Cognitive Effects of Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease

by

CHRISTINA E. MORRISON

A dissertation submitted to the Graduate Faculty in the Department of Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2001

Bell & Howell Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

10/11/00

Date

Joan Borod

Joan Borod, Ph.D., A.B.P.P.

Chair of Examining Committee

10/17/00

Date

Joseph Glick, Ph.D.

Executive Officer

Sarah Raskin, Ph.D., A.B.P.P.

Mitchell Brin, M.D.

Jeffery Halperin, Ph.D.

Yaakov Stern, Ph.D.

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

ABSTRACT

Cognitive Effects of Subthalamic Nucleus

Deep Brain Stimulation in Parkinson's Disease

by

CHRISTINA E. MORRISON

Advisor: Professor Joan C. Borod, Ph.D., A.B.P.P.

The cognitive effects of subthalamic nucleus (STN) stimulation have been investigated, however, there are no reported studies that evaluate, by incorporating a demographically and clinically matched disease control group, whether neuropsychological performance in surgical patients changes beyond the variability of the assessment measures. To address this issue, 17 Parkinson's disease (PD) patients (DBSPD) were tested before and 3.3 months (on average) after bilateral STN stimulator implantation, both on and off stimulation. Eleven demographically and clinically matched PD controls (CPD) were administered the same repeatable neuropsychological test battery twice (Morrison et al, 2000), separated by 2.4 months, with no surgical intervention during the interval. The standardized test scores were grouped by cognitive domain (i.e., Attention, Language, Visuospatial, Verbal Learning, Delayed Recall, Recognition Memory, and Executive), and composite scores for each domain were calculated. Depression was also evaluated. The primary analyses included two-way mixed MANOVAs (2x2) for the composite scores and for the variables within each cognitive domain to evaluate the individual effects of electrode implantation (Surgery

Comparison), high frequency STN stimulation (Stimulation Comparison), and the overall effects of the DBS procedure (Procedure Comparison). Secondary analyses evaluated the univariate Subject Group by Condition interaction for each variable in each comparison.

Relative to change seen in the control group across conditions, the surgery for bilateral electrode implantation adversely affected attention and concentration, and tended to negatively affect verbal learning, naming, and verbal fluency. STN stimulation had little effect on cognition, although there was the suggestion that it may have improved attention somewhat. The STN DBS procedure as a whole tended to result in mild decline in mental tracking, verbal learning, delayed verbal recall, and verbal fluency. Overall, there were no surgery, stimulation, or procedure effects on the depression scale scores. In contrast to these group findings, one DBS patient demonstrated significant cognitive decline following surgery such that he was not testable with stimulation-off but was able to complete most of the battery with stimulation-on. In conclusion, although most subjects experienced only minimal cognitive declines in isolated aspects of cognitive functioning following the STN DBS procedure, on rare occasions, some patients may develop more significant impairment.

ACKNOWLEDGMENTS

This research was supported by a predoctoral NRSA research fellowship from the National Institutes of Mental Health (1F31MH11809-01A1). I would like to thank Dr. Warren Olanow, Chairman of the Neurology Department at Mount Sinai Medical Center (MSMC), for inviting me to participate in the DBS research that he and his colleagues in the Movement Disorders Center at MSMC were conducting. Without his invitation to participate in the DBS projects, this study would not have been possible. I am very much indebted to Dr. Mitchell Brin for his constant advocacy and support of both me and this research. He facilitated access to DBS and control subjects, and generously took the time to tutor me in research, clinical, and academic areas during this project.

I would also like to thank Drs. Jean-Michel Gracies and Fabio Danisi who made themselves available to turn the stimulators on and off, collect baseline motor scale scores, and who were kind enough to be flexible with their schedules so that I could access the DBS subjects. At the New York University Medical Center-Hospital for Joint Diseases, there are three individuals who were enormously helpful in assisting me with accessing DBS subjects. Drs. Kenneth Perrine, Aleksandr Beric, and Djorje Stereo helped me identify DBS subjects and made both themselves and their office space available to me so that data for this study could be collected. During the data analysis phase, the statistical expertise of Dr. Martin Sliwinski was extremely helpful, and I am grateful to him for his assistance in clarifying approaches to analyze this complicated study design.

Finally, I am particularly thankful for the many years of research, clinical, and academic guidance I have received from my committee chair, Dr. Joan Borod.

TABLE OF CONTENTS

	Page
INTRODUCTION	
I. Parkinson's Disease	1
A. Symptoms and Pathophysiology	1-3
B. Cognitive Functioning	3-14
C. Deep Brain Stimulation	14-15
1. Subthalamic Nucleus Deep Brain Stimulation and Motor Functioning	16-18
2. Subthalamic Nucleus Deep Brain Stimulation and Cognitive Functioning	18-26
II. Objectives and Hypotheses	26-28
METHODS	
I. Subjects	29
A. DBS Patients	29-30
B. PD Control Patients	30
II. Procedure	30
A. Medication Status	30-31
B. Neuropsychological Testing	31-32
C. Test Battery	32-37
D. Surgical Procedure	37
III. Data Analysis	37
A. Bilateral DBS Subjects	37-46

B. Unilateral DBS Subjects 46-47

RESULTS

I. PD Control Group 47-48

II. Bilateral DBS Group 48-49

A. Composite Score Analysis 49-51

B. Cognitive Domain Analysis 51-55

C. Depression Scale Analysis 55

D. Correlational Analysis 55-56

III. Unilateral DBS Group 56

A. PD Patient 1 56-57

B. PD Patient 2 57-58

C. PD Patient 3 58-59

D. PD Patient 4 59-60

DISCUSSION 60

I. Surgery Comparison 61-65

II. Stimulation Comparison 65-69

III. Procedure Comparison 69-73

IV. Conclusions 73-77

TABLES 78-110

APPENDIX 111-115

REFERENCES 116-134

LIST OF TABLES

		Page
Table 1.	Diagram of the Study Design for Each of the Three Subject Group by Condition Comparison	78
Table 2.	Variables Assigned to Each Cognitive Domain and Which Variables Were Re-expressed as Logs or Analyzed Nonparametrically	79-80
Table 3.	Demographic and Clinical Characteristics of Control and Bilateral DBS Subjects	81-82
Table 4.	Control Group Mean Difference Scores From Time 1 to Time 2 for Each Variable	83-84
Table 5.	MANOVA and Follow-up ANOVA P-Values for Main and Interaction Effects for the Surgery Comparison	85
Table 6.	MANOVA P-Values for Main and Interaction Effects for the Stimulation Comparison	86
Table 7.	MANOVA and Follow-up ANOVA P-Values for Main Interaction Effects for the Procedure Comparison	87
Table 8.	P-Values for Condition by Subject Group Interaction Univariate F-Tests for Each Variable in Each Comparison	88-89
Table 9.	Descriptive Statistics for Control Subjects in Each Condition	90-92
Table 10.	Descriptive Statistics for Bilateral DBS Subjects in Each Condition	93-95
Table 11.	Descriptive Statistics for Each Variable Collapsed Across Subject Groups	96-99

Table 12. Descriptive Statistics for Each Variable Collapsed Across Conditions 100-103

Table 13. P-Values for Wilcoxon Signed Ranks Tests 104

Table 14. P-Values for Mann-Whitney U Tests 105

Table 15. Descriptive Statistics for Raw Geriatric Depression Scale Scores in Each Comparison 106

Table 16. Demographic and Clinical Characteristics of Unilateral DBS Subjects 107

Table 17. The Amount of Change (in SDs) that Each Unilateral DBS Subject Demonstrated in the Three Comparisons 108-110

INTRODUCTION

Patients with severe motor symptoms secondary to Parkinson's Disease have a choice of several surgical procedures that may reduce or even relieve their symptoms when they are no longer gaining sufficient medical benefit from antiparkinsonian medications. These include ablative procedures of thalamic and basal ganglia nuclei, and, more recently, chronic high frequency deep brain stimulation (DBS). Chronic DBS of the ventral intermediate (VIM) nucleus of the thalamus, subthalamic nucleus (STN), or the internal segment of the globus pallidus (GPi) via permanently implanted electrodes is one of the more recently explored surgical treatments. The DBS procedure has been found to successfully relieve or reduce parkinsonian symptoms, as well as abnormal motor fluctuations secondary to prolonged intake of anti-parkinsonian medications, such as levodopa. Thus far, the neuropsychological ramifications of this procedure have only been investigated to a very limited extent. Those data that are available have not always yielded consistent findings. Therefore, the present study attempts to broaden our understanding of the cognitive effects of the STN deep brain stimulation procedure in Parkinson's disease patients.

I. Parkinson's Disease

A. Symptoms and Pathophysiology

Parkinson's disease (PD) is a progressive degenerative akinetic movement disorder characterized by tremor, rigidity, bradykinesia/akinesia, and postural instability (Jankovic, 1992), though not all patients develop all of these cardinal symptoms. This disease results primarily from a loss of dopaminergic cells in the substantia nigra (SN)

(Hornykiewicz, 1966). Initially, this loss occurs largely in the ventral lateral aspect of the nigra (Gibb & Lees, 1991), although there is evidence for dopaminergic cell loss in the ventral tegmental area as well (Javoy-Agid & Agid, 1980). As dopamine (DA) modulates basal ganglia functioning by controlling cortical input to neurons in the striatum (caudate/putamen) (Young & Penney, 1993), decreased DA from the nigra is followed by a disruption of normal neurophysiological processes in the basal ganglia. The current proposed model of normal basal ganglia functioning, as described by Wichman and DeLong (1993), includes direct and indirect anatomical pathways between the primary basal ganglia input area, putamen, and the primary output areas, GPi and substantia nigra pars reticulata (SNr). These authors describe the direct path as a monosynaptic connection from the putamen to the GPi or SNr, resulting in inhibition of these structures. The more complex indirect path proceeds with a series of connections beginning with the putamen. The putamen inhibits the external segment of the globus pallidus (GPe), GPe inhibits STN, and STN excites GPi. As output from the GPi is inhibitory, the net result of the direct path is to reduce pallidal inhibition of thalamic motor areas (ventral lateral nuclei of the thalamus [VL]) while the indirect path increases pallidal inhibition of VL. See Figure 1. It has been suggested by Bergman, Wichman and DeLong (1990) that excessive activity in the STN might be one of the pathophysiological bases for the abnormal motor movements seen in PD. Their model proposes that decreased dopamine from the substantia nigra ultimately results in disinhibition of the STN. As projections from the STN to the GPi are glutaminergic, hyperactivity in the STN is followed by hyperactivity in the GPi. A final result of this abnormal basal ganglia activity is over inhibition of the VL by GPi. See Figure 2.

Although dopamine is the primary neurotransmitter affected in PD, there is evidence for other neurotransmitter changes. Decreases in neuroadrenaline, serotonin, and acetylcholine have been observed in PD patients (Agid, Ruberg, Dubois, & Pillon, 1987). In addition to neurotransmitter abnormalities in PD, there are other pathophysiological findings. Lewy bodies are another a pathophysiological hallmark of PD. These structures are eosinophilic neuronal inclusion bodies found primarily in the SN, locus ceruleus, dorsal vagus motor nucleus, and substantia innominata, although they are occasionally observed in the neocortex (Olichney, Galasko, Corey-Bloom, & Thal, 1995). The etiology of the pathophysiological processes observed in PD is not clearly understood. There is evidence pointing to both genetic and environmental factors (Golbe & Langston, 1993; Veldman, Wijn, Knoers, Praamstra, & Horstink, 1998).

B. Cognitive Functioning

From the time PD was first characterized by Parkinson in 1817 (Parkinson, 1938) until the 1950s, cognitive deficits were not generally believed to be a part of the disease's symptomotology (Botez & Barbeau, 1975). However, in more recent times, it has been noted that a significant number of individuals with PD do experience cognitive deficits in addition to their motor symptoms. It has been estimated that 40-60 percent of patients with PD experience decreased cognitive functioning (Mahler & Cummings, 1990). In some cases, these deficits are part of a global dementing process (Agid et al., 1987), but in many other cases, patients experience a pattern of cognitive deficits specific to PD that are not part of a dementia (Raskin, Borod, & Tweedy, 1992a; Taylor & Saint-Cyr, 1995). Specifically, areas that are commonly found to be impaired in non-demented patients with

PD are some aspects of executive functions, visuospatial ability, attention, memory, and, to a lesser extent, language (Beatty, Staton, Weir, Monson, & Whitaker, 1989; Levin, Tomer, & Rey, 1992; Matison, Mayeux, Rosen, & Fahn, 1982; Mohr et al., 1990; Raskin, Borod, & Tweedy, 1990; Starkstein, Bolduc, Preziosi, & Robinson, 1989; Taylor et al., 1995). Just as with the spectrum of motor symptoms, Parkinson's patients may experience deficits in some or all of these cognitive areas. As the present study included only non-demented patients, the following is a review of cognitive deficits frequently observed in non-demented PD patients.

1. Attention. In general, the majority of studies find the immediate span of attention, as measured by the Digit Span test, to be normal in PD patients (Huber, Freidenberg, Shuttleworth, Paulson, & Christy, 1989; Starkstein et al., 1989; Stern, Mayeux, & Cote, 1984; Taylor, Saint-Cyr, & Lang, 1987). Reports of normal digit span performance have included patients with and without depression and those in mild to severe stages of the disease. Generally, patients in these studies were tested while taking antiparkinsonian medications. In early untreated patients, Cooper, Sagar, Jordan et al., (1991) found normal performance on the digits forward component of the test but impaired performance on the digits backward aspect, as compared to healthy controls. Gabrieli, Singh, Stebbins, et al., (1996) found untreated PD patients to have an impaired verbal span relative to controls. Levodopa has been described as having a nonspecific arousal effect (Saint-Cyr, Taylor, & Lang, 1993). It is possible that the pathophysiological processes in PD cause a deficit in the immediate span of attention, but this deficit is, at least initially, masked by treatments with antiparkinsonian medications.

This is supported by the work of Hamel and Riklan (1975) who found that performance on the Digit Span test was improved after 42 months of treatment with levodopa as compared to performance prior to levodopa exposure. A similar pattern of findings was observed by Portin and Rinne (1980). Two to three months after first exposure to levodopa, their PD patients were found to have improved Digit Span performance relative to baseline. This benefit was lost after two to three years of treatment. When these PD subjects were tested 8-10 years after initiation of levodopa therapy, a further decline in Digit Span performance was noted. Interestingly, consistent with the findings in de novo patients in the earlier stages of the disease, Portin and Rinne (1980) found that in the patients who had been treated with levodopa for 8-10 years, performance on the digits backward component of the Digit Span test was more significantly different from controls than the difference between the two groups on the total score of the Digit Span test. Perhaps with the progression of the disease, the initial beneficial effect of levodopa treatment on this test of complex attention (digits backward) is lost.

Other aspects of attentional functioning have been found to be abnormal in PD. Wright, Burns, Geffen, et al. (1990), using Posner's paradigm (Posner, 1980), observed that PD patients disengaged from attended locations more readily than controls. This was interpreted as an impairment in vigilance, that is the maintenance of oriented attention. These findings are particularly interesting given work by Clark, Geffen, and Geffen (1987) who have shown that in animals and humans, forebrain dopamine pathways are necessary for integrated orienting behavior. Divided attention, or the ability to focus attentional resources on more than one task simultaneously, has also been found to be reduced. Sharpe (1996) found in early PD an impairment in the ability to divide attention

between two competing auditory stimuli, as compared to controls. Bennett, Waterman, Scarpa, et al. (1995) reported that, although orientation of attention was intact, "with the process of modulating the attentional focus or of managing more than one attentional task, dysfunction in PD became apparent".

2. *Memory.* Memory impairments are commonly found in PD, however, there are specific aspects of memory functioning that are affected more often than others in this disease. Short-term memory impairment for verbal and nonverbal material is a commonly recognized memory deficit in PD patients (Gabrieli, Singh, Stebbins, & Goetz, 1996; Sullivan & Sagar, 1991; Sullivan, Sagar, Cooper, & Jordan, 1993; Taylor, Saint-Cyr, & Lang, 1986; Tweedy, Langer, & McDowell, 1982). These individuals have also demonstrated a reduced ability to learn new information (Daum et al., 1995; El-Awar, Becker, Hammond, Nebes, & Boller, 1987; Ferraro, Balota, & Connor, 1993; Gabrieli et al., 1996; Taylor, Saint-Cyr, & Lang, 1990; Taylor et al., 1986). However, the ability to recall learned information after a delay appears to be intact in nondemented individuals (El-Awar et al., 1987; Sullivan et al., 1991). Reduced learning ability has been attributed to the PD patient's failure to use efficient learning strategies (Daum et al., 1995; Ferraro et al., 1993; Gabrieli et al., 1996; Taylor et al., 1990). Because planning, identification, and use of learning strategies are more appropriately characterized as executive functions, reduced learning ability for some types of material may be due to executive dysfunction, which is frequently observed in PD patients. Alternatively, reduced learning ability may be related to slowed cognitive processing speed. That is, patients are not processing information as fast as it is being presented to them, therefore, some of the presented

material is never encoded. A final hypothesis regarding reduced learning ability in Parkinson's patients is related to non-dopaminergic neurotransmitter changes seen in PD. Dubois, Ruberg, Javoy-Agid, et al. (1983) observed reduced levels of acetylcholine in PD patients as compared to healthy controls. As it has been well established that acetylcholine plays a critical role in learning and memory (Kopelman, 1986), abnormally low levels of this neurotransmitter may contribute to the reduced learning ability seen in many PD patients.

In contrast to these areas of impairment, recognition memory has generally been found to be intact in PD (Daum et al., 1995; El-Awar et al., 1987; Flowers, Pearce, & Pearce, 1984; Gabrieli et al., 1996; Taylor et al., 1986), although there have been exceptions to this prevalent finding (Tweedy et al., 1982; Haeske-Dewick, 1996). It is not surprising that recognition memory in PD patients has generally been found to be within normal limits. Data from human and primate research seems to indicate that recognition memory is primarily subserved by the temporal lobes (Milner, 1974; Mishkin, 1982). Structural temporal lobe pathology is not generally associated with PD.

3. Language. As a whole, language functions are generally regarded to be intact in PD. Even in demented PD patients, language functioning is largely spared (Cummings, Darkins, Mendez, Hill, & Benson, 1988). There are, however, some aspects of language ability that have been reported to be reduced in nondemented PD patients. Although it is not a frequent observation, there are some reports of diminished oral language comprehension in PD (Cummings et al., 1988; Grossman et al., 1991). More common are observations of change in language output ability. Reductions in the

syntactical complexity of speech output have been found by several investigators (Bayles, 1990; Cummings et al., 1988; Illes, Metter, Hanson, & Iritani, 1988). However, it is unclear if the use of simplified sentences represents a "language" impairment or a compensatory strategy on the part of PD patients to communicate effectively. Hypophonia and dysarthria which impair speech intelligibility may cause patients to shorten and/or simplify their sentences in order to communicate successfully. Support for this latter interpretation is found in a more recent study that evaluated written sentences from PD patients. Sentence length, syntactical complexity, and amount of information content were found to be normal in nondemented and mildly demented PD patients (Small, Lyons, & Kemper, 1997).

Confrontation naming and verbal fluency have also been found to be reduced by a number of investigators, although there are exceptions. In early groups of treated and untreated PD patients, naming ability has been found to unimpaired (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Cooper et al., 1992; Randolph, Braun, Goldberg, & Chase, 1993). Beatty, Monson, and Godkin (1989), however, have made a distinction between two subgroups of mild to moderate nondemented PD patients, those with and those without reduced naming ability. These data are consistent with those of Matison, et al. (1982) who also found impairment in naming ability in PD patients. It would seem that a confrontation naming deficit is a cognitive symptom not unlike some of the motor symptoms in PD, that is, it may or may not be present in the disease.

Varied results have also been observed when verbal fluency tasks are given to PD patients. Although there are a few exceptions (El-Awar et al., 1987; Stern et al., 1984), in general, verbal fluency to a phonemic cue (i.e., letter of the alphabet) appears to be

normal in most nondemented PD patients (Auriacombe et al., 1993; Beatty, Monson, & Goodkin, 1989; Cohen, Bouchard, Scherzer, & Whitaker, 1994; Downes, Sharp, Costall, Sagar, & Howe, 1993; Gabrieli et al., 1996; Matison et al., 1982; Raskin, Sliwinski, & Borod, 1992b; VanSpaendonck, Berger, Horstink, Borm, & Cools, 1996a). Timed generation of exemplars belonging to a semantic category (e.g., animals), however, is commonly found to be impaired (Auriacombe et al., 1993; Beatty et al., 1989; Cools, Van Den Bercken, Horstink, Van Spaendonck, & Berger, 1984; Matison et al., 1982; Randolph et al., 1993; Raskin et al., 1992b; Stern et al., 1984), although not always (Gabrieli et al., 1996; VanSpaendonck et al., 1996a). As noted above, Beatty, et al. (1989) divided their sample of PD subjects into those with and without a confrontation naming deficit. Interestingly, they found that, while all PD subjects performed normally on phonemic verbal fluency tests, in the group with impaired naming ability, semantic verbal fluency was also impaired. In their PD group with normal naming ability, semantic verbal fluency was also normal. These data are similar to those of Gurd and Ward (1989). They reported data that combined performance on phonemic and semantic verbal fluency tasks and found that PD patients were impaired relative to normal controls. This impaired verbal fluency performance correlated with performance on the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1978) while the verbal fluency scores of the normal controls did not.

