit Span task. Some authors have suggested that fluency deficits in PD may be related to a disease-related reduction in self-directed, goal-oriented behavior related to post-surgical apathy (Funkiewiez et al., 2004). Apathy may result from dysfunction in prefrontal cortex-basal ganglia circuits, which are believed to be involved in the generation and control of self-generated purposeful behavior (Levy & Dubois, 2005). Indeed, several reports have suggested that apathy increases after DBS surgery in PD; however, many of these studies suffer from methodological limitations such as inadequate screening measures, and results are conflicting (Van Horn, Schiess, & Soukup, 2001; Saint-Cyr et al., 2000; Drapier et al., 2006). Furthermore, one review concluded that the incidence of apathy following bilateral STN DBS was lower than 0.5% (Temel et al., 2006). A recent study aimed at characterizing the relationship between post-DBS fluency declines and apathy failed to document an association (Castelli et al., 2007).

It is difficult to determine the role of task difficulty in the finding that DBS patients performed more poorly on fluency measures, but not on Digit Span Backward, after undergoing surgery. Baseline T scores were slightly higher on the working memory measure than on either fluency measure. It is unclear whether group-specific declines would have emerged on a more challenging and sensitive task involving working memory or if patients had undergone bilateral, rather than unilateral surgery. Research implicates greater, and possibly more bilateral, involvement of prefrontal cortex with increasing working memory load (Jonides et al., 1997; Klingberg, O'Sullivan, & Roland, 1997). Future studies should employ more working memory tasks with varying difficulty levels to address this question.

Alternatively, the finding that DBS patients declined on verbal fluency but not on a working memory task may reflect a different mechanism underlying cognitive decline after DBS.

Group-specific declines on fluency measures may result not from current spread within subcortical target structures, but rather from direct damage to frontal areas along the electrode trajectory during the DBS surgical procedure. Several studies have documented similarly impaired cognitive performance both with stimulators turned "*on*" and "*off*." Such findings have been interpreted as providing evidence that cognitive declines after surgery may not be related to high frequency stimulation per sé, but rather from damage caused during implantation (Morrison et al., 2004; Daniele et al., 2003). However, there are several methodological problems with many of the "*on-off* DBS stimulation" studies. Most have employed a relatively short "wash-out period" separating the "*on*" and "*off*" conditions, and the effects of stimulation may have persisted well beyond the point at which stimulators were turned off. Additionally, other studies comparing performance with stimulators turned "*on*" and "*off*" have reported opposite findings, namely, that impairments were most prevalent in the "*on*" stimulation condition (Jahanshahi et al., 2000; Hershey et al., 2004; Pillon et al., 2000). In addition, other researchers have documented an association between impaired task performance on a response conflict task and decreased activation in anterior cingulate cortex when stimulators were turned "*on*" (Schroeder et al., 2002). Future research is needed to clarify these conflicting findings.

The second aim employed Reliable Change Indexes (RCIs), to supplement the inferential statistical approach of Aim 1. The finding that 45% of the DBS patients evidenced a significant cognitive decline on at least one measure of verbal fluency, as compared to only 11% in the control group, supports the notion that group-specific cognitive declines likely reflect large and meaningful declines in a subset of patients rather than negligible effects in most or all patients.

Researchers have posited that even when results suggest stable cognitive functioning overall in group studies, individual changes can vary greatly (Dujardin et al., 2001). This idea

was recently highlighted by the only published study using RCI analyses to investigate cognitive outcome six months after bilateral DBS surgery to the STN (York et al., 2007). The authors reported verbal fluency declines only at the trend level when using group comparisons, but they found that 40% of patients evidenced significant declines on their measure of semantic fluency and 26% on their measure of letter fluency. These findings are consistent with those of the present study. Also, this group documented a significant difference between the proportions of DBS and PD control patients experiencing declines, which was found in the present study.

Previous research attempting to identify baseline characteristics that predict which patients are more likely to experience cognitive decline after DBS surgery has been largely unsuccessful. Clinically, it is now generally recognized that very old age, frailty and compromised baseline cognitive functioning put patients at greater risk for cognitive side effects and other complications. For this reason, most centers routinely screen out older, frail individuals and those who are demented when assessing surgical candidacy (Okun et al., 2007). However, most studies have failed to document a significant linear relationship between these variables and cognitive outcome (Ory-Magne et al., 2007; Parsons et al., 2006; Voon et al., 2006). Indeed, rather than employing specific cut-off scores or looking at only one or two variables, most centers exclude patients evidencing frank dementia or very old patients with major comorbidities. In the present study, no patients in the DBS group were over the age of 70, and only patients in whom dementia was vigilantly ruled out were included as per the protocol for candidate selection used by the Movement Disorders Center at the University of Florida. The resultant limited range most likely accounts for the lack of association between age or baseline cognitive functioning and post-surgical cognitive changes in the present study.