4. Visuospatial. A deficit in the domain of visuospatial functioning has been defined as "difficulty in appreciating the relative position of stimulus-objects in space, difficulty in integrating those objects into a coherent spatial framework, and difficulty in

performing mental operations involving spatial concepts" (Boller et al., 1984). The frequency of visuospatial processing deficits has been reported to be up to 93% in PD patients (Pirozzolo, Hansch, Mortimer, Webster, & Kuskowski, 1982) and such deficits are often found to be independent of general intellectual functioning (Boller et al., 1984; Natsopoulos, Bostantzopoulou, Katsarou, Grouios, & Mentenopoulos, 1993). However, some authors claim that there are no visuospatial deficits in PD or that the decreased performance of these patients on visuospatial tasks is secondary to attention or frontal deficits (Bondi, Kaszniak, Bayles, & Vance, 1993; Brown & Marsden, 1986; Taylor et al., 1986). Discrepancies in the reported performance of PD patients in the visuospatial domain may be related to variable definitions and methodologies. There are many types of separable visuospatial functions, ranging from basic perception to complex integration, organization, and manipulation of visuospatial material, and numerous clinical and experimental measures have been used to assess them. The range of visuospatial functions has been divided into three (i.e., spatial perception, mental rotation, and spatial visualization) (Linn & Peterson, 1985) to five (e.g., spatial perception, spatial memory, spatial attention, spatial mental operations, and spatial construction) (Kritchevsky, 1988) main categories. Within these categories, more discrete functions have been characterized, such as that of personal and extrapersonal spatial orientation, and spatial updating (Montgomery, Silverstein, Wichmann, Fleischaker, & Andberg, 1993).

In studies that assessed a range of visuospatial functions, Taylor et al. (1986) found no deficits, Bondi et al. (1993) obtained mixed results, while Cronin-Golomb and Braun (1997) indicated their results supported a genuine selective visuospatial deficit. Perhaps the variability in the findings is related to the way groups of PD patients are

studied. For example, Boller et al. (1984) observed differences in visuospatial ability as a function of disease severity. Hoehn and Yahr stage 1 and 3 patients were found to be impaired relative to stage 2 patients, on several visuospatial tasks. Raskin, Borod, Wasserstein, et al., (1990) identified subgroups of PD patients with varying visuospatial ability; those who were either intact or impaired on the measures used and those with intact perception but impairment in visuospatial orientation. Boller et al. (1984) state that simple visuospatial tests discriminate better between patients with PD and normal controls than more complex visuospatial tasks. An excellent example of this observation is in the study of Natsopoulos, et al., (1993). They matched a group of PD patients and normal controls on the Raven's Progressive Matrices test, a difficult test of non-verbal intelligence requiring visuospatial perception and complex reasoning ability. Despite equal ability with controls on this difficult measure, the PD patients were found to be impaired on several tests dependent on a number of individual visuospatial functions.

Other studies have revealed deficits in basic perception and discrimination, generally assessed with matching to sample paradigms (Filoteo et al., 1995; Tang & Liu, 1993), and noted that this deficit progressed along with disease duration (Levin, Llabre, Ansley, Brown, & Weiner, 1984; Portin & Rinne, 1980). Stereovision with complex stimuli has also been reported to be impaired in moderate to severe PD patients, while no deficit in this function was found in mildly affected patients (Flowers & Robertson, 1995). A range of somewhat more complex visuospatial abilities, frequently including personal and extrapersonal visuospatial orientation, have also been found to be impaired in PD (Bowen, Burns, Brady, & Yahr, 1976; Bowen, Hoehn, & Yahr, 1972; Lee, Harris, & Calvert, 1998; Hovestadt, de Jong, & Meerwaldt, 1987), particularly in moderately

affected patients (Montgomery et al., 1993), although some studies did not observe this deficit (Brown et al., 1986; Duncombe, Bradshaw, Iansek, & Phillips, 1994; Levin et al., 1991).

5. "Frontal" and Executive. Executive functions consist of a range of higher order intellectual abilities and are often referred to as "frontal lobe" functions. The two terms are used interchangeably because it has been established that executive functions are largely subserved by the frontal lobes (Perecman, 1987). Further human and animal research has expanded this conclusion, supporting the idea that the neuroanatomical substrates of executive functions actually involve frontal-subcortical circuits, specifically those circuits including the thalamus and basal ganglia (Fuster, 1997), not just the frontal lobes. Given this broadened understanding of the neuroanatomical underpinnings of executive functions and the fact that PD neuropathology disrupts these circuits at the level of the basal ganglia, it is not surprising that executive functions are among the most frequently observed cognitive abilities to be adversely affected by PD. In fact, some authors argue that all cognitive deficits observed in PD (e.g., attention, visuospatial, and memory) are the result of impairment in various aspects of executive functioning (Bondi et al., 1993; Taylor et al., 1986) and not the result of impairment in each of the separate cognitive domains.

One executive deficit that has been widely reported on in PD patients is in the area of cognitive set (Cools et al., 1984; Downes et al., 1989; Fimm, Bartl, Zimmermann, & Wallesch, 1994; Owen et al., 1992; Taylor et al., 1990; VanSpaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1996b). Cognitive set has been defined as "a state of

brain activity that predisposes a subject to respond in one way when several alternatives are available" (Flowers & Robertson, 1985). Parkinson's patients have been described as having both a decreased "shifting aptitude" (Cools et al., 1984; Downes et al., 1989), which involves difficulty with altering response patterns from one to another set of response options, and as having instability in their response set (Downes et al., 1989; Flowers et al., 1985), which is identified as difficulty with maintaining a pattern of responding when multiple response options are available. These difficulties with cognitive set in PD patients have been observed in multiple modalities (Cools et al., 1984; Downes et al., 1993; McDonald, Brown, & Gorell, 1996; Flowers et al., 1985). A few authors have reported, however, that PD patients perform poorly on only some set-shifting tasks (Brown & Marsden, 1988; Downes et al., 1989; Downes et al., 1993; Inzelberg et al., 1996; Owen et al., 1993).

Based on this pattern of performance and an analysis of the various tasks used, a number of researchers have concluded that PD patients do not have difficulty performing tasks that require set-maintenance or set-shifting as long as there are explicit rules or external cues to guide the patient's behavior (Brown et al., 1988; Taylor et al., 1990; Van Spaendonck, Berger, Horstink, Borm, & Cools, 1995). What does seem to be impaired, however, is the PD patients' ability to generate internal cues or problem-solving strategies to guide and regulate behavior. In addition to difficulties with developing strategies, planning, and problem solving, other areas of executive impairment noted in Parkinson's patients include deficits in sequencing and inductive and deductive reasoning (Beatty & Monson, 1990; Channon, Jones, & Stephenson, 1993; Downes et al., 1993; Natsopoulos et al., 1997; Owen et al., 1995; Taylor et al., 1990; VanSpaendonck et al., 1996b).

Some aspects of memory functioning that are highly dependent on frontal lobe integrity have also been found to be impaired in PD. The temporal ordering of memories has been observed to be reduced in PD patients (Sager, Sullivan, Gabrieli, Corkin, & Growdon, 1988). In this case, recognition of learned material is intact, however, episodic memories are recalled in the incorrect chronological order. Finally, working memory, which has been defined as "the temporary storage of information in connection with performing other, more complex tasks" (Baddeley, 1995), can be reduced in PD patients (Cooper, Sagar, & Sullivan, 1993; Dalrympl, Kalders, Jones, & Watson, 1994; Gabrieli et al., 1996; Owen, Iddon, Hodges, Summers, & Robbins, 1997).

C. Deep Brain Stimulation

In the 1950's and 60's, successful treatment of PD symptoms was frequently achieved with surgical lesions of the pallidum or thalamus (Cooper, Bravo, Riklan, Davidson, & Gorek, 1958; Svennilson, Torvik, Lowe, & Leksell, 1960). The development of levodopa was followed by a decrease in the use of these surgical procedures because PD symptoms could be medically treated quite effectively without the morbidity and mortality associated with surgical treatments. As a result, over the last ~30 years, levodopa has been one of the primary treatments for the motor symptoms of PD. However, the drug-tolerance and the debilitating dyskinesias that develop from a combination of pharmacological and disease factors (i.e., long-term use of levodopa, altered pharmacodynamics, the disease process, and severity of symptoms) (Yahr, 1993) have precipitated renewed interest in neurosurgical treatments.

One of the newer surgical procedures for relief of severe Parkinsonian symptoms is chronic deep brain stimulation (DBS). It was observed during neurosurgical lesioning procedures that high frequency stimulation in specific neural areas had a similar effect as a lesion on movement disorder symptoms (Andy, 1983). Because of the success of stereotactic lesions for treating PD symptoms, it was proposed that high frequency stimulation could be applied, with permanently implanted electrodes, instead of a destructive lesion (Benabid et al., 1989). This procedure would result in a "functional" rather than a permanent lesion. Therefore, DBS attempts to achieve the same neuroanatomical (disruption of abnormal hyperactivity) and functional (reduction of PD symptoms) outcome as a surgical lesion (Goetz, DeLong, Penn, & Bakay, 1993).

From a clinical perspective, if both types of procedures achieve the same goals, the DBS procedure has several advantages over available destructive neurosurgical treatments, such as pallidotomy, which are not reversible or modifiable once performed. Given the proximity of potential target nuclei to critical structures such as the optic track and internal capsule, it is possible that during the lesioning process, surrounding structures may be adversely affected inadvertently. Therefore, if a reversible "lesion" could be made, then the clinical benefit of a lesion could be obtained without permanent tissue damage. If unacceptable side effects develop, the stimulation can be turned off, thus "reversing" the procedure. Another advantage the DBS procedure has over destructive procedures is that it permits modification of the stimulation parameters to optimize therapeutic benefits and reduce side effects.

1. STN DBS and Motor Functioning. Although several neuroanatomical targets that may be effective in reducing a range of parkinsonian symptoms have been identified (i.e., VIM, GPi, and STN), because the subjects in the present study underwent STN electrode placement, the discussion below will focus on reviewing what is known about STN DBS. As described above, it was proposed that loss of dopaminergic input to the putamen resulted in hyperactivity in the STN, therefore, lesioning the STN might result in clinical improvement of PD symptoms (Bergman, Wichmann, & DeLong, 1990). This hypothesis was supported by Bergman et al.'s (1990) observations of higher STN firing rates in parkinsonian monkeys as compared to normals, and STN lesions in the same animals resulting in reduced akinesia, tremor, and rigidity. Hyperactive STN firing has also been observed in human PD patients (Yokoyama et al., 1998). Therefore, "functional" lesioning of the STN, via DBS, to decrease hyperactivity in this nucleus may also decrease parkinsonian symptoms.

Though this model provides a good basis for experimentation, the anatomical connections among frontal and subcortical structures appears to be more complex than the model reflects (Parent & Hazrati, 1995), and the actual mechanisms of action of STN stimulation remain to be established. A few hypotheses regarding the mechanism of action have, however, been put forth. Benabid, Pollak, Seigneuret et al. (1993) proposed that high frequency stimulation disrupts abnormal firing activity by "jamming" neuronal networks. Others have suggested, based on electrophysiological data from 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP) -treated monkeys, that DBS reduces the abnormally high rate of firing to within normal limits, rather than eliminating all neuronal activity in the target (Boraud, Bezard, Bioulac, & Gross, 1996). This was suggested to

take place via stimulation of myelinated GABAergic afferent fiber tracts which inhibits the target nucleus.

Several studies evaluating motor symptoms have shown that chronic high frequency stimulation of the STN has a significant impact on PD symptoms. Reduction or elimination of parkinsonian motor features with STN stimulation has been observed in MPTP-treated monkeys (Benazzouz, Gross, Feger, Boraud, & Bioulac, 1993) and in humans with PD (rigidity, akinesia/bradykinesia, and motor fluctuations)(Benabid et al., 1994; Limousin et al., 1995; Olanow, Germano, Brin, Swope, & Weisz, 1996; Pollak et al., 1996). Inhibition of STN firing, via DBS or a lesion, has also been observed to reduce tremor in PD patients (Rodriguez et al., 1998).

Data from functional imaging studies provide information on physiological changes that occur with STN DBS. Significant motor-induced blood flow changes in the supplementary motor cortex, the cingulate cortex, and the DLPC have been observed during effective versus ineffective STN stimulation (Limousin et al., 1997). This report proposed that "STN stimulation produces its clinical effects by bringing the pattern of brain activity during movement back toward that described in control subjects". This hypothesis is supported by a more recent report of increased cerebral blood flow in the ipsilateral rostral supplementary motor area and premotor cortex during contralateral movement with STN stimulation as compared to the stimulation-off condition (Ceballos-Baumann et al., 1999).

Little is known about the long-term effects of DBS. In one sample of 20 patients with bilateral STN stimulators, at one year postimplantation, they continued to demonstrate significant improvement in motor and activities of daily living (ADL) scores

both on and off medications (Limousin et al., 1998). Van Blercom, Charles, Limousin, et al., (1999) reported on up to a four-year follow-up period. Their PD patients, all of whom had undergone bilateral STN DBS and had demonstrated significant improvement immediately postoperatively, continued to demonstrate improvement over baseline at two (n= 22), three (n=10), and four (n=5) years post implantation.

Although the DBS procedure with implantation in the STN is performed clinically for the treatment of PD symptoms, this therapy is still under clinical investigation. What has not been extensively reported on are the cognitive effects of the procedure. As a part of determining this procedure's clinical utility, it would be important to identify any cognitive changes associated with surgical placement of electrodes and with high frequency stimulation. From a theoretical standpoint, the DBS procedure offers a unique opportunity for investigating neuroanatomical substrates of cognition. The DBS procedure involves a largely reversible direct manipulation of brain structures. Unlike other time-limited procedures (e.g., intra-operative brain stimulation or the sodium amytal procedure), the manipulation in the DBS procedure is chronic and allows for extended testing to be conducted in the active condition. Therefore, it is possible to study how DBS affects various aspects of multiple cognitive domains in order to improve our understanding of what role certain subcortical structures play in different cognitive processes.

2. STN DBS and Cognitive Functioning. The role of the STN in cognitive functioning is largely unexplored, although there are some preliminary findings in the animal literature Rats with excitotoxic STN lesions have been found to be impaired in

discrimination accuracy and behavioral control, including premature anticipatory responding and perseverative responding on a five choice continuous performance-like task (Baunez & Robbins, 1997). Interestingly, some of these impairments were reduced with systemic administration of a dopamine agonist. These findings were replicated and extended by these authors in a more recent study. Rats with excitotoxic lesions to both the STN and substantia nigra were put through the same test procedures. The addition of the DA depleting lesion resulted in worsened premature responding but did not have an effect on any other deficit observed in the presence of just STN lesions (Baunez & Robbins, 1999a). In a third study, the excitatory inputs to the STN (primarily from cortex and thalamus) were blocked and inhibitory inputs (primarily globus pallidus) were stimulated via chemical manipulation. Under these circumstances, the rats demonstrated reduced choice accuracy, slowed correct responses, and increased omissions and perseverative responses on the same five choice serial reaction time test (Baunez & Robbins, 1999b). These data suggest that the STN, at least in rats, is involved in executive functioning, specifically attentional and behavioral control and integrative functions (Baunez et al., 1999b).

At present, there is only one study that preliminarily investigates the cognitive effects of stereotactic STN lesions and very few studies that have evaluated the cognitive effects of the "functional" STN lesions that are thought to result from the DBS procedure. In the subthalamic nucleotomy study, the authors reported no significant differences across conditions for any of the cognitive measures used (McCarter, Walton, Rowan, Gill, & Palomo, 2000). Their sample (n=12), however, was heterogeneous, in that some patients had unilateral lesions, some patients had a unilateral lesion and an STN

stimulator implanted on the contralateral side, and a third group of patients had bilateral lesions. Therefore, their lack of findings is unclear.

With respect to STN stimulation, Ardouin and colleagues (Ardouin et al., 1999b) reported on a series of PD patients who had undergone either bilateral STN (n=49) or GPi (n=14) electrode placement. In evaluating the effects of DBS in the entire sample (combining the STN and GPi patients) 3-6 months postoperatively, by comparing the presurgical baseline to the postsurgical stimulation-on condition, these investigators found a decline in verbal fluency and improvements on the Trail Making Test (TMT) parts A and B. Posthoc comparisons revealed that on both parts of the TMT, the STN patients improved while the GPi patients did not change. The investigators did not include a measure that might separate the individual effects of the purely motor versus the cognitive/psychomotor components of this task, however. Depression scores also significantly improved in their STN group at the time of the three to six month follow-up. At a 12-month follow-up, a subset (n=26) of these STN patients were evaluated following medication withdrawal (Ardouin et al., 1999a). At that time, the depression scores of this subset had returned to baseline levels.

In a much smaller sample of bilateral STN patients (n=7), comparison of baseline to stimulation-on performance revealed trends for reduced verbal fluency and improved "mental status", visuospatial reasoning skills, and delayed verbal recall at a nine month follow-up visit (Moro, Scerrati, Romito, Tonali, & Albanese, 1999). At a 12-month follow-up, Burchiel et al. (Burchiel, Anderson, Favre, & Hammerstad, 1999) found no changes in memory, attention, or visuomotor functioning in their sample of five bilateral STN patients. Hariz et al., (2000) report the case of a 53 year-old man with a ten year

history of PD and baseline moderate memory deficits who demonstrated cognitive deterioration postoperatively such that he was impaired in his ability to execute his ADL's despite the marked motor improvement he experienced as a result of his bilateral STN DBS. A more detailed description of the specific areas of cognitive decline was not provided.

The clinical findings mentioned above were the result of comparisons between baseline cognitive performance to performance in the stimulation-on condition. This comparison yields information about the overall cognitive effects of the DBS procedure but does not allow for examination of the individual effects of electrode placement versus of DBS. There are, however, a few preliminary reports on the cognitive effects of high frequency STN stimulation where the stimulation-off and stimulation-on conditions were available and directly compared. In the Ardouin et al (1999) study mentioned above, STN stimulation was found to have no effect on a "Frontal" cognitive factor score at three months, but this factor score was improved relative to baseline at 12 months. No change at either postoperative time point was observed in their "Attentional Control" factor score. Jahanshahi and colleagues (Jahanshahi et al., 1998) also testing PD patients following levodopa withdrawal, observed faster response times and improved performance on the Paced Auditory Serial Attention Test (PASAT), missing digits task, and a random number generation task with STN stimulation. A decrease in trial and error visual conditioned learning, however, was also noted. These authors did not report any baseline presurgical cognitive data.

It is clear that the limited available data regarding the cognitive effects of STN DBS are not firm and that a more comprehensive experimental design than has thus far

been utilized is needed to fully evaluate the cognitive effects of all aspects of this surgery. Such a design would allow for the individual evaluation of the cognitive effects of surgical implantation of chronically indwelling electrodes and of high frequency deep brain stimulation. In addition to the animal and clinical data presented above, there are several theoretical reasons that suggest the procedure for implanting the electrodes might have an impact on cognitive processes. The procedure involves stereotactic placement of electrodes into deep brain structures. In order to achieve optimum targeting of the electrodes, several passes (estimated 3-10) of the recording/stimulating probes through the brain may be required. The point of entry for the probes is three centimeters from the midline of the first gyrus anterior to the premotor gyrus. In addition to prefrontal cortex, other structures the electrodes are likely to pass through are the corona radiata, the lateral aspect of the head of the caudate, the nuclei dorsalisoralis (external) and ventraloralis (posterior) of the thalamus, and the internal capsule, as the electrodes angle ventromedially to their target, the STN, which is located one centimeter from the midline. Structures affected by the placement of the electrodes will vary with individual differences in anatomy. Subtle disruption of the fiber tracts, as well as the ventral tier nuclei of the thalamus, from placement of the electrodes could have consequences on cognition. Previous studies of the neuropsychological effects of stereotactic surgeries (i.e., pallidotomy and thalamotomy) have revealed cognitive decline following these procedures (Darley, Brown, & Swenson, 1975; Jurko & Andy, 1973; McFie, 1960; Riklan, Diller, Weiner, & Cooper, 1960), however, this is not always been the case (Asso, Crown, Russell, & Logue, 1969; Soukup et al., 1997).

Although stimulation of the STN is being performed for the purpose of relieving abnormal motor movements, despite the paucity of results reported thus far, neuroanatomical and clinical data suggest the theoretical possibility that disruption of abnormal firing, via DBS, in the STN could have an effect on cognition, particularly on functions heavily dependent on prefrontal cortical functioning. There is ample anatomical evidence demonstrating connections between the STN and the frontal lobes. Alexander, DeLong, and Strick (1986) compiled primate neuroanatomical data and proposed that, in addition to the "motor" circuit which links the basal ganglia and cortex, there are at least four other basal ganglia-thalamocortical circuits that are functionally and anatomically distinct from one another, but reliant on some of the same basal ganglia structures. Two of these additional "closed loops" are the "dorsolateral prefrontal" circuit and the "lateral orbitofrontal" circuit. These circuits, as summarized by Alexander et al. (1986), consist of dorsolateral and lateral orbitofrontal cortical projections to distinct areas of the caudate. The dorsolateral circuit continues with striatal projections to the dorsomedial one-third of the globus pallidus and to rostral portions of the substantia nigra pars reticulata (SNr). The dorsomedial portion of GPi has projections to the ventral anterior (parvocellular) thalamic nucleus (VApc) which in turn projects to the convexity of the frontal lobe. The medialdorsal (pars compacta) nucleus of the thalamus (MDpc) receives input from the rostrolateral SNr and subsequently projects to the dorsolateral prefrontal cortex, thus completing the dorsolateral loop. The lateral orbitofrontal circuit continues from the caudate to the dorsomedial GPi. Within this basal ganglia-thalamocortical circuit, there are also striatal projections to the rostromedial SNr. The circuit then continues with nigral projections to VAmc and MDmc and is completed by

thalamic connections to the lateral orbitofrontal cortex. The STN receives input from the frontal lobes and the external segment of the globus pallidus (GPe) (Young et al., 1993) and impacts both of these circuits (dorsolateral and lateral orbitofrontal) with excitatory input to the GPi and SNr. A more recent review confirms these anatomical relationships but also demonstrates that the circuitry is much more complex than is reflected in this model (Parent et al., 1995).

Evidence from patients with frontal lobe damage (Stuss & Benson, 1984) and from primate studies (Fuster, 1997) indicates that the DLPC and the lateral orbitofrontal cortex (LOFC) clearly play a role in cognition. Although the exact functions subserved by these areas are far from fully understood, some general statements have been made about their role in cognition. The DLPC is thought to be involved with temporal organization of behavior (Fuster, 1997), mental flexibility, reasoning (Mesulam, 1986), attention (Posner & Peterson, 1990), spatial memory (Alexander, Crutcher, & DeLong, 1990), working memory (Freedman & Oscar-Berman, 1989), and conditioned associate learning (Damasio & Anderson, 1993). While damage to the LOFC is more commonly associated with personality and affective changes (Damasio et al., 1993), cognitive deficits that result from damage to this area include difficulties with response inhibition (Lhermitte, 1986) and cognitive set (Stuss et al., 1984); confabulation, digressions in speech, and increased susceptibility to interference (Mattson & Levin, 1990); and perseveration (Alexander et al., 1990). It should be kept in mind, however, that there is considerable overlap in function (Stuss et al., 1984) and in terminal fields of thalamic projections between these two frontal areas (Groenewegen, Berendse, Wolters, & Lohman, 1990). In conclusion, from the anatomical circuits (dorsolateral and lateral

orbitofrontal) described by Alexander et al. (1986) and outlined above, it is suggested that stimulation of the STN could have an impact on the output of these functionally linked structures that are known to play a substantive role in cognition. Although it cannot be predicted with certainty which cognitive domains might be altered as a result of stimulating the STN, it is probable that, given the multiple neuroanatomical connections, functions subserved by the prefrontal cortex could be affected.

A couple of factors suggest that stimulation of the STN may also affect cognitive functions not primarily dependent on structures involved in the basal ganglia-thalamo-frontocortical circuits described above. First, the anatomical circuits described by Alexander et al. (1986) were proposed based on data from primates. Not only are the anatomical data incomplete, but there are likely to be cross species variations. It is possible that there are connections not yet identified in the human brain that are compromised by the pathophysiological processes underlying PD. In addition, "multiple subsidiary circuits appear to modify and modulate the flow of information through the major basal ganglia-thalamocortical pathways ... [providing] additional routes for influences to be exerted on other structures" (Alexander et al., 1990). In particular, the STN, which is normally associated with only the motor system, has been noted to "take part in various basal ganglion circuits with different functions" (Groenewegen et al., 1990). Abnormal physiological functioning in these secondary circuits may, in part, account for the non-executive deficits (e.g., visuospatial or memory functions) that are common to non-demented individuals with PD. Therefore, disrupting abnormally firing cells in the STN, with high frequency stimulation, may have an effect on non-executive cognitive functions often found to be reduced in PD patients. The second reason for

considering the possibility that cognitive functions other than executive areas might be affected by stimulation of the STN is that the frontal lobes are reciprocally connected with all other association cortices both directly and via indirect routes through the basal ganglia and thalamus (Fuster, 1997). Therefore, an alteration in basal ganglia or frontal lobe functioning could impact higher-order processing of information in other cortical association areas.

II Objectives and Hypotheses

Whenever a new medical intervention is developed, it is important to examine the ramifications of the procedure in all potentially affected domains, not just those of immediate interest (in this case motor) during its development. By examining the cognitive effects of different aspects of the chronic deep brain stimulation procedure, important and necessary clinical information can be obtained. This multi-objective preliminary study sought to address this under-explored area.

As indicated, currently there is a very limited amount of data available from which to develop hypotheses about which cognitive functions may be affected by the various aspects of this procedure and whether those effects might be positive or negative. Despite the paucity of information from which to draw upon, preliminary hypotheses have been developed, although they have been kept limited in their breadth and specificity. More highly developed and complex hypotheses would be premature at this stage of the DBS neuropsychological research. The three primary study objectives and the preliminary hypotheses are:

1.) To examine whether surgical implantation of chronically indwelling electrodes, independent of any effects DBS may have, results in a change in cognitive functioning (i.e., the Surgery Comparison). The procedure for electrode placement requires multiple passages of the canula and microrecording/stimulating electrodes through frontal cortical and subcortical structures. This process may result in micro-tissue damage along the electrode tract and at its tip. Although no prior study has examined this individual effect, it is hypothesized that the procedure for electrode placement may result in reduced areas of cognitive functioning.

2.) To assess cognitive changes that may result from chronically stimulating the STN (i.e., the Stimulation Comparison). Although the available preliminary data are mixed, based on the reported findings described above, it is hypothesized that STN stimulation will have little effect on cognitive functioning, however, mild improvements in attention and declines in learning may be observed.

3.) To evaluate the cognitive effects of the DBS procedure as a whole (i.e., the Procedure Comparison). Predictions on the cognitive effects of a "functional" STN lesion are limited by the contradictory findings thus far available in the literature. Overall, it is hypothesized that there may be declines on measures requiring executive control of behavioral responses and improvements in delayed verbal recall ability.

If it is found that, although movement symptoms are relieved, cognitive functioning, as a result of the surgical procedure for electrode implantation, is significantly impaired in some new way (Objective 1), the procedure may no longer be a viable treatment option for some patients. This might be especially true for those PD

patients who have some level of presurgical cognitive impairment associated with their disease. The procedure for implanting the electrodes, however, is just one part of this treatment method. Evaluation of any cognitive improvement or decline that may result from chronic deep brain stimulation in the STN (Objective 2) may provide unique insight into our currently very limited understanding of any role the STN may have in cognitive functioning. Finally, examination of the cognitive effects of the DBS procedure as a whole (Objective 3) will provide essential clinical information. If it is determined that there is improvement, or a lack of decline, in cognitive functioning associated with the DBS procedure, then the known benefits of this treatment are increased. If, however, intellectual decline, either generalized or in specific cognitive areas, is noted, then patients and their physicians will take this information under serious consideration when deciding if subthalamic chronic deep brain stimulation is the appropriate treatment option.

With these objectives in mind, the data gathered in this project will provide clinically useful information regarding the DBS procedure. The results of this study will also allow for a clearer understanding of how these neuroanatomical structures are involved in specific cognitive abilities (e.g., executive functioning), broaden our current understanding of cognitive functioning in individuals with PD, and possibly provide some illumination regarding brain/behavior mechanisms underlying specific cognitive functions typically affected in PD.

METHODS

I. Subjects

As one of the inclusion criteria for surgical candidacy and inclusion in the present study was the absence of dementia, all subjects were administered the Dementia Rating Scale (DRS) (Mattis, 1988). Patients achieving a score in the demented range (i.e., <123/144) were not included. The DRS total score was used as an index of current global cognitive ability. In order to estimate premorbid intellectual functioning, all subjects were administered the National Adult Reading Test-Revised (NART-R) (Blair & Spreen, 1989) and an estimated IQ score was calculated. Both of these measures were administered to patients while they were on medications prior to the baseline condition. Written informed consent was obtained from all participants.

A. DBS Patients

Surgical inclusion criteria were as follows: a diagnosis of idiopathic Parkinson's disease as determined by clinical presence of three of the four cardinal features (tremor, rigidity, bradykinesia, or postural instability) and good levodopa response; other medical problems were stable or well controlled and did not interfere with the proposed intervention; PD medications were stable for one month prior to enrollment; absence of either psychiatric symptoms or hallucinations due to dopaminergic and anti-cholinergic therapy at least one month prior to surgery; and age 30-75, either gender, and any ethnicity. Severity of motor symptoms was evaluated prior to surgery using the Hoehn and Yahr Scale (Hoehn & Yahr, 1967) when the patient was in the medication "off" state. Subjects were not surgical candidates if they had cardiac pacemakers, required repeated

MRIs, had a history of substance abuse, had secondary or drug-induced parkinsonism, or had had a sustained depression with vegetative symptoms and suicidal thoughts or intents.

In order to investigate the three study objectives, surgical patients were tested in three conditions: baseline, postsurgically with stimulation off, and postsurgically with stimulation on.

B. PD Controls

A PD control group was also included. These individuals consisted of PD patients who were clinically and demographically similar to the PD surgical group but had not undergone any type of neurosurgical procedure and who had no history of neurosurgery.

II. Procedure

This study utilized the Program for Neuropsychological Investigation of Deep Brain Stimulation (PNIDBS) (Morrison et al., 2000b) in order to examine the cognitive effects of the various aspects of the DBS procedure.

A. Medication Status

Pharmacotherapies used to treat Parkinson's disease may include levodopa, dopamine agonists, anticholinergics, monoamine oxidase (MAO) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors (Olanow & Koller, 1998). While it is clear some of these medications can adversely affect cognition (e.g., anticholinergics)

(Reid et al., 1992; Van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1993; Walkup, 1991), evidence regarding the cognitive effects of levodopa and dopamine agonists is less consistent (Botez et al., 1975; Mohr, Fabbrini, Ruggier, Fedio, & Chase, 1987; Mortimer, 1996; Reid et al., 1992; Reus, 1986; Stern, Mayeux, Ilson, Fahn, & Cote, 1984). In addition, the dosages required following neurosurgical treatment may change as compared to presurgical levels. Therefore, in an attempt to study the effects of the DBS surgical procedure independently from possible pharmacological variables, whenever possible, patients underwent cognitive testing following withdrawal of antiparkinsonian medications. This was accomplished by testing patients the morning after their usual and customary last pre-midnight dose resulting in a 10-12 hour period of withdrawal. However, some patients were not be able to tolerate any period of drug withdrawal. Therefore, in order to evaluate the cognitive effects of DBS, when it was not possible to test patients in the ideal "drug free" state, an attempt was made to keep drug dosages relatively constant across testing conditions. In the current sample, it was possible to test 9/21 surgical patients in all conditions following antiparkinsonian drug withdrawal. All of the PD control subjects were tested following a 10-12 hour withdrawal of their antiparkinsonian medications at both testing times.

B. Neuropsychological Testing

In the baseline condition, subjects were administered a short battery of standard neuropsychological tests (1-1.5 hours). For the surgical group, the second and third test days took place an average of 13.3 (7.8 SDs) weeks postsurgically with a mean of 9.7 (7.7 SDs) days between the two postoperative conditions. During each of the postsurgical

sessions, alternate equivalent versions of the test battery administered on the presurgical day, were given. One session consisted of the neuropsychological tests being administered while the patient's stimulator was on and the other while it was turned off. The order of the alternate forms of the three randomized test batteries was counterbalanced across subjects, as was the order of the postsurgical conditions (stimulator on or off first). The control group underwent two testing sessions (baseline and time 2) with an average of 9.7 (7.4 SDs) weeks between sessions.

C. Test Battery

The neuropsychological test battery included in the PNIDBS (Morrison et al., 2000b) was utilized in the present study. Several criteria were used during the development of this battery (see list of tests and test descriptions below). First, most of these tests are commonly used in clinical research settings and are known to be reasonably reliable with regard to the cognitive functions they purport to measure. Also, many of them have been found to be good discriminators of specific deficits found in PD (e.g., Raskin et al., 1990). Second, where appropriate, the selected tests have alternate equivalent versions, thereby reducing practice effects. Third, the response format for all tests is verbal/oral. Many other potentially appropriate tests were not selected because they require a motor response, and motor movements are likely to be severely limited due to abnormal motor functioning and/or medication withdrawal. Fourth, the tests are relatively brief. It was anticipated that subjects would fatigue easily and that patients would not want to be withdrawn from their medications for long periods of time. Therefore, whenever possible, brief tests or reliable shortened versions of longer tests

were selected. Finally, standardized tests were chosen over experimental tasks in order to facilitate comparison of the data collected here with those from other studies that have examined cognition in this population. The PNIDBS battery assesses several areas of cognitive functioning, including attention, executive, memory, language, and visuospatial functions. The tasks were administered in a fixed order to minimize interference among tests.

The following functions and specific tests are included in the PNIDBS battery:

1. Attention.

Digit Span (Randt & Brown, 1984)- The Digit Span subtest consists of two parts, the digits forward and digits backward components. These components assess basic attention span and mental tracking abilities. The Randt Memory Test contains five alternate equivalent versions of this subtest.

Brief Test of Attention (BTA) (Schretlen, 1989)- This task assesses more sustained attention and concentration ability. The test is administered via an audio tape and there are two parts. The listener is first required to count the number of letters that occur in ten successively longer alphanumeric sequences. Part two requires counting the number of numbers that occur in the same set of progressively longer alphanumeric sequences. In order to shorten administration time and create two alternate versions for a repeatable test battery, the two parts were used individually.

2. Memory.

Randt Memory Test-Pictures (Randt et al., 1984)- This task assesses visual recognition memory of common objects, both immediately after presentation of the targets and after a five-minute delay. It has five alternate equivalent versions.

Randt Memory Test-Passages (Randt et al., 1984)- This task assess memory for verbal material presented in the contextual format of a prose passage. There is an immediate recall and a five-minute delayed recall trial. It has five alternate equivalent versions.

Hopkins Verbal Learning Test-R (HVLT-R) (Benedict, Schretlen, Groninger, & Brandt, 1998)- modified administration- This task requires the subject to learn up to 12 nouns, belonging to three different semantic categories, over three presentation trials. Because PD patients have been observed to learn and process information slowly, two additional learning trials were added to more fully appreciate the learning curve. In addition, an immediate and cued recall trials were added to make the test more similar to measures commonly used in clinical practice (e.g., California Verbal Learning Test). The HVLT-R was modified and used in this study because it has six alternate equivalent forms to be used in a repeatable battery.

3. Language.

Boston Naming Test- short version (BNT) (Mack, Freed, Williams, & Henderson, 1992)- This task assesses confrontation naming of pictured objects. It has four alternate equivalent versions.

Verbal Fluency (Benton & Hamsher, 1989)- This task requires the timed generation of exemplars to either phonemic or semantic categories. For each condition, subjects were asked to generate words to one phonemic cue and one semantic cue. The phonemic cues used were the letters C, L, and P. The semantic cues that were used were Food, Kitchen Items, and Occupations. These cues were randomized across conditions for each subject.

Automatized Sequences- This task is used as an assessment of oral motor speed and includes three automatized sequence measures, (i.e., the number of seconds required to recite the alphabet, the months of the year, and numbers from 1-20). The average time to complete these three sequences was used.

4. Visuospatial.

Visual Form Discrimination Test (VFDT) (Benton, Hamsher, Varney, & Spreen, 1983)- This task assesses basic visual perception and discrimination abilities. It requires subjects to match a target array of geometric shapes to one of four choices.

Judgement of Line Orientation Test- short form (JLOT) (Woodard et al., 1997)- This task assesses extra personal visuospatial orientation. Subjects are asked to judge the orientation of target lines by visually matching them to an array of 11 choices that are equally spaced across 180 degrees. There are two alternate equivalent versions.

Standardized Test of Direction Sense (STDS) (Money, 1976)- This task assesses personal visuospatial orientation by requiring the subject to mentally make right-left discriminations as they follow a preselected route on a street map presented on an

8.5" x 11" page. In order to perform the task the subjects must mentally rotate themselves in space in order to make the correct right-left determinations.

5. Executive.

Odd Man Out Test (OMOT) (Richards, Cote, & Stern, 1993)- This task assesses cognitive set maintenance and shifting ability and, to a lesser extent, conceptualization and problem solving. Subjects are asked to identify two strategies for grouping objects and to switch back and forth between using these two strategies. They receive feedback about their responses and must use this feedback to improve their performance.

Stroop Color and Word Test (SCWT) (Stroop, 1935)- This task assesses the ability to maintain a cognitive response set despite the interference effect of competing stimulus characteristics. Subjects were tested on three 45" trials. They were asked to first read color words, then say color names, and in the third trial they were instructed to state the color of ink a color word is printed in instead of reading the color word.

Alternating Verbal Fluency (Newcombe, 1969)- This task assesses cognitive set-shifting in the verbal modality. Subjects are first required to generate words beginning with the letter F for 60 seconds. During the next 60-second trial, they are required to generate words beginning with the letters A and S in alternation (Raskin et al., 1992a).

6. Mood.

Geriatric Depression Scale (Yesavage et al., 1983)- This is a self-report questionnaire of depression symptoms designed to account for the fact that many individuals may experience the vegetative symptoms of depression in association with medical conditions rather than as a result of depressed mood.

D. Surgical Procedure.

Utilizing standard methods of imaging and stereotactic techniques, the target coordinates were determined. Next, under local anesthesia, accepted methods of localization and stereotaxy were used to pass first a recording electrode and then a stimulation electrode through frontal and subcortical structures until the target was reached (Germano & Heilbrun, 1998). The final coordinates for the implanted electrode were fine-tuned based on the patterns of microelectrode recordings, the effects of test stimulation (Weisz & Yang, 1998), and intra-operative imaging. The stimulator was implanted in a subclavicular, subcutaneous pocket, under general anesthesia. Following surgery, stimulation parameters were adjusted on an individual basis, by the treating neurologists, so that maximum clinical benefit on motor symptoms was achieved.

III. Data Analysis

A. Bilateral DBS Subjects

Because of the unique nature of this data set, although the sample size is somewhat limited, multiple statistical approaches were utilized. The different approaches are described below. All statistical approaches were used to investigate the three separate

objectives of this study. The first objective was to investigate the potential cognitive effects of electrode placement. This was done by comparing the presurgical baseline condition to the postsurgical stimulation-off condition (Surgery Comparison). The second objective was to examine the effects of chronic deep brain stimulation. To accomplish this, the stimulation-off and stimulation-on conditions were compared to one another (Stimulation Comparison). Finally, the third objective was to explore the overall cognitive effects of the DBS procedure as a whole. This was accomplished by comparing the presurgical baseline and stimulation-on conditions (Procedure Comparison). In each of these three comparisons, the goal was to investigate whether a greater degree of change occurred in the DBS group across surgical conditions than occurred across the test re-test conditions of the control group.

1. Analysis of Cognitive Data

a. Overview. The primary statistical approach employed multivariate analyses of variance (MANOVAs). This primary approach was taken in order to perform a relatively parsimonious analysis, given the small sample size and the large number of variables. The secondary statistical approach examined the variables on an individual basis using univariate analyses of variance (ANOVAs). This secondary investigation provided greater detail regarding how the two groups performed on each of the measures. Both the primary (MANOVAs) and secondary (ANOVAs) approaches were used to evaluate all three comparisons (Surgery, Stimulation, and Procedure) and were applied to composite score analyses, as well as cognitive domain analyses (see C.1. and C.2. below). See Table 1 for a diagram of the three comparisons.

b. Standardization of the Data. In order to prepare the raw data for analysis, the baseline scores from the bilateral surgical (n=17) and control groups (n=11) were combined (total number of subjects = 28) to generate variable means and standard deviations for each of the 22 cognitive variables. These overall means and standard deviations were then used to standardize the data from each variable by generating z-scores for each subject's raw score in all experimental conditions.

To determine whether the standardized data met the assumptions of the (M)ANOVA (i.e., that the data were normally distributed and that the variances of the two subject groups were not significantly different from each other), tests of distribution normality and homogeneity of variance were performed. For the Surgery and Procedure Comparisons, the Time 1 data for the controls and the presurgical data for the DBS subjects served as the baseline data set. Using the standardized scores, analyses of the normality of the distributions (Shapiro-Wilk test of normality for a sample size of <50, [Maxwell & Delaney, 1990]) and the homogeneity of variances between the bilateral DBS and control groups (Levene's Test) for each of the 22 cognitive variables were performed. None of the variables were found to have unequal variances, however, four variables were not normally distributed (BNT, immediate and delayed RMT Picture Recognition, and HVLT-R delayed free recall). Log transformations of the HVLT-R delayed free recall variable allowed for re-expression of the scores such that they were normally distributed. No standard transformation technique adequately normalized the RMT Picture Recognition immediate and delayed scores or the BNT score, therefore,

these three variables were analyzed separately using nonparametric approaches (see below).

For the Stimulation Comparison, the stimulation-off condition served as the baseline for the DBS group, therefore, the same analyses of distribution normality and homogeneity of variances were performed with the control group Time 1 (11 subjects) data and the stimulation-off data from the DBS group (13 subjects). There were no homogeneity of variance differences between the bilateral surgical and control groups for any of the 22 cognitive variables. The distributions for six variables (immediate and delayed RMT Picture Recognition scores, HVLT-R total recall and recognition scores, STDS, and OMOT) were found to have significant departures from normality. The HVLT-R total recall score, the STDS score, and the OMOT score failed the Shapiro-Wilk test of normality, but easily passed once scores were re-expressed using log transformations. The HVLT-R recognition score and the RMT Picture Recognition immediate and delayed scores could not be normalized using a log transformation, therefore, these three variables were analyzed separately using nonparametric techniques (see below).

c. Experimental Analyses.

1.) Composite Score Analysis- Because of the relatively small sample sizes and the relatively large number of variables, the first statistical approach was conservative and sought to a) increase the power of the analyses by reducing the number of dependent variables, and b) broadly examine whether there were changes within particular cognitive domains for each of the three condition comparisons. To this end, the

composite score statistical approach involved combining variables to create global cognitive domain composite scores. These composite scores served as the dependent variables in both the primary and secondary analyses.