The only variable that predicted a significant amount of the variance in cognitive change was side of surgery such that left-sided surgery was associated with greater declines in semantic fluency. The vast majority of the literature on DBS outcomes has not addressed this question, as most patients now undergo simultaneous or closely staged bilateral procedures. Nevertheless, many researchers have documented greater declines in a variety of cognitive tests, including fluency, following left-sided ablative procedures (i.e., pallidotomy or subthalamic nucleotomy) for PD (Tröster, Woods, & Fields, 2003; Cahn et al., 1998; Obwegeser et al., 2000; McCarter et al., 2000). In one of the only studies of this kind in DBS patients, Rothlind et al. (2007) recently reported that in a group of patients undergoing staged bilateral DBS to either GPi or STN, performance on the Animal Fluency Test declined more in patients whose initial surgery was to their left, as opposed to their right brain.

Given that letter fluency seems to be more left lateralized than semantic fluency, which seems to activate both left and right cortical areas (Billingsley et al., 2004; Szatkowska, Grabowska, & Szymanska, 2000), it is somewhat surprising that left-sided surgery was strongly related only to semantic fluency declines. While both fluency tasks require some of the same processing abilities (i.e., retrieval strategies, generating words, monitoring and inhibiting the tendency to perseverate), semantic fluency requires the additional ability to produce category exemplars. Respondents must possess adequate knowledge of the attributes that define a semantic category. For this reason, semantic fluency tasks are considered more sensitive to the breakdown in the structure of semantic knowledge than are letter fluency tasks, which can be completed with phonemic or lexical cues (Newcombe, 1969; Butters et al., 1987). Thus, while both letter and semantic fluency engage frontally-mediated processes and are sensitive to frontal damage, semantic fluency is thought to rely on the overall integrity of the whole left hemisphere

(Jurado et al., 2000). Thus, our finding of greater semantic fluency, but not letter fluency, declines following left-sided DBS may reflect dysfunction in regions of the left hemisphere other than the frontal lobes.

Interestingly, our data suggests that patients who showed a poorer response to surgery (i.e., showed smaller reductions in motor symptom severity after surgery) more often experienced significant declines in verbal fluency. It is possible that electrode misplacement in a subset of patients led to their obtaining less motor benefit due to inadequate stimulation in sensorimotor subregions and concomitant increased stimulation in associative subregions. Stimulation in these latter regions may lead to cognitive dysfunction via disruption of the associative basal ganglia-thalamocortical circuit. The implication that cognitive deficits are related to a lack of motor improvement is not prevalent in the literature; however, most studies have merely dismissed this explanation in light of overall cognitive declines that appear in the context of motor improvements in the same group of patients. However, the logic in using group comparisons to address this question is flawed in that averaging outcomes might mask associations that exist in individual patients. While this approach tests for a systematic relationship between motor and cognitive changes, it does not examine motor changes in a particular patient experiencing significant decline. One group that attempted to characterize the relationship between motor and non-motor outcome by comparing patients who were stratified based on relatively arbitrary cut-offs failed to identify an association between cognitive decline and poor motor response (Perriol et al., 2006). However, these authors only assessed patients using a global measure of cognition (DRS-2).

Study Limitations

The sample used in the present study comprised a relatively small number of both DBS and control patients. A recent meta-analysis highlighted how widespread and problematic this

limitation is in the extant literature on post-DBS cognitive morbidity (Woods et al., 2006). These authors recommended that future studies should aim to include at least 48 surgical patients in order to demonstrate adequate power and reduce the risk of Type II error, which could lead to an overestimation of the cognitive safety of DBS procedures. The present study attempted to address this limitation by its not relying solely on inferential statistical procedures. Reliable Change Indexes were used in order to capture individual changes that may have been masked by group averaging. Indeed, the finding that 45% of DBS patients evidenced a decline in verbal fluency despite small effect sizes in repeated-measures analyses of variance underscores the importance of increased consideration of these issues.

Another limitation of the present study is its lack of sample diversity. The generalizability of findings is limited due to the fact that the vast majority of patients (i.e., 37 of 39) were Caucasian. Furthermore, as mentioned above, the lack of diversity with regard to patients' age and baseline cognitive functioning reduces both the generalizability as well as the interpretability of results. Findings would also have been enhanced by the inclusion of more neuropsychological tests. Only five measures were selected in accordance with the specific hypotheses set forth; however, recent studies have identified other tests that may be sensitive to post-DBS changes (York et al., 2007).

An important limitation of the present study lies in its failure to more fully match DBS and PD control groups. As compared to control patients, DBS patients reported having parkinsonian symptoms for a longer period of time and were experiencing more severe motor dysfunction when assessed "*off*" medication. These important differences make it impossible to completely rule out the contribution of the disease process to our finding of DBS-specific

cognitive declines. As highlighted in Chapter 1, PD itself is associated with particular cognitive impairments, including verbal fluency deficits.