The primary analyses included three two-way (2x2) mixed MANOVAs, one for each of the comparisons (Surgery, Stimulation, and Procedure). The MANOVAs consisted of one between-subjects variable (Subject Group: Bilateral DBS and PD Control subjects) and one within-subjects variable (Condition: Condition 1 and Condition 2). See Table 1 for a description of each condition for each subject group. For each of the three comparisons (Surgery, Stimulation, and Procedure), a p-value of .05 was selected, and significant multivariate F-tests were followed by univariate two-way mixed ANOVAs for each of the composite score dependent variables.

As the focus of this preliminary study was to investigate whether neuropsychological test performance changed following the DBS procedure beyond the inherent variability of the measures used, the secondary analyses included examination of the Condition (DBS- baseline, stimulation-off, and stimulation-on; Controls- Time 1 and Time 2) by Subject Group (Bilateral DBS and PD Controls) interaction for the univariate ANOVAs for each composite score in each of the three comparisons (Surgery, Stimulation, and Procedure). These univariate analyses were performed regardless of the significance of the MANOVA interaction effects.

To create the composite scores, variables were first grouped into the seven cognitive domains on an *a priori* basis, according to the cognitive function they are purported to reflect (i.e., Attention, Language, Visuospatial, Verbal Learning, Verbal Recall, Recognition Memory, and Executive; see Introduction). See Table 2 for a listing

of the cognitive domains to which each of the individual variables was assigned. Next, on a subject-by-subject basis, the standardized scores for each variable within a domain were summed to create the composite scores. All 22 variables were included. Thus, every subject had seven composite score dependent variables for each condition.

2.) Cognitive Domain Analysis- In keeping with the preliminary nature of this study, an additional more detailed analysis was performed. When data reduction procedures are executed, as in the case of the composite scores described above, though the analysis is simplified, information regarding the details of each subject's performance on individual tasks is lost. Therefore, the primary and secondary statistical approaches were applied to the cognitive domain analyses.

The primary approach involved performing MANOVAs for each cognitive domain, using the standardized scores from the measures in that domain, for each of the three comparisons (Surgery, Stimulation, and Procedure). This allowed for examination of how the bilateral DBS subjects performed on the individual cognitive variables, in comparison to controls, while still performing a relatively parsimonious analysis. An example of this approach includes an Attention MANOVA being performed for the Surgery, Stimulation, and Procedure Comparisons, which compares the control group to the DBS group, across two conditions, on the attention dependent variables. The structure of these MANOVAs was the same as that described for the composite score MANOVAs, and again, a p-value of .05 was selected.

For the Surgery and Procedure Comparisons, of the three variables assigned to the recognition memory domain, only one was normally distributed (HVLT-R recognition). Therefore, instead of a recognition memory MANOVA, a two-way mixed

ANOVA for the HVLT-R recognition variable, in both comparisons, was performed. For the Stimulation Comparison, a recognition memory MANOVA could not be performed because none of the three variables in this domain were normally distributed. Nonparametric analysis of non-normally distributed variables is discussed below. See Table 2 for which variables in which comparison were analyzed using parametric or non parametric procedures.

As in the case of the composite score analyses, secondary analyses were also performed for each cognitive domain. The procedure was identical to that described above and included examination of the Condition (Condition 1 and Condition 2) by Subject Group (Bilateral DBS and PD Control subjects) interaction from the univariate ANOVA for each variable in each cognitive domain in all three comparisons (Surgery, Stimulation, and Procedure). These univariate analyses were performed regardless of the significance of the MANOVA interaction effects.

The variables that were re-expressed as logs were included in the above described primary and secondary cognitive domain analyses (i.e., Surgery/Procedure baseline: HVLT-R delayed free recall; Stimulation baseline: HVLT-R total recall, OMOT, and STDS). For the variables where log transformations would not adequately normalize the distributions, nonparametric procedures were used to separately examine whether there was change across conditions within an individual subject group and if there was an interaction between the magnitude of change across conditions and the two subject groups. To accomplish this, using the standardized scores, separate (one for each subject group) Wilcoxon Signed Ranks Tests for related samples were performed for the BNT and RMT Picture Recognition immediate and delayed scores to determine whether

there was a significant difference between conditions for the Surgery and Procedure Comparisons. For the Stimulation Comparison, the Wilcoxon Signed Ranks Test was applied in the same manner to the HVLT-R recognition and RMT Picture Recognition immediate and delayed scores. It was anticipated that there would be no changes for any variable across conditions in the control group but that there may be changes in the DBS group. However, if there were changes in the control group, then interpretation of any changes that occur in the DBS group must take into account the control group finding.

The second component of the nonparametric analysis involved looking at the difference between the amount of change that occurred in each subject group across the conditions (i.e., the interaction between Condition and Subject Group). This was examined by performing Mann-Whitney U Tests for independent samples on the change scores (i.e., the second condition minus the first condition) for each group. Again, for the Surgery and Procedure Comparisons, the variables that were analyzed in this manner included the BNT and RMT Picture Recognition immediate and delayed scores, and for the Stimulation Comparison the variables analyzed were the HVLT-R recognition and RMT Picture Recognition immediate and delayed scores. Significant findings would indicate that one group demonstrated a greater degree of change across conditions than the other.

2. *Analysis of Depression Scores.* The depressions scores were analyzed independently of the cognitive scores using a two-way (2x2) mixed analyses of variance (ANOVA), with Subject Group (DBS and PD controls) as the between-subject factor and Condition (Condition 1 and Condition 2) as the within-subjects factor, for each of the

three comparisons (Surgery, Stimulation, and Procedure). Before the ANOVAs were performed, it was determined that variances were not significantly different between the two groups and the data were normally distributed. For the ANOVAs, a p-value of .05 was selected.

3. Correlational Analysis. In order to investigate whether subject characteristics were related to the degree of change observed for each of the 22 cognitive variables and the depression score, correlations were computed between relevant subject characteristics (i.e., age in years, years of education, estimated premorbid IQ via the NART-R, Dementia Rating Scale [DRS] total score, disease duration in years, and total number of electrode passes during the implantation procedure[1]) and specific cognitive change scores from each of the three comparisons.

Demographic (i.e., age and years of education) and general intellectual characteristics (i.e., IQ and performance on measures of global cognitive ability such as the DRS), have all been shown to be related to the level of cognitive impairment observed following brain injury (Lezak, 1983). Therefore, it is possible that these demographic and general intellectual variables may be related to whether changes in cognitive functioning occur following a neurosurgical procedure.

In terms of clinical characteristics, the degree of brain injury has also been found to be related to the level of post-injury cognitive impairment observed (Lezak, 1983). As PD is a progressive degenerative disorder, the number of years of disease duration is an

[1] Information regarding the number of electrode passes during surgery could not be accessed for three of the bilateral DBS subjects

indirect measure of the severity of striatal-nigral degeneration. The number of recording electrode passes required to place the permanent stimulating electrodes may also be an indirect index of possible brain injury sustained during DBS surgery. Therefore, it was also of interest to correlate these two clinical variables with the change scores for each of the three comparisons.

Using the data from the bilateral DBS subject group, the change scores were derived by subtracting the standardized scores for each of the 23 dependent variables described above in the first condition from the scores in the second condition, for each of the three comparisons. Except for the depression variable, positive change scores reflected improvement, and negative scores reflected decline. Three sets of Pearson correlations, one for each of the three comparisons, were then performed. These three analyses correlated the six subject characteristics described above with the 23 change scores associated with a particular comparison (Surgery, Stimulation, and Procedure). For example, a negative correlation between number of electrode passes and the HVLT-R total recall change score would suggest that as the number of electrode passes increased, the ability to learn verbal material across trials on the HVLT-R declined. Because of the large number of correlations (i.e., 414), the more stringent p-value of .01 was used for the correlation analyses.

B. Unilateral DBS Subjects

As only four unilateral DBS patients were available, formal statistical analyses for this group were not possible. Therefore, the data from these subjects were examined with a descriptive approach. For these unilateral DBS subjects, the data were reviewed on a

case-by-case and variable-by-variable basis in order to identify whether their performance changed between conditions beyond the inherent test-retest variability of the measures used. This was accomplished by using change scores to evaluate whether the surgical subjects changed (from one condition to the next on each variable) to a greater extent than did the control group. This process of evaluating each of the four unilateral DBS subjects' change scores, as compared to the control group, for each variable was carried out for each of the three comparisons.

Using the raw scores from the control group (n=11), the mean change score and change score standard deviation from Time 1 to Time 2 (i.e., Time 2 - Time 1 = change score) for each of the 23 measures (22 cognitive variables and one depression variable) were calculated. With these descriptive statistics, for each of the four unilateral DBS subjects, change scores (condition 2 raw score - condition 1 raw score = change score) in each of the three comparisons (Surgery, Stimulation, and Procedure) were converted to z-scores for all of the 23 variables. In order to determine if the amount of change observed in each of the unilateral subjects was meaningful, a criterion of plus or minus two standard deviations from the control group mean for each variable was used.

RESULTS

I. PD Control Group

The PD control group consisted of 11 nondemented (M DRS score = 136.8 [4.2]) subjects of average intelligence (M NART score = 103.5 [10.0]) with moderate to severe idiopathic PD (M Hoehn & Yahr score = 3.3 [.6]). Comparison of demographic and clinical characteristics between the control and bilateral DBS group revealed that overall,

the two groups were fairly well matched. The only significant difference found between the two groups indicted that the surgical group had a higher occupational level ($p = .05$) than the controls. Demographic and clinical characteristics appear in Table 3. It should also be noted that all subjects in the control group were being considered for surgical treatment of their PD. After completing their participation in the present study, many of the PD control subjects went on to have a surgical procedure for treatment of their PD symptoms. Most of those who have not yet been operated on are currently on a surgical waiting list. Thus, the PD control subjects did not posses some unique clinical or personality characteristic that made them inherently different from subjects in the DBS surgical group.

Overall, there was relatively little variability observed in the performance of the control subjects across conditions (Time 1 to Time 2). On average, only two of the 22 cognitive variables resulted in a change score greater than one point and neither of these exceeded 1.3 points. Depression scores also remained stable. The control group change score means and standard deviations for each variable appear in Table 4.

II. Bilateral DBS Group

The bilateral DBS PD group consisted of 17 nondemented (M DRS score = 137.8 [5.6]) subjects of average intelligence (M NART score = 110.3 [8.2]) with moderate to severe idiopathic PD (M Hoehn & Yahr score = 3.3 [.8]). Two subjects underwent staged placement of the stimulating electrodes while the remaining 15 underwent simultaneous bilateral placement. Two subjects had a prior history of right-sided pallidotomy several years prior to undergoing the DBS procedure. Thirteen of the 17 bilateral patients were

tested in all three experimental conditions. Four of the 17 bilateral patients declined to be tested in the stimulation-off condition. Twelve patients declined to undergo the experimental procedures following medication withdrawal. Therefore, they were tested in all conditions with their anitparkinsonian medications. Although findings in the literature have been heterogeneous regarding the cognitive effects of levodopa, a more recent report (Morrison, Borod, Brin, & Olanow, 2000a) found no difference in performance on the PNIDBS battery in the optimally medicated state versus the medication off state (i.e., following a 10-12 hour period of PD medication withdrawal) in moderate to severe PD. Therefore, the medicated and unmedicated bilateral DBS patients were combined for analysis.

A. Composite Score Analysis

See Tables 5-7 for a listing of the p-values for the main effects of the composite score MANOVAs and Table 8 for the p-values for the interaction effect from the composite score ANOVAs. Tables 9 and 10 list the standardized score (i.e., z-score) means and standard deviations for each variable, in each condition, for the control and bilateral DBS groups respectively.

1. Surgery Comparison. In the primary analyses, none of the multivariate F-tests (i.e., Condition, Subject Group, and Condition by Subject Group interaction main effects) for the Surgery Comparison composite score MANOVA were significant.

In the secondary analyses, the only univariate Condition by Subject Group interaction that reached significance was the attention composite score ($p = .031$). In this

case, the controls improved (Time 1 M = -.03[1.95]; Time 2 M = .24[2.21]), while the DBS subjects declined (Baseline M = .01[2.56]; Stimulation-off M = -1.14[2.31]) across conditions. There was a trend for the language composite score Condition by Subject Group interaction (p = .054), wherein the controls tended to stay the same across conditions (Time 1 M = -.96[2.08]; Time 2 M = -.95[2.53]), while the DBS subjects tended to decline (Baseline M = .62[2.23]; Stimulation-off M = -.60[3.44])

2. Stimulation Comparison. In the primary analyses, none of the multivariate F-tests for the Stimulation Comparison composite score MANOVA were significant, although there was a trend for the Condition by Subject Group interaction (p = .069).

In the secondary analyses, none of the composite score Condition by Subject Group interaction univariate F-tests for the Stimulation Comparison were significant. There was a trend for the delayed recall composite score (p = .067), wherein the controls improved (Time 1 M = -.59[2.28]; Time 2 M = -.21[2.59]) and the DBS subjects declined (Stimulation-off M = -.09[3.64]; Stimulation-on M = -.81[3.37]) across conditions.

3. Procedure Comparison. In the primary analyses, none of the multivariate F-tests for the Procedure Comparison composite score MANOVA were significant.

In the secondary analyses, only the delayed recall composite score Condition by Subject Group interaction F-test was significant (.050). In this case, the controls improved (Time 1 M = -.59[2.28]; Time 2 M = -.21[2.59]), and the DBS subjects declined (Baseline M = .38[2.78]; Stimulation-on M = -.81[3.37]) across conditions. There was a trend for the language composite score Condition by Subject Group

interaction F-test (p = .054), wherein the controls did not change (Time 1 M = -.96[2.08]; Time 2 M = -.95[2.53]) and the DBS subjects declined (Baseline M = .62[2.23]; Stimulation-on M = -.63[2.71]) across conditions. There was also a trend for the verbal learning composite score Condition by Subject Group interaction F-test. For this variable, the controls improved (Time 1 M = -.48[1.72]; Time 2 M = -.18[2.39]), while the DBS subjects declined (Baseline M = .32[2.86]; Stimulation-on M = -.88[3.60])

B. Cognitive Domain Analysis

See Tables 5-7 for a listing of the p-values for the cognitive domain MANOVAs and follow-up univariate F tests, Table 8 for the p-values for the interactions from the ANOVAs, Table 11 for standardized score (i.e., z-score) means and standard deviations for each variable, in each condition, collapsed across subject groups, and Table 12 for standardized score (i.e., z-score) means and standard deviations for the two subject groups collapsed across conditions. The Appendix contains the raw data for each variable in each condition.

1. Surgery Comparison. In the primary analyses, the attention (p = .037) and verbal learning (p = .023) domain MANOVAs both yielded significant main effects for the Condition factor. Follow-up univariate analyses for the attention Condition main effect found that digit span backward performance declined across the conditions (Baseline/Time 1 M = 0.00[1.0]; Stimulation-off/Time 2 M = -.4[1.06]; p = .006). There were no significant follow-up univariate analyses to the verbal learning Condition main effect. The attention (p = .022) and executive (p = .020) domain MANOVAs both

resulted in significant main effects of the Subject Group factor. Follow-up univariate analyses to the Subject Group main effect in the attention domain MANOVA were not significant. Follow-up univariate analyses to the Subject Group main effect of the executive domain MANOVA revealed that the controls (M = .49[.67]) performed better than the DBS subjects (M = -.21[1.0]) on the SCWT-Interference score (p = .045). As two out of the three recognition memory domain dependent variables were not normally distributed and required nonparametric analyses, a univariate ANOVA was performed for the HVLT-R recognition score as part of the primary data analysis. None of the univariate main effects for this variable were significant for the Surgery Comparison.

For the variables requiring nonparametric analysis in this comparison (BNT and immediate and delayed Picture Recognition), there were no significant differences between conditions on the Wilcoxon Signed Ranks Test for the control group. For the DBS group, there were no significant differences between conditions for the immediate and delayed Picture Recognition scores. However, there was a difference for the BNT scores (p = .039), wherein the sum of the negative ranks (i.e., baseline BNT ranks > stimulation-off ranks) was greater than the sum of the positive ranks (i.e., baseline BNT ranks < stimulation-off ranks). This pattern indicates a decline in the stimulation-off condition as compared to baseline, in the DBS group. None of the Mann-Whitney U Tests comparing the change scores between the two groups were significant. See Table 13 for a listing of the p-values for the Wilcoxon Signed Ranks Tests and Table 14 for a listing of the p-values for the Mann-Whitney U Tests.

The secondary analyses yielded no significant findings, although there were a few trends. For the phonemic fluency variable (p = .087), the controls improved (Time 1 M =

-.23[.61]; Time 2 M = -.12[.85]) and the DBS subjects declined (Baseline M = .15[1.18]; Stimulation-off M = -.26[1.47]) across conditions. The HVLT-R total recall scores (p = .058) tended to decline very slightly across conditions for the control group (i.e., .09 standard deviations) (Time 1 M = -.26[.73]; Time 2 M = -.35[.92]), while they declined more substantially for the DBS subjects (Baseline M = .17[1.13]; Stimulation-off M = -.60[1.74]).

2. Stimulation Comparison. In the primary analyses, none of the multivariate F-tests for any of the Stimulation Comparison cognitive domain MANOVAs were significant. For the variables requiring nonparametric analysis, the Wilcoxon Signed Ranks Tests revealed no significant differences between conditions for either the control or DBS groups for any of the three variables (Picture Recognition immediate and delayed trials, HVLT-R recognition trial). None of the Mann-Whitney U Tests comparing the change scores between the two groups were significant.

For the secondary analyses, none of the univariate Condition by Subject Group interactions were significant, although there were two trends. For both of the digit span variables (forward and backward), the controls tended to decline somewhat (Forward- Time 1 M = .13[1.03], Time 2 M = -.04[.97]; Backward- Time 1 M = -.23[.87], Time 2 M = -.43[1.02]), while the performance of the DBS subjects tended to improve somewhat (Forward- Stimulation-off M = -.37[.81], Stimulation-on M = -.11[1.06], p = .086; Backward- Stimulation-off M = -.37[1.13], Stimulation-on M = -.11[1.07], p = .092).

3. Procedure Comparison. In the primary analyses, the attention ($p = .020$) and executive ($p = .033$) domain MANOVAs for the Procedure Comparison both resulted in significant main effects of the Subject Group factor. A similar pattern of results to what occurred in the Surgery Comparison was observed in the Procedure Comparison follow-up analyses. No significant results were obtained in the follow-up univariate analyses of the attention variables. Follow-up univariate analyses of the executive variables again found that the controls ($M = .49[.67]$) performed better than the DBS subjects ($M = -.23[1.05]$) on the SCWT-Interference score ($p = .034$). For the language cognitive domain MANOVA, there was a trend for the Condition by Subject Group interaction main effect ($p = .080$). Again, because two out of the three recognition memory domain dependent variables were not normally distributed and required nonparametric analysis, a univariate ANOVA was performed for the HVLT-R recognition score as part of the primary data analyses. None of the univariate main effects for this variable were significant for the Procedure Comparison.

For the variables requiring nonparametric procedures in this comparison (BNT and immediate and delayed Picture Recognition), there were no significant differences between conditions for either the control group or the DBS group using the Wilcoxon Signed Ranks Test. None of the Mann-Whitney U Tests comparing the change scores between the two groups were significant.

The secondary analyses yielded one significant finding and three trends. The BTA Condition by Subject Group interaction was significant ($p = .037$). For this variable, the controls improved across conditions (Time 1 $M = .07[.68]$; Time 2 $M = .71[.79]$), while the DBS subjects declined (Baseline $M = -.05[1.18]$; Stimulation-on $M = -.35[1.19]$).

There were trends for differences across conditions for the semantic fluency, alternating fluency, and HVLT-R total recall variables. For both the semantic fluency ($p = .071$) and the alternating fluency ($p = .086$) scores, the controls improved (semantic fluency- Time 1 $\underline{M}$ = -.22[.81], Time 2 $\underline{M}$ = -.09[.81]; alternating fluency- Time 1 $\underline{M}$ = .03[1.09], Time 2 $\underline{M}$ = .25[.82]), and the DBS subjects declined across conditions (semantic fluency- Baseline $\underline{M}$ = .14[1.10], Stimulation-on $\underline{M}$ = -.55[1.15]; alternating fluency- Baseline $\underline{M}$ = -.01[.97], Stimulation-on $\underline{M}$ = -.65[1.10]). For the HVLT-R total recall score, both groups tended to decline across conditions, however, the change was slight in the controls (Time 1 $\underline{M}$ = -.26[.73]; Time 2 $\underline{M}$ = -.35[.92]) and more substantial in the DBS group (Baseline $\underline{M}$ = .17[1.13]; Stimulation-on $\underline{M}$ = -.60[1.52]) ($p = .064$).

C. Depression Score ANOVAs

None of the univariate F-tests for any of the three depression score ANOVAs (Surgery, Stimulation, and Procedure) were significant. See Table 15 for group means in each condition.

D. Correlation Analyses

1. Surgery. Among the Surgery Comparison change scores, there were two significant findings. A negative correlation between the RMT Story immediate recall change score and the number of electrode passes was noted such that as the number of electrode passes increased, performance in the Story immediate recall trial declined ($p = .01$). A negative correlation between the surgery change scores for the depression variable and estimated premorbid IQ was also observed ($p = .001$). Because an increase

in depression scores indicates a greater number of depression symptoms, this correlation suggested that decreasing depression levels across conditions was related to higher IQ.

2. Stimulation. Two of the Stimulation Comparison change score correlations reached significance. The delayed recall change score from the RMT Story subtest increased, indicating improvement, as the number of years of disease duration increased ($p = .01$). The second finding was noted between the VFDT change score and the total number of points obtained on the DRS. As the VFDT change score increased, indicating improvement, the DRS total decreased ($p = .01$).

3. Procedure. Three of the Procedure Comparison change score correlations were significant, and all three were in the negative direction. Performance on the digit span forward and the HVLT-R delayed cued recall variables declined across conditions as the number of years of disease duration increased ($p = .01$). The last significant correlation involved a relationship between the change score on the alternating fluency task and the total number of electrode passes. As the number of passes increased, performance on the alternating fluency task declined across conditions ($p = .01$).

III. Unilateral DBS Patients

A. PD Patient 1 (PD1)

PD1 is a 72 year-old, right handed male with 14 years of education. Prior to surgery, he was not demented (DRS = 131), and he was estimated to have had average-range intelligence (NART-R = 103). He has a 12-year history of PD, and at baseline

while off parkinsonian medications, his Hoehn & Yahr score was three. PD1 underwent placement of a stimulating electrode in his left STN. He was tested in all pre and postoperative conditions following parkinsonian medication withdrawal. See Table 16 for demographic and clinical characteristics.

In the Surgery comparison, on the 23 possible measures, PD1 demonstrated a moderate amount of change (23%). His digit span backward score improved, while performance on measures of language functioning (naming and phonemic fluency) and verbal recall (i.e., story delayed recall and HVLT-R delayed cued recall) declined. In the Stimulation Comparison, again a moderate amount of change was observed (23%). His naming improved, however, in several other areas, including attention, memory, and executive functions (digit span backward, HVLT-R total recall, delayed picture recognition, and alternating fluency), performance declined. The overall effect of the DBS procedure in this patient resulted in a minimal (Procedure Comparison = 18% of the measures changed) decline in performance on the measures used. Memory (HVLT-R delayed cued recall and delayed picture recognition) and executive variables (SCWT Interference and alternating fluency scores) declined in the stimulation-on as compared to baseline condition. PD1's depression scores were within the nondepressed range in all three conditions. See Table 17 for the amount of change observed in each comparison.

B. PD Patient 2 (PD2)

PD2 is a 64 year-old, right handed male with 16 years of education. Prior to surgery, he was not demented (DRS = 136) and he was estimated to have had average range intelligence (NART-R = 105). He has a nine-year history of PD, and at baseline

while off parkinsonian medications his Hoehn & Yahr score was five. PD2 underwent placement of a stimulating electrode in his left STN. He was tested in all pre and postoperative conditions following parkinsonian medication withdrawal. See Table 16 for demographic and clinical characteristics.

Minimal change was observed in this patient across the three comparisons. Following surgery, PD2 demonstrated declines in his HVLT-R total recall and in HVLT-R semantic cluster scores (9% change). In the Stimulation Comparison, none of the change scores exceeded two standard deviations from the Control Group mean. The overall effects of the procedure in PD2 was decline on a measure of verbal learning (HVLT total recall) and mixed improvement (OMOT) and decline (HVLT-R semantic clustering) on measures of executive functioning (14% change). PD2's depression scores were within the nondepressed range in all three conditions. See Table 17 for the amount of change observed in each comparison.

C. PD Patient 3 (PD3)

PD3 is a 65 year-old, right-handed male with 20 years of education. Prior to surgery, he was not demented (DRS = 142) and he was estimated to have had high average intelligence (NART-R = 111). He has a 12 year history of PD, and at baseline while off parkinsonian medications his Hoehn & Yahr score was three. PD3 underwent placement of a stimulating electrode in his right STN. He was tested in all pre and postoperative conditions following parkinsonian medication withdrawal. See Table 16 for demographic and clinical characteristics.

PD3 demonstrated minimal to moderate amounts of change. In the Surgery Comparison, 22% of the measures significantly changed. Measures of verbal memory (immediate and delayed story recall) and executive functioning (SCWT-Interference score) improved, while delayed recognition memory for pictures declined. The Stimulation Comparison revealed a 27% change with some variables improving and others declining. Some of the variables that improved following surgery, declined with stimulation (i.e., immediate and delayed story recall). Several additional variables declined in this comparison as well, including BTA, semantic and phonemic fluency. One measure of executive functioning (alternating fluency) improved in the Stimulation Comparison. The overall effects of the DBS procedure resulted in minimal change in PD3 (14%). Phonemic fluency and delayed picture recognition declined in the Procedure Comparison, while the alternating fluency variable improved. At baseline, PD3's depression scores were within normal limits, however, postsurgery with the stimulation off, he scored in the mildly depressed range. When tested with the stimulation on, his depression score returned to within normal limits. See Table 17 for the amount of change observed in each comparison.

D. PD Patient 4 (PD4)

PD4 is a 65 year-old, right-handed male with 16 years of education. Prior to surgery, he was not demented (DRS = 130), and he was estimated to have had average range intelligence (NART = 109). He has a 10-year history of PD, and at baseline while off parkinsonian medications, his Hoehn & Yahr score was three. PD4 underwent placement of a stimulating electrode in his left STN. He was tested in all pre and

postoperative conditions following parkinsonian medication withdrawal. See Table 16 for demographic and clinical characteristics.

This patient demonstrated minimal change across all three comparisons. In the Surgery Comparison, only semantic fluency declined (5% change). In the Stimulation Comparison, digit span backward performance improved, while delayed recall of the story declined (9% change). In the Procedure Comparison, his digit span forward improved, while verbal recognition on the HVLT-R declined for a total of 9% change. PD4's depression scores were within the nondepressed range in all three conditions. See Table 17 for the amount of change observed in each comparison.

DISCUSSION

This preliminary study sought to examine the cognitive effects of subthalamic nucleus deep brain stimulation. Though many institutions are studying the motor effects of this procedure, there have been very few investigations of the cognitive effects of STN DBS. Using the methodology and neuropsychological test battery described in the PNIDBS (Morrison et al., 2000b), the individual effects of electrode placement (Surgery Comparison), high frequency STN stimulation (Stimulation Comparison), and the overall effects of the DBS procedure as a whole (Procedure Comparison) were studied. The methodology utilized is somewhat unique in that very few investigators have examined DBS subjects at baseline and postsurgically with stimulation both off and on. Furthermore, to date, there have been no studies that have evaluated, by incorporating a demographically and clinically matched control group, whether there is cognitive change

following the DBS procedure beyond the inherent variability of the measures used to assess that change.

The neuropsychological test battery used (i.e., the PNIDBS) assesses functions in multiple cognitive domains, includes several measures that are sensitive to deficits previously found in PD patients, is brief, repeatable, and can be completed by patients with severe motor deficits. The mean change scores observed in the PD control group and the variance associated with each mean score were relatively modest, given the number of points possible on each measure (see Table 4). This suggests, at least using this type of analysis, that the measures included in the PNIDBS test battery have minimal practice effects across testing sessions.

I. Surgery Comparison

For the bilateral DBS group as a whole, the surgery for electrode placement appeared to have mild adverse effects on some aspects of cognitive functioning. In the attention domain MANOVA, there was a main effect of Subject Group, where controls performed better than DBS subjects, and a main effect of Condition where condition 1-baseline performance was better than condition 2-postsurgical performance. This condition effect appeared to be largely due to a decline in digit span forward performance in the combined groups. Although the Condition by Subject Group interaction for the attention domain MANOVA was not significant ($p = .198$), an exploratory post hoc review of the baseline means for each attention variable in the two separate groups indicated that at baseline, the performance of the two groups was very similar. This combined pattern of findings suggests that the Subject Group main effect was primarily

due to a decline in the DBS subjects in the postsurgical condition. Some support for this pattern comes from the secondary analyses. The Condition by Subject Group interaction for the attention composite score was significant. A review of the group means showed that the control subjects improved across conditions by nearly one third of a standard deviation while the DBS subjects declined by more than one standard deviation postsurgically.

Some aspects of memory functioning also appeared to be adversely affected by the surgery for electrode implantation. There was a main effect of Condition for the verbal learning domain MANOVA. Although follow-up univariate tests were not significant, there was a trend in the secondary analyses for the HVLT-R total recall interaction, where the performance of the control group changed minimally (-.1 standard deviation) across conditions and the DBS group declined more substantially (nearly .8 standard deviations) following surgery. Interestingly, there was a negative correlation between the number of electrode passes during surgery and performance on one of the other verbal learning measures. As the number of passes increased, and hence the potential for tissue damage, the number of story elements recalled immediately after presentation decreased.

For the language domain, while there were no significant findings in the primary analyses, there were some interesting trends in the secondary analyses. The language composite score and the phonemic fluency Condition by Subject Group interactions tended toward significance. Again, the familiar pattern of improvement or minimal change in the Control group and decline in the DBS group across conditions emerged. Finally, in the language domain, the nonparametric analyses indicated that confrontation

naming ability in the control group did not change across conditions, however, performance on this measure by the DBS group declined after surgery.

The significant findings in the executive domain Surgery Comparison analyses did not follow the pattern seen above. The significant main effect of Subject Group in the executive domain MANOVA appeared to be primarily related to actual differences between the two groups on only one variable. Follow-up univariate analyses found that the control group performed better than the DBS group on only the SCWT interference score. The Condition by Subject Group interaction for this variable was not significant.

The unilateral DBS subjects demonstrated minimal amounts of change in the Surgery Comparison. In four subjects with 22 cognitive variables each (i.e., 88 potential significant changes), only 13.6 percent of the measures were noted to change, with significant decline across conditions in eight of these 12 instances of change. The majority of change in the Surgery Comparison occurred in memory and language areas. All of the significant changes in language variables and most of the significant changes in memory variables were in the negative direction, indicating that unilateral subjects declined in these measures following surgery.

Although the statistical analyses of the bilateral subjects as a group and the review of the individual unilateral subject's performance revealed only isolated areas of mild cognitive decline following surgery, relative to PD controls, a dramatic decline occurred in one of the bilateral subjects. The individual data for the bilateral DBS subjects were not reviewed, however, this patient's decline was very obvious both behaviorally and by virtue of the fact that he was unable to complete most of the test battery with stimulation off at 12 weeks post implantation. He was able to complete the Digit Span, Picture

Recognition, and Short Stories subtests of the RMT, the BNT, and the VFDT. He was unable to comply with the task demands on the remaining measures due to his cognitive impairments. A postoperative MRI revealed that the electrodes were located in the STN and there was no evidence of hemorrhage or infarct.

In reviewing this subject's demographic, general intellectual, and clinical characteristics, as compared to the means of the bilateral DBS group as a whole, on most variables, he was within 1 standard deviation from the group mean. In two cases, however, he seemed to be different from the group (i.e., +/-1.5 SDs). He was 14 years older (age 74 years) than the group mean at the time of surgery, and he was 12 years older than the group mean (age 61 years) at the time of his disease onset. This subject was also one of the two individuals who had undergone staged implantation and was one of the five bilateral subjects tested in all conditions following PD medication withdrawal. At this point, it is difficult to know if a single or multiple factors put him at risk for cognitive decline following the second procedure. The other subject in this study who underwent staged placement of his electrodes and the two subjects with a prior history of right-sided pallidotomy did not demonstrate the dramatic changes noted in this individual. Previous DBS studies that have included subjects with prior history of neurosurgery have not reported global cognitive declines following DBS surgery (Fraix et al., 2000; Moro et al., 2000). However, as will be discussed below, this may be due to the fact that most studies do not assess cognitive functioning in the stimulation-off condition.

For both the bilateral DBS group and the unilateral DBS subjects, there was no change in the average number of depression symptoms reported. There was, however, an interesting correlation involving the Surgery Comparison depression change scores and

baseline IQ scores. This negative correlation indicated that as IQ increased, depression change scores decreased. Although this suggests a pattern whereby the higher the IQ a subject has at baseline, the fewer the number of depression symptoms he/she can be expected to report postsurgically, such a conclusion is proposed cautiously. In this sample, not only is it difficult to interpret such a correlation because of the sample size, but also because this significant finding may be a false positive result[2]. However, if it is a true positive finding, it may indicate that subjects with a higher IQ can expect to experience fewer depression symptoms following surgery than subjects with lower levels of baseline intellectual ability. This very preliminary finding will certainly have to be replicated before firmer conclusions can be drawn.

Overall, the observation of some cognitive decline following surgery, excluding any effect STN stimulation may have, is consistent with what was hypothesized. In this study, decline was primarily noted in attention, verbal learning, and language areas. Given the trajectory of the electrodes as the pass through the brain (i.e., through frontal regions), it is not entirely surprising that functions such as attention, mental tracking, new learning, and verbal fluency were somewhat negatively affected.

II. Stimulation Comparison

In the bilateral group, on average, the individual effects of STN stimulation appeared to have very little effect on neuropsychological test performance. The multivariate analyses of both the composite scores and the individual cognitive domains

[2] A total of 414 correlations were performed. Using a p-value of .01, approximately four of the seven significant correlations may have occurred by chance.

were not significant. The secondary Condition by Subject Group interaction analyses also revealed very minimal effects, although a few trends were noted. Digit span forward and backward performance tended to improve with stimulation, while in the control group, digit span performance declined slightly across testing conditions. However, when the group means were reviewed, the magnitude of change was found to be minimal in all cases. For digit span forward, the DBS group improved by only .26 standard deviations while the control group declined by .17 standard deviations. For digit span backward, again the DBS group improved by .26 standard deviations while the control group declined by -.20 standard deviations. Though the strength of the findings for this comparison is not strong, the general pattern is somewhat consistent with the available reports in the literature. Ardouin et al. (1999a) found no change in "frontal" and attention composite scores at a three month follow-up, however, Jahanshahi et al. (1999) noted improvement with STN stimulation on measures of attention and concentration.

A slightly larger trend for change was observed in the Condition by Subject Group interaction for the delayed recall composite score. In this case, the controls tended to improve by nearly .4 standard deviations, while the DBS subjects tended to decline by more than .7 standard deviations when stimulation was applied. Jahanshahi et al. (1998) reported a decline in their DBS subjects on a visual conditioned learning task with stimulation on, as compared to off, however, this type of task is not comparable to the memory tasks administered to the current sample. Therefore, a direct comparison between the two findings cannot be made.

In general, the unilateral DBS subjects exhibited minimal amounts of cognitive change when stimulation was turned on. Among the unilateral subjects, across all the

measures, only 14 percent of the variables changed by more than two standard deviations. Ten of the 13 variables that changed, did so in the negative direction, indicating decline on those measures. The changes were generally observed in the attention, language, and memory domains. Although in the memory domain all of the scores that changed declined, there was no clear pattern of change within the other domains. Decline on memory measures is broadly consistent with the trend for lower delayed recall performance observed in the bilateral DBS group.

In contrast to these group findings, one individual demonstrated dramatic improvement when tested with the stimulation on as compared to off. This individual was the subject described earlier who was not able to complete most of the test battery following the surgery for electrode implantation. When tested with stimulation on, he was able to complete nearly all of the tests, the one exception being the OMOT. It is unclear why there was such a dramatic effect of stimulation in this one patient. It may be the case that cognitive change following the administration of STN stimulation is only observed in the severely cognitively impaired. However, there may potentially be alternate explanations for this outcome. At the moment, there are no other reports describing this type of phenomena in the literature.

Correlation of subject demographic, general intellectual, and clinical characteristics with stimulation change scores revealed only two findings. First, there was a negative correlation between performance on a visual discrimination task (VFDT) and baseline performance on a measure of general intellectual functioning (DRS). This correlation suggests that a greater degree of improvement as a result of stimulation was observed on this visuospatial task in patients with a lower baseline level of global

cognitive ability. This pattern would not be inconsistent with what was observed in the single case described above, wherein this patient with the lowest "baseline" (in this comparison the stimulation-off condition) improved the most as a result of STN stimulation. The second correlation suggested that as the number of years of disease duration increased, and hence the degree of striato-nigral pathology, a greater degree of improvement was observed on a delayed verbal memory task (RMT delayed story recall). This correlation could also be considered to be broadly consistent with the other Stimulation Comparison findings described above. The direction of the correlation intimates that a greater level of baseline neuropathology (and possibly impairment) is associated with a greater degree of cognitive improvement as a result of high frequency STN stimulation. As in the case of the significant Surgery Comparison correlations, the interpretations above are proposed cautiously as these two significant correlations may be among the four potential false positive findings that could be expected.

On average, the number of depression symptoms reported by the surgical patients appeared not to be affected by STN DBS. There were no group changes in the bilateral DBS subjects, and three of the four unilateral subjects' GDS scores remained within normal limits across the stimulation-off and stimulation-on conditions. In one unilateral subject, a mild range GDS score was reduced to within the normal range when stimulation was turned on. Heck, Steinvorth, Tronnier, and Fogel (2000) found no effect of STN stimulation on the number of "positive" or "negative" symptoms endorsed on an adjective checklist. Contrary to this report and the present findings, Bejjani et al., (1999) reported a case where stimulation elicited a profound depression which immediately resolved when stimulation was turned off. Their report, however, indicated that while the

target of the electrodes was the STN, a postoperative MRI revealed that the electrode contact that elicited this effect was actually located in the substantia nigra. Therefore, it is difficult to make a comparison between their case and the lack of change observed in the present study.

The findings from the Stimulation Comparison analyses generally conform to the preliminary hypotheses presented. Overall, there was very little effect of STN stimulation on cognitive functioning, although there was slight improvement on attention tasks and decline in delayed recall performance. There was one subject who experienced dramatic cognitive benefit from STN stimulation and other findings that pointed to the possibility that STN stimulation may only effect cognitive change in those patients with lower "baseline" levels of cognitive ability. At this point, however, given the sample size, and other factors (e.g., the possibility that some of the findings may be false positive results), such a conjecture is largely speculative. It will certainly be interesting to see if this pattern is observed by other investigators. Prior studies have not thus far reported such changes, though this is likely because the stimulation-off condition is generally not included in the research designs of previous studies.

III. Procedure Comparison

The overall cognitive effects of the DBS procedure appeared to be isolated minimal declines in attention, memory, and language domains. In the attention domain, there were subtle findings suggesting increased difficulty with sustained attention and concentration following the procedure. Although the Subject Group main effect of the attention domain MANOVA was significant, there were no remarkable findings in the

follow-up analyses. As indicated in the discussion of the Surgery Comparison, the baseline means for the two groups on the attention variables were comparable, perhaps suggesting that the Subject Group main effect was largely due to decline in the DBS group. As in the case of the Surgery Comparison, some support for this conclusion is found in the secondary analyses. These analyses found that the control group improved on the BTA while the DBS group declined on this measure across conditions. The correlational analyses identified a relationship between decline on an attention variable and one of the subject clinical characteristics. In this case, digit span forward performance decreased as the number of years of disease duration increased.

In the memory domain, the primary analyses indicated no significant cognitive changes between the two groups across conditions, however, the secondary analyses suggested that there may actually be some subtle cognitive changes in this domain. There were trends for verbal learning to be adversely affected by the DBS procedure. For the verbal learning composite score and the HVLT-R total recall score, there was minimal change in the control group across conditions (-.1 and .3 standard deviations respectively), while in the DBS group both variables declined (-1.2 and -.8 standard deviations respectively) in the Procedure Comparison. Long-term memory was significantly affected by the procedure. The delayed recall composite score improved in the control group and declined in the DBS group. One of the measures of delayed recall, the HVLT-R delayed cued recall variable, was significantly inversely correlated with a subject clinical characteristic. As the number of years of disease duration increased, the greater the decline in delayed cued recall following the procedure. The finding of reduced delayed recall performance is contrary to a previous report of improvement in

this function following the DBS procedure (Moro et al., 1999). As both the present and the reported samples were very small and very few findings were significant, it will take more extensive research to determine how long-term memory is affected by STN DBS.

As in the case of the memory domain analyses, for language variables, the primary analyses were unremarkable but trends consistent with the general observation of mild decline following the DBS procedure were noted in the secondary analyses. For the language composite and the semantic fluency scores, there were mild improvements in the control group and larger declines in the DBS group across conditions. Decline in verbal fluency performance has generally been one of the few consistent findings in studies of cognition following STN DBS (Alegret, Valldeoriola, Junque, Vendrell, & Tolosa, 2000; Ardouin et al., 1999b; Moro et al., 1999).

Analysis of the executive domain variables indicated that in general, the control group achieved higher SCWT interference scores than the DBS group. This outcome appeared unrelated to the procedure as the Condition by Subject Group interaction for this variable was not significant. In the secondary analyses, the control group tended to improve on the alternating fluency task and the DBS group tended to decline. Decline on the alternating fluency task by the DBS subjects was also associated with a greater number of electrode passes during surgery. It was hypothesized, based on animal data, that a "functional" lesion of the STN might adversely affect response control. Decline on the verbal set-shifting task may reflect this type of impairment, however, the previously noted reductions in verbal fluency performance may also account for this effect. At this point, a discrimination between whether the decline on the alternating fluency task

reflects the above noted difficulty with verbal fluency or an additional difficulty with mental control and cognitive flexibility cannot be made.

As in the case of the two other comparisons, for the unilateral subjects, there was a minimal amount of cognitive change as a result of undergoing the DBS procedure. Across the subjects, only 13.6 percent (12/88 possible instances of change) of the measures changed by more than two standard deviations, with nine of these 12 instances of change indicating decline. The majority of these changes occurred in memory and executive areas. Of the memory variables that changed, all were in the negative direction, and of the executive variables that changed, most were in the negative direction.