A strength of the present study was its inclusion of a PD control group. While the ideal PD control group would be one that is wait-listed to have DBS surgery, methodological and ethical issues related to the availability and recognized efficacy of DBS make such a group difficult to obtain. To date, no controlled studies in the extant literature have adequately resolved this problem. In many studies, groups were not matched on at least one important disease variable (York et al., 2007; Smeding et al., 2006) or had very small sample sizes (Moretti et al., 2003; Morrison et al., 2004; Gironell et al., 2003).

In the present study, including the variables UPDRS "*off*" and disease duration as covariates in the analyses of variance conducted as part of Aim 1 rendered all effects non-significant. While no main effects were found for either of these variables, the power of these analyses was so low as to make it impossible to draw conclusions. Correlational analyses identified no significant associations between verbal fluency change and either UPDRS "*off*" or disease duration. Finally, there were no significant differences between decliners and non-decliners on either of these variables. Thus, while the data does not seem to suggest that the identified DBS-specific cognitive changes are more related to disease duration or severity than to surgery, it is not possible to completely elucidate the relative contributions of these variables.

Finally, the present study made no attempt to characterize the real-world significance of the identified deterioration in verbal fluency. It is possible that these declines do not significantly impact on patients' everyday functioning or quality of life or that they are considered negligible by patients in the face of motor symptom improvement and the resultant enhancement of functional abilities. Current research on the ecological validity of neuropsychological tests

suggests that commonly-used measures possess only a moderate ability to predict everyday functioning (Burgess et al., 1998; Chaytor & Schmitter-Edgecomb, 2003). Unfortunately, other researchers interested in non-motor outcomes following DBS surgery for PD have similarly made little effort to address this important issue.

However, these declines may point to bona fide problems that enter some patients' lives after undergoing DBS. One study that documented significant worsening on neuropsychological tests qualitatively reported that declines *were* of concern to patients and that many of these patients stated that they would not have decided positively for the surgery had they known beforehand that they would experience them (Smeding et al., 2006). Another group interpreted worsening patient scores on the Cognition subscale of the Parkinson's Disease Quality of Life Scale (PDQ-39), a ubiquitous, multifactorial measure of quality of life in PD, combined with non-significant changes on formal neuropsychological tests as suggesting that these instruments do not fully capture the subjective experience of patients with regard to their cognitive functioning (Ory-Magne et al., 2007). Drapier et al. (2005) documented a dissociation between changes in physical and other aspects of quality of life scales. In this study of only 27 patients, cognitive items on the PDQ-39 did not show improvement, and the Communication subscale showed a trend to worsen. These findings could reflect the role of verbal fluency impairments in patients' real-world functioning.

Directions for Future Research

Our study provides evidence that DBS surgery is associated with verbal fluency declines in a subset of PD patients. As highlighted above, future research is needed in order to explicate the effects of Deep Brain Stimulation surgery on other cognitive domains, namely, working memory, verbal information processing, and specific tasks of executive function. These studies would also be informed by a more systematic investigation of the outcome differences in left vs.

right DBS that are revealed by the present study. Neuropsychological tasks that may be more sensitive to right-brain dysfunction (e.g. Tower of London) may be appropriate in this regard.

The present study was unable to address differences in outcome related to surgery site (i.e., GPi vs. STN). This question is important for determining the ideal site for individual patients and should be investigated with larger samples and randomization protocols. An ongoing NIH-funded study at the University of Florida is currently addressing the topic of DBS surgery site in relation to outcome and laterality. Also, the present study looked only at unilateral DBS, and additional research is needed to compare unilateral and bilateral procedures in order to establish whether neuropsychological deficits associated with DBS are incremental. Future studies should also aspire to longer follow-up in order to determine the persistence and stability of these deficits.

Another important area for future study involves differentiating the effects of the DBS neurosurgical procedure and high frequency stimulation per sé. The former could be partly captured by examining variables such as duration of the operation, the number of electrode passes, intra-operative complications and post-surgical recovery time, while the latter may be characterized by systematically analyzing the effects of stimulation parameters (e.g. pulse width, electrode location, frequency) as well as through well-designed studies in which the same patients are tested "*on*" and "*off*" stimulation.

Finally, future efforts should be directed toward investigating the real-world significance of DBS-related cognitive changes. Since the relationship between neuropsychological tests and everyday functioning is likely moderated by other factors such as depression levels and social support (Chaytor et al., 2007; Okun et al., 2008), researchers should be cognizant of these

variables when drawing conclusions. Tests of everyday functioning and patient and caregiver self-report measures could be developed to address this question.

To conclude, the present study adds to the literature by providing additional support for the existence of verbal fluency declines after DBS surgery. Further, the findings lend support to the view that declines in semantic fluency appear more often after surgery to left subcortical target structures. Also, results suggested that fluency changes are not systematically related to the patient characteristics of age, baseline cognitive status or pre-operative depressive symptomatology. Finally, classification based on Reliable Change highlights the impact of individual variability in outcome, as results indicated that fluency declines reflected significant changes in a subset of DBS patients that was proportionally larger than that of controls and who may have demonstrated a relatively poor surgical outcome in general.

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BIOGRAPHICAL SKETCH

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