Depression scores were not affected by the procedure as a whole. There were no significant changes in the bilateral subjects, as compared to controls, in the Procedure Comparison. Among the unilateral subjects, all depression scale scores were within normal limits at both baseline and in the stimulation-on condition. Although one prior report noted improvement in mood at the three-month assessment, this effect was lost at the 12-month follow-up (Ardouin et al., 1999b). The general lack of reduction in depression symptoms following the DBS procedure in the present study was surprising as one might expecte that patients would be less depressed with improvement in their motor functioning. Group means indicated that, on average, subjects were minimally depressed in all conditions, however, there was a great deal of variability in the raw scores. See Table 15. It is possible that the marked variability within the groups in each condition obscured possible changes across conditions.

Based on animal STN lesion and human STN DBS studies, it was hypothesized that the DBS procedure might result in decreased executive control of behavioral

responding and improved delayed verbal recall. These predictions were generally not borne out by data from this sample. Although the DBS subjects tended to decline on a measure requiring controlled alternation between response sets, this decline may have been secondary to the observed decline in verbal fluency ability rather than to impaired executive control of responding. The measures administered to these subjects could not distinguish between the two effects. It was also hypothesized that delayed verbal recall would improve, however, the opposite pattern emerged in the present sample. Mild declines in learning and recall were noted. In addition to these declines, mild worsening of sustained attention and mental tracking ability occurred. The correlation analyses all revealed a pattern whereby increased neuropathology, in terms of either longer disease duration or larger numbers of electrode passes, was associated with increased impairment on some cognitive measures.

IV. Conclusions

In the Surgery Comparison, the general pattern of findings suggested mild decline on attention, memory, and language measures. On average, in the Stimulation Comparison, there was very little cognitive change. In the Procedure Comparison, there was a similar pattern of cognitive change to what occurred in the Surgery Comparison, including mild declines in attention, memory, and language areas. This suggests that the procedure for electrode placement may largely account for the cognitive changes that followed the DBS procedure. As indicated (see Introduction above), the surgery for electrode placement involves several passes of the recording electrode through prefrontal cortex and the underlying frontal white matter as it is maneuvered to the target. Therefore

it is not surprising that attention and retrieval of episodic and semantic knowledge, functions that are heavily dependant on frontal lobe integrity, were subtly affected by the procedure.

In contrast to the minimal changes in the group as a whole, one subject demonstrated substantial cognitive decline following surgery and better than average cognitive improvement with stimulation. Though he demonstrated motor and cognitive benefit from STN DBS, his overall decline in functioning following the procedure was such that he had to move from an independent to an assisted living situation because of new impairments in his ability to manage his activities of daily living. There is one other case report of a man, 53 years old, who demonstrated significant motor benefit but global cognitive decline following STN DBS (Hariz et al., 2000). Though the impaired subject from the present sample was older at the time of disease onset and at the time of surgery than the rest of the group, Hariz et al.'s (2000) case was much younger (21 years) than this individual (age 72) at the time of surgery. This suggests that age is not necessarily the primary or the sole predictive factor for the development of cognitive impairment following the DBS procedure.

As the present study and most of the available reports in the literature have found mild to no cognitive change in most subjects following STN DBS, it may be the case that in general, the DBS procedure in this brain nucleus has a limited impact on cognitive functioning. However, these conclusions must be viewed from the perspective of the limitations of the study. Because the present study was a preliminary attempt to implement a rather ambitious and complex study design, given the patient population and procedure under investigation, the sample size was somewhat small. This small sample

size, however, limited the power of the data analyses. In addition, there were very few significant findings and these may have occurred by chance.

A second factor that may partially account for the limited amount of cognitive change observed relates to the test battery. The PNIDBS battery is brief, hence there was a limited range of cognitive functions that were tested. It is possible that STN DBS does significantly affect a wider range of cognitive functions although those functions were not assessed by the measures in the PNIDBS battery. Unfortunately, in order to make the battery feasible to execute to this population of patients, all aspects of every cognitive domain could not be tested comprehensibly. An additional limitation of the test battery was that some of the measures had ceiling effects (i.e., BNT and RMT Picture Recognition subtest). This limited the range of scores and the potential for detecting change across conditions. Despite these limitations of the PNIDBS battery, it is important to note that the present findings are generally similar to those reported in other studies.

A third factor that may have prevented stronger statistical findings could be the heterogeneity of several subject characteristics within the bilateral subject group. Two subjects had staged, as opposed to simultaneous, electrode implantation; two subjects had a history or right-sided pallidotomy; and five subjects underwent all conditions following parkinsonian medication withdrawal. Although previous reports have suggested that PD medications have no effect on performance on the PNIDBS battery (Morrison et al., 2000a) and that subjects with a prior history of neurosurgery do not necessarily demonstrate cognitive decline following DBS (Fraix et al., 2000; Moro et al., 2000), it is unclear how much variance these subject characteristics contributed to the outcome of the

present study. Future studies may wish to systematically analyze, on an *a priori* basis, whether there are differences in neuropsychological test performance following STN DBS as a result of these factors. The present sample was too small and the risk of Type I error too high, however, to perform such subanalyses.

Finally, heterogeneity of factors such as the final locations of stimulating electrodes within the STN and the degree of motor benefit obtained from STN stimulation may have also added to the variance within the bilateral group. Because the STN maintains a rigorous somatotopic organization throughout, it is possible that there are relationships between cognitive changes and the location within the STN that is stimulated and/or the degree of motor change that is obtained with stimulation. If a dramatic motor benefit is observed, then the electrodes are more likely affecting neurons in one of the motor prefrontal-subcortical loops described by Alexander et al. (1986). In this case, cognitive change would be less likely to occur. If, however, subjects derive little motor change from STN stimulation, then the stimulating electrode may be affecting one of the prefrontal-subcortical loops that is more involved with cognitive processes. In this situation, a larger degree of cognitive change might be expected to occur. Unfortunately, it was not possible to collect postoperative MRIs on all subjects to verify that electrodes were in the same area of the STN in all subjects or to collect postoperative ratings on the degree of motor benefit each subject obtained from the procedure.

As research that seeks to improve our understanding of the cognitive effects of the deep brain stimulation procedure continues, each of these methodological and subject issues should be addressed to the greatest possible degree. Finally, given the generally mild but sometimes significant cognitive declines following the DBS procedure observed

in this study, two areas that should be addressed by future studies are immediately apparent. First, in order to assess the clinical relevance of the cognitive declines noted in this and other studies, future studies should include assessment of functioning outside the neuropsychology laboratory by evaluating patients' abilities to complete activities of daily living and their general quality of life as compared to presurgical levels. At this time, it is unknown if the modest declines on neuropsychological measures following the DBS procedure have any impact on functioning in the daily living environment or whether quality of life is affected as a result of these cognitive changes. This information would be important to obtain both to further assess the overall impact of the DBS procedure and to determine how much of a change on neuropsychological test measures is needed before daily functioning is compromised. The second area that should be addressed by future investigations is whether the neuropsychological changes that may occur following the DBS procedure are transient or whether some degree of recovery can be expected. Follow up of patients 1-2 years after electrode placement would address this issue. With this in mind, one-year follow-up testing of the DBS patients in this sample was recently initiated.

Table 1.

Diagram of the Study Design for Each of the Three Subject Group by Condition Comparisons

Comparison	PD Group	Condition 1	Condition 2
Surgery	DBS	Baseline	Stimulation-off
	Control	Time 1	Time 2
Stimulation	DBS	Stimulation-off	Stimulation-on
	Control	Time 1	Time 2
Procedure	DBS	Baseline	Stimulation-on
	Control	Time 1	Time 2

Table 2.

Variables Assigned to Each Cognitive Domain and Which Variables Were Re-expressed as Logs or Analyzed Nonparametrically

Domain	Cognitive variable assigned to each domain	Surgery/Procedure Comparison	Stimulation Comparison
Attention	Digit Span Forward	*	
	Digit Span Backward		
	Brief Test of Attention		
Language	Phonemic Fluency		
	Semantic Fluency		
	Boston Naming Test	nonpar.	
Visuospatial	Visual Form Discrimination		
	Judgement of Line Orientation		
	Test of Direction Sense		log
Verbal Learning	Story-immediate recall		
	HVLT-R-total recall		log
	HVLT-R-immediate cued recall		
Delayed Recall	Story-delayed recall		
	HVLT-R-delayed free recall	log	
	HVLT-R-delayed cued recall		

(table continues)

Domain	Cognitive variable assigned to each domain	Surgery/Procedure Comparison	Stimulation Comparison
Recognition Memory	HVLT-R-recognition		nonpar.
	Pictures-immediate recognition	nonpar.	nonpar.
	Pictures-delayed recognition	nonpar.	nonpar.
Executive	Odd Man Out Test		log
	SCWT-Interference		
	Alternating Fluency		
	HVLT-R-semantic clustering		

Note. *Where no alteration is specified, the standardized variable was retained for the analysis; HVLT-R- Hopkins Verbal Learning Test-Revised; log- log transformation was used on this variable; nonpar.- nonparametric analysis used; SCWT- Stroop Color and Word Test.

Table 3.

Demographic and Clinical Characteristics of Control and Bilateral DBS Subjects

Group	Gender		Age	Educ. (yrs)	Occ.	Age at Onset	Disease Duration (yrs)	Hoehn & Yahr Score†	Surgery to T2*	T1 to T2**	NART- IQ	DRS Total
DBS	13M/4F	M	59.9	15.4	6.7	48.9	10.8	3.2	13.3		110.3	137.8
PD		SD	7.7	2.6	1.9	7.2	3.4	.8	7.8		8.2	5.6
PD	10M/1F	M	62.7	13.8	5.2	52.8	10	3.3		9.7	103.5	136.8
Controls		SD	11.5	2.6	2	12.4	3	.6		7.4	10	4.2
t-test			-.77	1.53	2.06	-1.05	.70	1.16	1. 22		1.95	.48
df			26	26	26	26	26	26	2 6		26	26
p-value			.45	.14	**.05**	.30	.49	.29	.2 3		.06	.63

Note. *The number of weeks from the date of surgery to the date of the first postsurgical condition; **The number of weeks between the time 1 and time 2 test sessions that the controls underwent; †Assessed at baseline following a 12 hour withdrawal of PD

medications; DBS PD- bilateral deep brain stimulation Parkinson's disease subjects; PD Controls- Parkinson's disease patients that did not undergo surgery; Educ.- education in years; Occ.- occupational status on a nine point scale (Hollingshead, 1977); T1- time 1; T2- time 2; NART- National Adult Reading Test (Blair et al., 1989); DRS- Dementia Rating Scale (Mattis, 1988).

Table 4.

Control Group Mean Difference Scores From Time 1 to Time 2 for Each Variable

Measure	Possible Range*	PD Mean	PD SD
Digit Span Forward	14	-0.45	1.57
Digit Span Backward	14	-0.38	1.34
Brief Test of Attention	10	1.27	1.42
Phonemic Fluency	nul	0.43	2.59
Semantic Fluency	nul	0.68	4.17
Boston Naming Test	15	-0.36	1.57
Visual Form Discrimination	32	0.91	2.66
Judgement of Line Orientation	15	-0.64	1.91
Test of Direction Sense	32	-1.27	2.69
Story-immediate recall	20	0.91	2.55
HVLT-R-total recall	60	-0.73	4.54
HVLT-R-immediate cued recall	12	0.09	2.70
Story-delayed recall	20	0.31	1.60
HVLT-R-delayed free recall	12	0.36	2.20
HVLT-R-delayed cued recall	12	0.36	1.75
Pictures-immediate recognition	15	0.27	0.65
Pictures-delayed recognition	15	0.13	0.85

(table continues)

Measure	Possible Range*	PD Mean	PD SD
HVLT-R-recognition	24	0.55	1.57
Odd Man Out Test	40	0.04	3.10
SCWT-Interference	nul	-0.67	4.57
Alternating Fluency	nul	0.19	0.96
HVLT-R-semantic clustering	45	0.09	4.91
Geriatric Depression Scale	30	0.82	3.71

Note. Means are in z-score units. *Possible Range- total number of points possible on the measure: Mean- the mean difference scores calculated using the standardized scores; SD- the standard deviations for the means; nul- no upper limit to the points possible on the measure; HVLT-R- Hopkins Verbal Learning Test-Revised; SCWT- Stroop Color and Word Test.

Table 5.

MANOVA and Follow-up ANOVA P-values for Main and Interaction Effects for the Surgery Comparison

Analysis	MANOVA			ANOVA	
	Condition	Subject	C x S Interaction	Condition	Subject
Composite Scores	0.568	0.648	0.198		
Attention	**0.037**	**0.022**	0.141	Digit Span Backward-.006	NS
Language	0.499	0.908	0.190		
Visuospatial	0.393	0.963	0.795		
Verbal Learning	**0.023**	0.474	0.286	NS	
Delayed Recall	0.418	0.735	0.415		
Recognition Memory	n/a	n/a	n/a	HVLT-R Recog- .562	HVLT-R Recog- .952
Executive	0.565	**0.020**	0.219		SCWT-I - .045

Note. MANOVA- multivariate analysis of variance; ANOVA- analysis of variance; NS- none of the follow-up univariate F-tests were significant; n/a- a MANOVA was not performed for this cognitive domain; HVLT-R Recog- Hopkins Verbal Learning Test-Revised recognition score; SCWT-I- Stroop Color and Words Test interference score.

Table 6.

MANOVA P-values for Main and Interaction Effects for the Stimulation Comparison

Analysis	MANOVA		
	Condition	Subject	C x S Interaction
Composite Scores	0.657	0.743	0.069
Attention	0.242	0.108	0.137
Language	0.814	0.391	0.447
Visuospatial	0.278	0.784	0.838
Verbal Learning	0.946	0.301	0.553
Delayed Recall	0.883	0.358	0.357
Executive	0.976	0.077	0.858

Table 7.

MANOVA and Follow-up ANOVA P-values for Main and Interaction Effects for the Procedure Comparison

Analysis	MANOVA			ANOVA	
	Condition	Subject	C x S Interaction	Condition	Subject
Composite Scores	0.404	0.552	0.195		
Attention	0.404	**0.020**	0.219		NS
Language	0.348	0.860	0.080		
Visuospatial	0.402	0.728	0.640		
Verbal Learning	0.901	0.089	0.254		
Delayed Recall	0.697	0.827	0.402		
Recognition Memory	n/a	n/a	n/a	HVLT-R Recog- .939	HVLT-R Recog- .720
Executive	0.634	**0.033**	0.223		SCWT-I - .034

Note. MANOVA- multivariate analysis of variance; ANOVA- analysis of variance; NS- none of the follow-up univariate F-tests were significant; n/a- a MANOVA was not performed for this cognitive domain; HVLT-R Recog- Hopkins Verbal Learning Test-Revised recognition score; SCWT-I- Stroop Color and Words Test interference score.

Table 8.

P-values for Condition by Subject Group Interaction Univariate F-tests for Each Variable in Each Comparison

Cognitive Variable	Surgery	Stimulation	Procedure
Attention Composite Score	**0.031**	0.234	0.187
Digit Span Forward	0.444	0.086	0.582
Digit Span Backward	0.111	0.092	0.870
Brief Test of Attention	0.113	0.660	**0.037**
Language Composite Score	0.054	0.900	0.054
Phonemic Fluency	0.087	0.852	0.124
Semantic Fluency	0.238	0.359	0.071
Boston Naming Test	nonpara.	0.154	nonpara.
Visuospatial Composite Score	0.407	0.228	0.573
Visual Form Discrimination	0.320	0.545	0.717
Judgement of Line Orientation	0.670	0.454	0.517
Test of Direction Sense	0.555	0.888	0.366
Learning Composite Score	0.105	0.420	0.071
Story-immediate recall	0.767	0.223	0.313
HVLT-R-total recall	0.058	0.989	0.064
HVLT-R-immediate cued recall	0.307	0.977	0.378

(table continues)

Cognitive Variable	Surgery	Stimulation	Procedure
Delayed Recall Composite Score	0.131	0.067	**0.05**
Story-delayed recall	0.830	0.323	0.427
HVLT-R-delayed free recall	0.155	0.180	0.335
HVLT-R-delayed cued recall	0.118	0.165	0.125
Recognition Composite Score	0.140	0.663	0.335
Pictures-immediate recognition	nonpara.	nonpara.	nonpara.
Pictures-delayed recognition	nonpara.	nonpara.	nonpara.
HVLT-R-recognition	0.253	nonpara.	0.185
Executive Composite Score	0.203	0.448	0.111
Odd Man Out Test	0.426	0.750	0.284
SCWT-Interference	0.182	0.459	0.372
Alternating Fluency	0.245	0.439	0.086
HVLT-R-semantic clustering	0.151	0.716	0.301
Geriatric Depression Scale	0.169	0.69	0.42

Note. nonpar.- nonparametric analyses were used; HVLT-R- Hopkins Verbal Learning Test-Revised; SCWT- Stroop Color and Word Test.

Table 9.

Descriptive Statistics for Control Subjects in Each Condition

Cognitive Variable	Time 1 (n=11)				Time 2 (n=11)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Attention Composite Score	-3.10	3.76	-0.03	1.95	-2.79	3.63	0.24	2.21
Digit Span Forward	-1.81	1.62	0.13	1.03	-1.81	1.62	-0.04	0.97
Digit Span Backward	-1.12	1.57	-0.23	0.87	-2.19	1.57	-0.43	1.02
Brief Test of Attention	-0.94	1.08	0.07	0.68	-0.43	1.59	0.71	0.79
Language Composite Score	-4.59	1.65	-0.96	2.08	-5.48	2.20	-0.95	2.53
Phonemic Fluency	-1.53	0.56	-0.23	0.61	-1.53	1.30	-0.12	0.85
Semantic Fluency	-1.46	0.80	-0.22	0.81	-1.08	1.36	-0.09	0.81
Boston Naming Test	-2.19	0.79	-0.51	1.12	-3.98	0.79	-0.73	1.61

(table continues)

Cognitive Variable	Time 1 (n=11)				Time 2 (n=11)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Visuospatial Composite Score	-4.72	3.20	0.11	2.41	-5.31	3.31	-0.20	2.76
Visual Form Discrimination	-2.00	1.23	0.03	1.06	-1.41	1.23	0.29	1.01
Judgement of Line Orientation	-1.34	1.45	0.15	0.94	-1.34	1.45	-0.11	0.97
Test of Direction Sense	-1.78	1.04	-0.06	0.99	-2.55	1.04	-0.39	1.37
Learning Composite Score	-3.05	1.76	-0.48	1.72	-4.46	2.52	-0.18	2.39
Story-immediate recall	-1.60	1.07	-0.14	0.85	-0.84	1.07	0.21	0.68
HVLT-R-total recall	-1.35	0.70	-0.26	0.73	-1.86	0.96	-0.35	0.92
HVLT-R-immediate cued recall	-2.14	1.38	-0.08	1.02	-2.14	1.38	-0.04	1.07
Delayed Recall Composite Score	-5.39	1.95	-0.59	2.28	-4.91	3.04	-0.21	2.59
Story-delayed recall	-1.23	1.07	-0.19	0.75	-1.56	1.39	-0.08	0.85
HVLT-R-delayed free recall	-2.83	0.84	-0.23	1.09	-2.10	1.20	-0.10	1.01
HVLT-R-delayed cued recall	-1.99	1.21	-0.17	0.88	-1.59	0.81	-0.02	0.87

(table continues)

Cognitive Variable	Time 1 (n=11)				Time 2 (n=11)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Recognition Composite Score	-5.23	2.43	-0.57	2.08	-4.09	2.43	0.01	1.7
Pictures-immediate recognition	-0.66	0.50	-0.08	0.37	-0.66	0.50	0.08	0.46
Pictures-delayed recognition	-1.68	0.82	-0.20	0.72	-1.68	0.82	-0.09	0.79
HVLT-R recognition	-2.89	1.11	-0.29	1.15	-1.74	1.11	0.02	0.94
Executive Composite Score	-3.86	4.44	0.19	2.21	-2.02	2.66	0.35	1.53
Odd Man Out Test	-1.00	0.95	0.07	0.73	-1.59	1.34	0.08	0.85
SCWT-Interference	-0.63	1.82	0.53	0.77	-0.70	1.33	0.45	0.59
Alternating Fluency	-2.47	1.35	0.03	1.09	-1.08	1.35	0.25	0.82
HVLT-R-semantic clustering	-1.22	1.21	-0.43	0.63	-1.32	1.63	-0.42	0.81
Geriatric Depression Scale	-1.26	1.78	-0.07	1.10	-1.40	2.44	0.03	1.20

Note. Means are in z-score units. HVLT-R- Hopkins Verbal Learning Test-Revised; SCWT- Stroop Color and Word Test.

Table 10.

Descriptive Statistics for Bilateral DBS Subjects in Each Condition

Cognitive Variable	Baseline (n=17)				Stimulation- Off (n =13)				Stimulation- On (n =17)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Attention Composite Score	-4.11	4.55	0.01	2.56	-5.63	2.90	-1.14	2.31	-6.33	5.34	-0.56	2.79
Digit Span Forward	-1.43	1.62	-0.08	1.01	-1.43	1.24	-0.37	0.81	-2.19	1.62	-0.11	1.06
Digit Span Backward	-1.12	2.65	0.15	1.07	-1.66	2.11	-0.37	1.13	-2.19	2.65	-0.11	1.07
Brief Test of Attention	-2.20	1.59	-0.05	1.18	-3.46	1.08	-0.40	1.31	-2.96	1.08	-0.35	1.19
Language Composite Score	-3.95	4.49	0.62	2.23	-9.07	2.76	-0.60	3.44	-6.47	3.82	-0.63	2.71
Phonemic Fluency	-2.40	2.16	0.15	1.18	-3.14	1.54	-0.26	1.47	-2.64	2.28	-0.19	1.38
Semantic Fluency	-1.84	1.73	0.14	1.10	-3.15	2.11	-0.22	1.40	-2.02	1.73	-0.55	1.15
Boston Naming Test	-2.19	0.79	0.33	0.77	-2.79	0.79	-0.13	1.05	-2.79	0.79	0.12	0.96

(table continues)

Cognitive Variable	Baseline (n=17)				Stimulation- Off (n =13)				Stimulation- On (n =17)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Visuospatial Composite Score	-3.91	2.58	-0.07	1.99	-13.40	2.54	-1.20	4.61	-6.65	3.46	-0.02	2.77
Visual Form Discrimination	-2.29	1.23	-0.02	0.99	-1.71	1.23	0.03	1.09	-2.00	1.23	0.09	1.14
Judgement of Line Orientation	-2.14	1.45	-0.10	1.05	-4.53	1.45	-0.45	1.85	-2.14	1.45	-0.14	1.07
Test of Direction Sense	-2.81	1.04	0.04	1.03	-7.17	1.04	-0.78	2.24	-2.81	1.04	0.04	1.06
Learning Composite Score	-5.10	4.81	0.32	2.86	-9.80	3.15	-0.63	3.78	-6.51	4.94	-0.88	3.60
Story-immediate recall	-1.98	2.22	0.09	1.10	-1.98	2.22	0.40	1.13	-1.60	2.60	-0.05	1.14
HVLT-R-total recall	-1.99	1.98	0.17	1.13	-5.07	1.08	-0.60	1.74	-3.27	1.60	-0.60	1.52
HVLT-R-immediate cued recall	-1.64	1.38	0.06	1.02	-4.65	1.38	-0.42	1.57	-3.15	1.38	-0.28	1.40
Delayed Recall Composite Score	-6.07	3.81	0.38	2.78	-9.00	3.37	-0.09	3.64	-6.41	4.06	-0.81	3.37
Story-delayed recall	-2.21	2.38	0.12	1.14	-2.21	1.72	0.23	1.22	-2.21	2.05	-0.05	1.10
HVLT-R-delayed free recall	-1.73	1.20	0.15	0.94	-3.19	1.20	-0.21	1.35	-3.19	1.20	-0.44	1.31
HVLT-R-delayed cued recall	-2.79	1.21	0.11	1.08	-3.59	1.21	-0.11	1.32	-2.39	1.21	-0.32	1.23

(table continues)

Cognitive Variable	Baseline (n=17)				Stimulation- Off (n =13)				Stimulation- On (n =17)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Recognition Composite Score	-9.25	2.43	0.37	2.81	-13.5	2.43	-0.08	4.48	-6.31	2.43	0.1	2.93
Pictures-immediate recognition	-4.73	0.50	0.06	1.26	-0.66	0.50	0.32	0.37	-1.24	0.50	0.23	0.51
Pictures-delayed recognition	-3.35	0.82	0.13	1.15	-2.52	0.82	0.24	1.04	-3.35	0.82	0.03	1.27
HVLT-R recognition	-1.74	1.11	0.19	0.88	-12.60	1.11	-0.64	3.74	-3.46	1.11	-0.16	1.60
Executive Composite Score	-6.93	5.70	-0.13	3.30	-9.07	3.20	-1.24	3.91	-10.26	2.71	-1.55	3.94
Odd Man Out Test	-2.56	1.34	-0.05	1.16	-6.47	1.34	-0.57	2.19	-6.47	1.34	-0.73	2.41
SCWT-Interference	-2.63	0.94	-0.34	1.00	-1.96	1.78	-0.04	1.02	-2.45	1.32	-0.13	1.11
Alternating Fluency	-1.78	1.70	-0.01	0.97	-2.47	1.35	-0.57	1.06	-2.47	0.65	-0.65	1.10
HVLT-R-semantic clustering	-1.01	2.26	0.28	1.11	-1.64	1.63	-0.06	0.96	-1.43	2.05	-0.05	1.06
Geriatric Depression Scale	-1.13	1.65	0.05	0.96	-1.40	1.91	-0.23	1.11	-1.40	1.91	-0.15	1.12

Note. Means are in z-score units. HVLT-R- Hopkins Verbal Learning Test-Revised; SCWT- Stroop Color and Word Test.

Table 11.

Descriptive Statistics for Each Variable Collapsed Across Subject Groups

Cognitive Variable	Baseline/Time 1 (n=28)				Stimulation-Off/Time 1 (n=24)				Stimulation-Off/Time 2 (n=24)				Stimulation-On/Time 2 (n=28)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Attention Composite	-4.11	4.55	0.00	2.30	-5.63	3.63	-0.51	2.32	-5.63	3.63	-0.51	2.32	-6.33	5.34	-0.25	2.56
Digit Span Forward	-1.81	1.62	0.00	1.00	-1.81	1.62	-0.14	0.93	-1.81	1.62	-0.22	0.88	-2.19	1.62	-0.08	1.01
Digit Span Backward	-1.12	2.65	0.00	1.00	-1.66	2.11	-0.31	1.00	-2.19	2.11	-0.40	1.06	-2.19	2.65	-0.24	1.05
Brief Test of Attention	-2.20	1.59	0.00	1.00	-3.46	1.08	-0.18	1.07	-3.46	1.59	0.11	1.22	-2.96	1.59	0.07	1.16
Language Composite	-4.59	4.49	0.00	2.28	-9.07	2.76	-0.76	3.00	-9.07	2.76	-0.76	3.00	-6.47	3.82	-0.75	2.60
Phonemic Fluency	-2.40	2.16	0.00	1.00	-3.14	1.54	-0.24	1.14	-3.14	1.54	-0.20	1.20	-2.64	2.28	-0.17	1.18

(table continues)

Cognitive Variable	Baseline/Time 1 (n=28)				Stimulation-Off/Time 1 (n=24)				Stimulation-Off/Time 2 (n=24)				Stimulation-On/Time 2 (n=28)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Semantic Fluency	-1.84	1.73	0.00	1.00	-3.15	2.11	-0.22	1.14	-3.15	2.11	-0.16	1.14	-2.02	1.73	-0.37	1.04
Boston Naming Test	-2.19	0.79	0.00	1.00	-2.79	0.79	-0.31	1.08	-3.98	0.79	-0.40	1.34	-3.98	0.79	-0.21	1.30
Visuospatial Composite	-4.72	3.20	0.00	2.12	-13.40	3.31	-0.74	3.83	-13.40	3.31	-0.74	3.83	-6.65	3.46	-0.09	2.72
VFDT	-2.29	1.23	0.00	1.00	-2.00	1.23	0.03	1.05	-1.71	1.23	0.15	1.04	-2.00	1.23	0.17	1.08
JLOT	-2.14	1.45	0.00	1.00	-4.53	1.45	-0.18	1.50	-4.53	1.45	-0.29	1.49	-2.14	1.45	-0.13	1.01
STDS	-2.81	1.04	0.00	1.00	-7.17	1.04	-0.45	1.78	-7.17	1.04	-0.60	1.86	-2.81	1.04	-0.13	1.19
Learning Composite	-5.10	4.80	0.00	2.47	-9.80	3.50	-0.56	2.96	-9.80	3.15	-0.42	3.16	-6.51	4.94	-0.61	3.15
Story-1 Recall	-1.98	2.22	0.00	1.00	-1.98	2.22	0.15	1.02	-1.98	2.22	0.31	0.93	-1.60	2.60	0.08	0.98
HVLT-R- Total	-1.99	1.98	0.00	1.00	-5.07	1.08	-0.44	1.36	-5.07	1.08	-0.49	1.40	-3.27	1.60	-0.50	1.30

(table continues)

Cognitive Variable	Baseline/Time 1 (n=28)				Stimulation-Off/Time 1 (n=24)				Stimulation-Off/Time 2 (n=24)				Stimulation-On/Time 2 (n=28)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
HVLT-R- IC Recall	-2.14	1.38	0.00	1.00	-4.65	1.38	-0.27	1.33	-4.65	1.38	-0.25	1.35	-3.15	1.38	-0.18	1.26
Delayed Recall Composite	-6.07	3.81	0.00	2.60	-9.00	3.37	-0.32	3.04	-9.00	3.37	-0.14	3.10	-6.41	4.06	-0.57	3.10
Story- D Recall	-2.21	2.38	0.00	1.00	-2.21	1.72	0.04	1.03	-2.21	1.72	0.09	1.06	-2.21	2.05	-0.07	0.99
HVLT-R- DF Recall	-2.83	1.20	0.00	1.00	-3.19	1.20	-0.22	1.21	-3.19	1.20	-0.16	1.19	-3.19	1.20	-0.30	1.19
HVLT-R- DC Recall	-2.79	1.21	0.00	1.00	-3.59	1.21	-0.14	1.12	-3.59	1.21	-0.07	1.11	-2.39	1.21	-0.20	1.10
Recognition Composite	-9.25	2.43	0.00	2.55	-13.53	2.43	-0.31	3.50	-13.53	2.43	-0.04	3.40	-6.31	2.43	0.06	2.50
Pictures- I Recog.	-4.73	0.50	0.00	1.00	-0.66	0.50	0.14	0.41	-0.66	0.50	0.21	0.42	-1.24	0.50	0.17	0.49
Pictures- D Recog.	-3.35	0.82	0.00	1.00	-2.52	0.82	0.04	0.92	-2.52	0.82	0.09	0.93	-3.35	0.82	-0.07	1.09
HVLT-R- Recog.	-2.89	1.11	0.00	1.00	-12.60	1.11	-0.48	2.81	-12.60	1.11	-0.34	2.79	-3.46	1.11	-0.09	1.36

(table continues)

Cognitive Variable	Baseline/Time 1 (n=28)				Stimulation-Off/Time 1 (n=24)				Stimulation-Off/Time 2 (n=24)				Stimulation-On/Time 2 (n=28)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Executive Composite	-6.93	5.70	0.00	2.88	-9.07	3.20	-0.51	3.11	-9.07	3.20	-0.51	3.11	-10.26	2.71	-0.80	3.31
OMOT	-2.56	1.34	0.00	1.00	-6.47	1.34	-0.27	1.69	-6.47	1.34	-0.27	1.71	-6.47	1.34	-0.41	1.97
SCWT- Interference	-2.63	1.82	0.00	1.00	-1.96	1.82	0.22	0.94	-1.96	1.78	0.18	0.87	-2.45	1.33	0.10	0.97
Alternating Fluency	-2.47	1.70	0.00	1.00	-2.47	1.35	-0.30	1.09	-2.47	1.35	-0.20	1.02	-2.47	1.35	-0.30	1.08
HVLT-R- Sem. Cl.	-1.22	2.26	0.00	1.00	-1.64	1.63	-0.23	0.83	-1.64	1.63	-0.23	0.90	-1.43	2.05	-0.19	0.97
GDS*	-1.26	1.78	0.00	1.00	-1.40	1.91	-0.15	1.08	-1.40	2.44	-0.10	1.14	-1.40	2.44	-0.08	1.13

Note. Means are in z-score units. *Higher z-score represents a greater number of depression symptoms; VFDT-Visual Form Discrimination Test; JLOT- Judgement of Line Orientation; STDS- Standardized Test of Direction Sense; HVLT-R- Hopkins Verbal Learning Test-Revised; I- immediate; IC- immediate cued; D- delayed; DF- delayed free; DC- delayed cued; Recog.- recognition; OMOT- Odd Man Out Test; SCWT- Stroop Color and Word Test; Sem. Cl.- semantic clustering score; GDS- Geriatric Depression Scale.

Table 12.

Descriptive Statistics for Each Variable Collapsed Across Conditions

Cognitive Variable	Time 1/Time 2 (n=22)				Surgery (n = 26)				Stimulation (n = 2 6)				Procedure (n = 34)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Attention Composite	-3.10	3.76	0.10	2.04	-5.63	4.55	-0.43	2.56	-6.33	5.34	-0.54	2.61	-6.33	5.34	-0.27	2.65
Digit Span Forward	-1.81	1.62	0.04	0.98	-1.43	1.62	-0.17	0.96	-2.19	1.62	-0.21	1.00	-2.19	1.62	-0.10	1.02
Digit Span Backward	-2.19	1.57	-0.33	0.93	-1.66	2.65	-0.02	1.17	-2.19	2.65	-0.15	1.14	-2.19	2.65	0.02	1.07
Brief Test of Attention	-0.94	1.59	0.39	0.79	-3.46	1.59	-0.24	1.23	-3.46	1.08	-0.18	1.11	-2.96	1.59	-0.20	1.17
Language Composite	-5.48	2.20	-0.96	2.26	-9.07	4.49	0.09	2.94	-9.07	3.82	-0.55	3.14	-6.47	4.49	0.00	2.53
Phonemic Fluency	-1.53	1.30	-0.18	0.72	-3.14	2.16	0.00	1.32	-3.14	2.28	-0.18	1.40	-2.64	2.28	-0.02	1.27
Semantic Fluency	-1.46	1.36	-0.16	0.79	-3.15	2.11	-0.01	1.22	-3.15	2.11	-0.36	1.30	-2.02	1.73	-0.21	1.16

(table continues)

Cognitive Variable	Time 1/Time 2 (n=22)				Surgery (n = 26)				Stimulation (n = 2 6)				Procedure (n = 34)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Boston Naming Test	-3.98	0.79	-0.62	1.36	-2.79	0.79	0.10	0.96	-2.79	0.79	-0.02	1.05	-2.79	0.79	0.23	0.87
Visuospatial Composite	-5.31	3.31	-0.04	2.53	-13.40	2.58	-0.52	3.53	-13.40	3.46	-0.72	3.82	-6.65	3.46	-0.04	2.38
VFDT	-2.00	1.23	0.16	1.02	-1.71	1.23	0.12	0.92	-2.00	1.23	0.06	1 11	-2.29	1.23	0.04	1.06
JLOT	-1.34	1.45	0.02	0.94	-4.53	1.45	-0.22	1.50	-4.53	1.45	-0.39	1 50	-2.14	1.45	-0.12	1.05
STDS	-2.55	1.04	-0.22	1.18	-7.17	1.04	-0.42	1.78	-7.17	1.04	-0.39	1.80	-2.81	1.04	0.04	1.03
Learning Composite	-4.46	2.52	-0.33	2.04	-9.80	4.81	-0.05	3.34	-9.80	4.94	-0.82	3.62	-6.51	4.94	-0.28	3.26
Story- I Recall	-1.60	1.07	0.03	0.77	-1.98	2.22	0.29	1.13	-1.98	2.60	0.22	1.16	-1.98	2.60	0.04	1.11
HVLT-R- Total	-1.86	0.96	-0.30	0.81	-5.07	1.98	-0.16	1.47	-5.07	1 60	-0.65	1.55	-3.27	1.98	-0.22	1.37
HVLT-R- IC Recall	-2.14	1.38	-0.06	1.02	-4.65	1.38	-0.17	1.33	-4.65	1.38	-0.39	1.49	-3.15	1.38	-0.11	1.22

(table continues)

Cognitive Variable	Time 1/Time 2 (n=22)				Surgery (n = 26)				Stimulation (n = 26)				Procedure (n = 34)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Delayed Recall Composite	-5.39	3.04	-0.40	2.39	-9.00	3.81	0.31	3.09	-9.00	4.06	-0.56	3.51	-6.41	4.06	-0.21	3.10
Story- D Recall	-1.56	1.39	-0.14	0.78	-2.21	2.38	0.22	1.20	-2.21	2.05	0.10	1.12	-2.21	2.38	0.04	1.11
HVLT-R- DF Recall	-2.83	1.20	-0.16	1.03	-3.19	1.20	0.00	1.14	-3.19	1.20	-0.36	1.35	-3.19	1.20	-0.14	1.16
HVLT-R- DC Recall	-1.99	1.21	-0.10	0.86	-3.59	1.21	0.08	1.10	-3.59	1.21	-0.30	1.29	-2.79	1.21	-0.10	1.16
Recognition Composite	-5.23	2.43	-0.28	1.87	-13.53	2.43	0.57	3.28	-13.53	2.43	0.00	3.61	-9.25	2.43	0.23	2.83
Pictures- I Recog.	-0.66	0.50	0.00	0.41	-0.66	0.50	0.34	0.31	-0.66	0.50	0.30	0.37	-4.73	0.50	0.14	0.95
Pictures- D Recog.	-1.68	0.82	-0.15	0.74	-2.52	0.82	0.40	0.79	-3.35	0.82	0.14	1.11	-3.35	0.82	0.08	1.19
HVLT-R- Recog.	-2.89	1.11	-0.13	1.04	-12.60	1.11	-0.17	2.70	-12.60	1.11	-0.45	2.83	-3.46	1.11	0.01	1.28

(table continues)

Cognitive Variable	Time 1/Time 2 (n=22)				Surgery (n = 26)				Stimulation (n = 26)				Procedure (n = 34)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Executive Composite	-3.86	4.44	0.27	1.86	-9.07	4.19	-0.73	3.53	-10.26	3.20	-1.50	3.96	-10.26	5.70	-0.84	3.65
OMOT	-1.59	1.34	0.08	0.77	-6.47	1.34	-0.32	1.74	-6.47	1.34	-0.74	2.38	-6.47	1.34	-0.39	1.89
SCWT- Interference	-0.70	1.82	0.49	0.67	-2.63	1.78	-0.21	1.00	-2.45	1.78	0.03	1.04	-2.63	1.32	-0.23	1.05
Alternating Fluency	-2.47	1.35	0.14	0.95	-2.47	1.35	-0.36	1.03	-2.47	1.35	-0.69	1.09	-2.47	1.70	-0.33	1.07
HVLT-R- Sem. Cl.	-1.32	1.63	-0.43	0.71	-1.64	2.26	0.15	1.00	-1.64	2.05	-0.10	0.95	-1.43	2.26	0.12	1.08
GDS*	-1.40	2.44	-0.02	1.12	-1.40	1.91	-0.07	1.02	-1.40	1.91	-0.18	1.10	-1.40	1.91	-0.18	1.10

Note. Means are in z-score units. *Higher z-score represents a greater number of depression symptoms; VFDT-Visual Form Discrimination Test; JLOT- Judgement of Line Orientation; STDS- Standardized Test of Direction Sense; HVLT-R- Hopkins Verbal Learning Test-Revised; I- immediate; IC- immediate cued; D- delayed; DF- delayed free; DC- delayed cued; Recog.- recognition; OMOT- Odd Man Out Test; SCWT- Stroop Color and Word Test; Sem. Cl.- semantic clustering score; GDS- Geriatric Depression Scale.

Table 13.

P-values for Wilcoxon Signed Rank Tests

Variable	PD Control	DBS PD		
	Time1/Time2	Surgery	Stimulation	Procedure
Boston Naming Test	0.431	**0.039**		0.197
Picture Recognition- immediate	0.18	0.655	0.739	0.726
Picture Recognition- delayed	0.51	0.157	0.429	0.819
HVLT-R- recognition	0.271		0.72	

Note. HVLT-R- Hopkins Verbal Learning Test-Revised.

Table 14.

P-values for Mann-Whitney U Tests

Variable	Surgery	Stimulation	Procedure
Boston Naming Test	0.476		0.961
Picture Recognition- immediate	0.19	0.657	0.445
Picture Recognition- delayed	0.166	0.343	0.529
HVLT-R- recognition		0.29	

Note. HVLT-R- Hopkins Verbal Learning Test-Revised.

Table 15.

Descriptive Statistics for Raw Geriatric Depression Scale Scores in Each Condition

Group	Condition	N	Min.	Max.	Mean	SD
DBS	Baseline	17	2	23	10.9	7.28
	Stimulation-off	13	0	25	8.83	8.41
	Stimulation-on	17	0	25	9.44	8.49
PD Control	Time 1	11	1	24	10	8.28
	Time 2	11	0	29	10.8	9.05

Table 16.

Demographic and Clinical Characteristics of Unilateral DBS Subjects

Subject	Gender	Age	Educ. (yrs.)	Occ.	Age at Onset	Disease Duration (yrs.)	Hoehn & Yahr Score*	Surgery to T2**	NART-IQ	DRS Total	Side of Surgery
PD1	M	72	14	6	61	12	3	4	103	131	Left
PD2	M	64	16	9	55	9	5	5.3	105	136	Left
PD3	M	65	20	9	53	12	3	3.9	111	142	Right
PD4	M	65	16	7	55	10	3	4	109	139	Left

Note. *Assessed at baseline following a 12 hour withdrawal of PD medications; **The number of weeks from the date of surgery to the date of the first postsurgical condition; Educ.- education in years; Occ.- occupational status on a nine point scale (Hollingshead, 1977); T2- first postsurgical testing; NART- National Adult Reading Test (Blair et al., 1989); DRS- Dementia Rating Scale (Mattis, 1988).

Table 17.

The Amount of Change (in SDs) that Each Unilateral DBS Subject Demonstrated in the Three Comparisons

Measure	Surgery				Stimulation				Procedure			
	PD1	PD2	PD3	PD4	PD1	PD2	PD3	PD4	PD1	PD2	PD3	PD4
Digit Span Forward	-0.35	-0.35	0.92	0.92	-0.35	0.92	-0.35	1.56	-0.99	0.29	0.29	**2.20**
Digit Span Backward	**3.27**	0.28	0.28	-0.46	**-2.70**	-0.46	0.28	**2.52**	0.28	-0.46	0.28	1.78
Brief Test of Attention	-0.89	-1.60	0.51	-0.89	-1.60	-0.19	**-2.30**	-0.19	-1.60	-0.89	-0.89	-0.19
Pictures-immediate recognition	1.12	-1.95	-0.42	-0.42	-1.95	1.12	-1.95	-0.42	-0.42	-0.42	-1.95	-0.42
Pictures-delayed recognition	-0.15	1.02	**-3.68**	-0.15	**-2.51**	-0.15	-1.33	-0.15	**-2.51**	1.02	**-4.86**	-0.15
Story-immediate recall	-1.14	1.21	**3.17**	-0.36	0.82	-1.93	**-4.67**	-1.53	0.04	-0.36	-1.14	-1.53
Story-delayed recall	**-2.69**	0.43	**2.31**	0.43	1.68	-0.19	**-3.32**	**-2.07**	-0.82	0.43	-0.82	-1.44
HVLT-R-total recall	1.70	**-2.92**	-0.94	-0.06	**-2.70**	0.16	-0.06	-0.94	-1.16	**-2.92**	-1.16	-1.16
HVLT-R-immediate cued recall	-1.51	0.34	-0.77	n/a	0.34	0.34	0.34	-0.40	-1.14	0.71	-0.40	n/a

(table continues)

Measure	Surgery				Stimulation				Procedure			
	PD1	PD2	PD3	PD4	PD1	PD2	PD3	PD4	PD1	PD2	PD3	PD4
HVLT-R-delayed free recall	-0.16	0.29	-1.07	0.29	-1.98	-0.62	1.20	-0.62	-1.98	-0.16	0.29	-0.16
HVLT-R-delayed cued recall	**-2.49**	-1.35	-1.92	-0.21	-0.78	0.37	1.51	-0.78	**-3.06**	-0.78	-0.21	-0.78
HVLT-R-recognition	-1.62	-0.35	-0.99	-1.62	0.29	-0.35	0.92	-0.99	-0.99	-0.35	0.29	**-2.26**
Phonemic Fluency	**-2.29**	-0.17	-0.36	0.22	1.19	-0.36	**-2.29**	0.03	-0.94	-0.36	**-2.48**	0.41
Semantic Fluency	-1.60	-0.16	1.76	**-2.56**	-0.40	1.52	**-2.80**	1.76	-1.84	1.52	-0.88	-0.64
Boston Naming Test	**-2.96**	0.23	0.87	0.87	**2.78**	0.23	-0.41	-1.04	-0.41	0.23	0.23	-0.41
Visual Form Discrimination	-1.09	-1.09	-0.72	-0.72	0.03	0.79	-0.34	0.41	-0.72	0.03	-0.72	0.03
Judgement of Line Orientation	-0.19	1.38	-0.19	-1.24	-0.19	-0.71	1.38	-0.19	-0.71	0.34	0.86	-1.76
Test of Direction Sense	1.22	0.47	0.47	0.10	-0.64	0.47	-0.27	-1.01	0.10	0.47	-0.27	-1.39
Odd Man Out Test	-0.98	1.28	0.31	-0.66	-0.01	0.95	0.31	0.63	-0.98	**2.25**	0.63	-0.01
SCWT-Interference	-1.28	-0.28	**2.00**	-0.18	-1.20	-0.60	-0.02	-1.09	**-2.63**	-1.03	1.83	-1.42
Alternating Fluency	1.68	-0.20	-1.75	0.73	**-3.94**	-1.44	**4.16**	-0.20	**-2.06**	-1.44	**2.60**	0.73

(table continues)

Measure	Surgery				Stimulation				Procedure			
	PD1	PD2	PD3	PD4	PD1	PD2	PD3	PD4	PD1	PD2	PD3	PD4
HVLT-R-semantic clustering	1.41	**-2.46**	-0.83	1.20	-0.43	-0.83	0.19	-1.65	1.00	**-3.28**	-0.63	-0.43
Geriatric Depression Scale	0.32	0.05	1.40	-1.03	-0.49	-0.76	**-2.11**	-0.22	0.05	-0.49	-0.49	-1.03

Note. Table values are in z-score units. HVLT-R- Hopkins Verbal Learning; SCWT- Stroop Color and Word Test; n/a- due to examiner error, the HVLT-R immediate cued recall variable was not collected in the baseline condition.

APPENDIX

Table A.

Control Group Raw Data

Cognitive Variable	Time 1 (n=11)				Time 2 (n=11)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Digit Span Forward	4.00	13.00	9.09	2.70	4.00	13.00	8.64	2.54
Digit Span Backward	4.00	9.00	5.65	1.62	2.00	9.00	5.27	1.90
Brief Test of Attention	5.00	9.00	7.00	1.34	6.00	10.00	8.27	1.56
Phonemic Fluency	7.00	15.00	11.80	2.46	7.00	18.00	12.23	3.45
Semantic Fluency	9.00	21.00	15.59	4.31	11.00	24.00	16.27	4.31
Boston Naming Test	10.00	15.00	12.82	1.89	7.00	15.00	12.45	2.70
Visual Form Discrimination	21.00	32.00	27.91	3.62	23.00	32.00	28.82	3.46
Judgement of Line Orientation	8.00	15.00	11.73	2.37	8.00	15.00	11.09	2.43
Test of Direction Sense	21.00	32.00	27.73	3.88	18.00	32.00	26.45	5.34
Story-immediate recall	3.00	10.00	6.82	2.23	5.00	10.00	7.73	1.79
HVLT-R-total recall	29.00	45.00	37.55	5.72	25.00	47.00	36.82	7.19
HVLT-R-immediate cued recall	5.00	12.00	9.09	2.02	5.00	12.00	9.18	2.14
Story-delayed recall	3.00	10.00	6.18	2.27	2.00	11.00	6.49	2.58
HVLT-R-delayed free recall	1.00	11.00	8.09	2.98	3.00	12.00	8.45	2.77
HVLT-R-delayed cued recall	4.00	12.00	8.55	2.21	5.00	11.00	8.91	2.17

(table continues)

Cognitive Variable	Time 1 (n=11)				Time 2 (n=11)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Pictures-immediate recognition	13.00	15.00	14.00	0.63	13.00	15.00	14.27	0.79
Pictures-delayed recognition	12.00	15.00	13.78	0.87	12.00	15.00	13.91	0.94
HVLT-R-recognition	17.00	24.00	21.55	2.02	19.00	24.00	22.09	1.64
Odd Man Out Test	28.00	38.00	33.50	3.72	25.00	40.00	33.55	4.37
SCWT-Interference	-3.05	17.06	6.46	6.28	-3.59	13.02	5.79	4.86
Alternating Fluency	-1.52	1.76	0.62	0.94	-0.33	1.76	0.81	0.70
HVLT-R-semantic clustering	4.00	27.00	11.45	5.99	3.00	31.00	11.55	7.72

Table B.

DBS Group Raw Data

Cognitive Variable	Baseline (n=17)				Stimulation- Off (n =13)				Stimulation- On (n =17)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Digit Span Forward	5.00	13.00	8.53	2.65	5.00	12.00	7.77	2.13	3.00	13.00	8.47	2.79
Digit Span Backward	4.00	11.00	6.35	2.00	3.00	10.00	5.38	2.10	2.00	11.00	5.88	2.00
Brief Test of Attention	2.50	10.00	6.76	2.33	0.00	9.00	6.08	2.60	1.00	9.00	6.18	2.35
Phonemic Fluency	3.00	21.50	13.32	4.80	0.00	19.00	11.69	5.98	2.00	22.00	11.94	5.59
Semantic Fluency	7.00	26.00	17.53	5.87	0.00	28.00	15.62	7.42	6.00	26.00	13.82	6.10
Boston Naming Test	10.00	15.00	14.24	1.30	9.00	15.00	13.46	1.76	9.00	15.00	13.88	1.62
Visual Form Discrimination	20.00	32.00	27.76	3.38	22.00	32.00	27.92	3.71	21.00	32.00	28.12	3.90
Judgement of Line Orientation	6.00	15.00	11.12	2.64	0.00	15.00	10.23	4.64	6.00	15.00	11.00	2.69
Test of Direction Sense	17.00	32.00	28.12	4.03	0.00	32.00	24.92	8.73	17.00	32.00	28.12	4.15

(table continues)

Cognitive Variable	Baseline (n=17)				Stimulation- Off (n =13)				Stimulation- On (n =17)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Story-immediate recall	2.00	13.00	7.44	2.89	2.00	13.00	8.23	2.95	3.00	14.00	7.18	2.98
HVLT-R-total recall	24.00	55.00	40.83	8.81	0.00	48.00	34.85	13.55	14.00	52.00	34.88	11.84
HVLT-R-immediate cued recall	6.00	12.00	9.38	2.03	0.00	12.00	8.42	3.12	3.00	12.00	8.71	2.78
Story-delayed recall	0.00	14.00	7.13	3.48	0.00	12.00	7.46	3.73	0.00	13.00	6.59	3.36
HVLT-R-delayed free recall	4.00	12.00	9.13	2.57	0.00	12.00	8.15	3.69	0.00	12.00	7.53	3.57
HVLT-R-delayed cued recall	2.00	12.00	9.25	2.70	0.00	12.00	8.69	3.30	3.00	12.00	8.18	3.09
Pictures-immediate recognition	6.00	15.00	14.24	2.17	13.00	15.00	14.69	0.63	12.00	15.00	14.53	0.87
Pictures-delayed recognition	10.00	15.00	14.18	1.38	11.00	15.00	14.31	1.25	10.00	15.00	14.06	1.52
HVLT-R-recognition	19.00	24.00	22.38	1.54	0.00	24.00	20.92	6.54	16.00	24.00	21.76	2.80
Odd Man Out Test	20.00	40.00	32.88	5.95	0.00	40.00	30.23	11.22	0.00	40.00	29.41	12.33
SCWT-Interference	-19.38	9.81	-0.67	8.21	-13.91	16.68	1.77	8.36	-17.96	12.96	1.09	9.09

(table continues)

Cognitive Variable	Baseline (n=17)				Stimulation- Off (n =13)				Stimulation- On (n =17)			
	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Mean	SD
Alternating Fluency	-0.93	2.06	0.59	0.83	-1.52	1.76	0.11	0.91	-1.52	1.16	0.04	0.94
HVLT-R-semantic clustering	6.00	37.00	18.20	10.50	0.00	31.00	15.00	9.12	2.00	35.00	15.12	10.04

REFEREENCES

Agid, Y., Ruberg, M., Dubois, B., & Pillon, B. (1987). Anatomoclinical and biochemical concepts of subcortical dementia. In S.M.Stahl, S. D. Iversen, & E. C. Goodman (Eds.), Cognitive Neurochemistry (pp. 248-271). Oxford: Oxford University Press.

Alegret, M., Valldeoriola, F., Junque, C., Vendrell, P. R. J., & Tolosa, E. (2000). Effects of bilateral subthalamic nucleus high frequency stimulation on cognitive function in parkinsonian patients. Movement Disorders, 15, 68

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. In H.B.M.Uylings, C. G. VanEden, J. P. C. DeBruin, M. A. Corner, & M. G. P. Feenstra (Eds.), Progress in Brain Research (pp. 119-146). Elsevier Science Research.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience, 9, 357-381.

Andy, P. J. (1983). Thalamic stimulation for control of movement disorders. Applied Neurophysiology, 46, 107-111.

Ardouin, C., Klinger, H., Limousin, P., Krack, P., Xie, J., Van Blercom, N., Benabid, A.-L., & Pollak, P. (1999a). The effect of bilateral subthalamic nucleus stimulation on cognitive functions. Neurology, 52, A514.

Ardouin, C., Pillon, B., Peiffer, E., Bejjani, P., Limousin, P., Damier, P., Arnulf, I., Benabid, A. L., Agid, Y., & Pollak, P. (1999b). Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions. Annals of Neurology, 46, 217-223.

Asso, D., Crown, S., Russell, J. A., & Logue, v. (1969). Psychological aspects of the stereotactic treatment of parkinsonism. British Journal of Psychiatry, 115, 541-553.

Auriacombe, S., Grossman, M., Carvell, S., Gollomp, S., Stern, M. B., & Hurtig, H. I. (1993). Verbal fluency deficits in Parkinson's disease. Neuropsychology, 7, 182-192.

Baddeley, A. (1995). Working Memory. In M.S.Gazzaniga (Ed.), The Cognitive Neurosciences (pp. 755-764). Boston: Massachusetts Institute of Technology.

Baunez, C. & Robbins, T. W. (1997). Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. European Journal of Neuroscience, 9, 2086-2099.

Baunez, C. & Robbins, T. W. (1999a). Effects of dopamine depletion of the dorsal striatum and further interaction with subthalamic nucleus lesions in an attentional task in the rat. Neuroscience, 92, 1343-1356.

Baunez, C. & Robbins, T. W. (1999b). Effects of transient inactivation of the subthalamic nucleus by local muscimol and APV infusions on performance on the five-choice serial reaction time task in rats. Psychopharmacology-Berlin, 141, 57-65.

Bayles, K. A. (1990). Language and Parkinson's Disease. Alzheimer Disease and Associated Disorders, 4, 171-180.

Beatty, W. W. & Monson, N. (1990). Picture and motor sequencing in Parkinson's disease. Journal of Geriatric Psychiatry and Neurology, 3, 192-197.

Beatty, W. W., Monson, N., & Goodkin, D. E. (1989). Access to semantic memory in Parkinson's disease and Multiple Sclerosis. Journal of Geriatric Psychiatry and Neurology, 2, 153-162.

Beatty, W. W., Staton, R. D., Weir, W. S., Monson, N., & Whitaker, H. A. (1989). Cognitive disturbances in Parkinson's disease. Journal of Geriatric Psychiatry and Neurology, 2, 22-33.

Bejjani, B.-P., Damier, P., Arnulf, I., Thivard, L., Bonnet, A.-M., Dormont, D., Cornu, P., Pipoux, B., Samson, Y., & Agid, Y. (1999). Transient acute depression induced by high-frequency deep-brain stimulation. The New England Journal of Medicine, 340, 1476-1502.

Benabid, A. L., Pollak, P., Gross, C., Hoffman, D., Benazzouz, A., Gao, D. M., Laurent, A., Gentil, M., & Perret, J. (1994). Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. Stereotactic and Functional Neurosurgery, 62, 76-84.

Benabid, A. L., Pollak, P., Louveau, A., Hommel, M., Perret, P., & DeRougemont, J. (1989). Chronic VIM-thalamic stimulation in movement disorders. Current Problems in Neurology, 9, 413-415.

Benabid, A. L., Pollak, P., Seigneuret, E., Hoffmann, D., Gay, E., & Perret, J. (1993). Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor, and extra-pyramidal dyskinesias. Acta Neurochirurgica, Suppl, 39-44.

Benazzouz, A., Gross, C., Feger, J., Boraud, T., & Bioulac, B. (1993). Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. European Journal of Neuroscience, 5, 382-389.

Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test-Revised: normative data and analysis of inter-form and test-retest reliability. The Clinical Neuropsychologist, 12, 43-55.

Bennett, K. M. B., Waterman, C., Scarpa, M., & Castiello, U. (1995). Covert visuospatial attentional mechanisms in Parkinson's disease. Brain, 118, 153-166.

Benton, A. & Hamsher, K. (1989). Multilingual Aphasia Examination. Iowa City, Iowa: AJA Associates.

Benton, A., Hamsher, K., Varney, N., & Spreen, O. (1983). Contributions to Neuropsychological Assessment. New York: Oxford, University Press.

Bergman, H., Wichmann, T., & DeLong, M. R. (1990). Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science, 249, 1436-1438.

Blair, J. R. & Spreen, O. (1989). Predicting Premorbid IQ: a revision of the National Adult Reading Test. The Clinical Neuropsychologist, 3, 129-136.

Boller, F., Passafiume, D., Keefe, N. C., Rogers, K., Morrow, L., & Kim, Y. (1984). Visuospatial impairment in Parkinson's disease. Archives of Neurology, 41, 485-490.

Bondi, M. W., Kaszniak, A. W., Bayles, K. A., & Vance, K. T. (1993). Contributions of frontal system dysfunction to memory and perceptual abilities in Parkinson's disease. Neuropsychology, 7, 89-102.

Boraud, T., Bezard, E., Bioulac, B., & Gross, C. (1996). High frequency stimulatio of the internal globus palllidus (GPi) simultaneously improves parkinsonian symptoms and reduces firing frequency of GPi neurons in the MPTP-treated monkey. Neuroscience Letters, 215, 17-20.

Botez, M. I. & Barbeau, A. (1975). Neuropsychological findings in Parkinson's disease: a comparison between various tests during long-term levodopa therapy. International Journal of Neurology, 10, 222-229.

Bowen, F. P., Burns, M. M., Brady, E. M., & Yahr, M. D. (1976). A note on alterations of personal orientation in parkinsonism. Neuropsychologia, 14, 425-429.

Bowen, F. P., Hoehn, M. M., & Yahr, M. D. (1972). Parkinsonism: Alterations in spatial orientation as determined by a route-walking test. Neuropsychologia, 10, 355-361.

Brown, R. G. & Marsden, C. D. (1986). Visuospatial function in Parkinson's disease. Brain, 109, 987-1002.

Brown, R. G. & Marsden, C. D. (1988). An investigation of the phenomenon of "set" in Parkinson's disease. Movement Disorders, 3, 152-161.

Burchiel, K. J., Anderson, V. C., Favre, J., & Hammerstad, J. P. (1999). Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. Neurosurgery, 45, 1375-1384.

Ceballos-Baumann, A. O., Boecker, H., Bartenstein, P., von Falkenhayn, I., Riescher, H., Conrad, B., Moringlane, J. R., & Alesch, F. (1999). A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson's disease. Archives of Neurology, 56, 997-1003.

Channon, S., Jones, M.-C., & Stephenson, S. (1993). Cognitive strategies and hypothesis testing during discrimination learning in Parkinson's Disease. Neuropsychologia, 31, 75-82.

Clark, C. R., Geffen, G. M., & Geffen, L. B. (1987). Catecholamines and attention I: animal and clinical studies. Neuroscience Biobehavior Review, 11, 341-352.

Cohen, H., Bouchard, S., Scherzer, P., & Whitaker, H. (1994). Language and verbal reasoning in Parkinson's disease. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 7, 166-175.

Cools, A. R., Van Den Bercken, J. H. L., Horstink, M. W. I., Van Spaendonck, K. P. M., & Berger, H. J. C. (1984). Cognitive and motor shifting aptitude disorder in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 47, 443-453.

Cooper, I. S., Bravo, G., Riklan, M., Davidson, N., & Gorek, E. (1958). Chemopallidectomy and chemothalamectomy for parkinsonism. Geriatrics, 13, 127-147.

Cooper, J. A., Sagar, H. J., Doherty, S. M., Jordan, N., Tidswell, P., & Sullivan, E. V. (1992). Different effects of dopaminergic and anticholoinergic therapies on cognitive and motor function in Parkinson's disease. Brain, 115, 1701-1725.

Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. V. (1991). Cognitive impaiment in early, untreated Parkinson's disease and its relationship to motor disability. Brain, 114, 2095-2122.

Cooper, J. A., Sagar, H. J., & Sullivan, E. V. (1993). Short-term memory and temporal ordering in early Parkinson's disease" effects of disease chronicity and medication. Neuropsychologia, 31, 933-949.

Cronin-Golomb, A. & Braun, A. E. (1997). Visuospatial dysfunction and problem solving in Parkinson's disease. Neuropsychology, 11, 44-52.

Cummings, J. L., Darkins, A., Mendez, M., Hill, M. A., & Benson, D. F. (1988). Alzheimer's disease and Parkinson's disease: comparison of speech and language alterations. Neurology, 38, 680-684.

Dalrympl, A. J. C., Kalders, A. S., Jones, R. S., & Watson, R. W. (1994). A central executive deficit in patients with Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 57, 360-367.

Damasio, A. R. & Anderson, S. W. (1993). The Frontal Lobes. In K.M.Heilman & E. Valenstein (Eds.), Clinical Neuropsychology (3rd ed., pp. 409-460). New York: Oxford University Press.

Darley, F. L., Brown, J. R., & Swenson, W. M. (1975). Language changes after neurosurgery for parkinsonism. Brain and Language, 2, 65-69.

Daum, I., Schugens, M. M., Spieker, S., Poser, U., Schonle, P. W., & Birbaumer, N. (1995). Memory and skill acquisition in Parkinson's disease and frontal lobe dysfunction. Cortex, 31, 413-432.

Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Morris, R. G., & Robbins, T. W. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: Evidence for a specific attentional dysfunction. Neuropsychologia, 27, 1329-1343.

Downes, J. J., Sharp, H. M., Costall, B. M., Sagar, H. J., & Howe, J. (1993). Alternating fluency in Parkinson's disease. Brain, 116, 887-902.

Dubois, B., Ruberg, M., Javoy-Agid, F., Ploska, A., & Agid, Y. (1983). A subcortico-cortical cholinergic system is affected in Parkinson's disease. Brain Research, 288, 213-218.

Duncombe, M. E., Bradshaw, J. L., Iansek, R., & Phillips, J. G. (1994). Parkinsonian patients without dementia or depression do not suffer from bradyphrenia as indexed by performance in mental rotation tasks with and without advance information. Neuropsychologia, 32, 1383-1396.

El-Awar, M., Becker, J. T., Hammond, K. M., Nebes, R. D., & Boller, F. (1987). Learning deficit in Parkinson's disease. Archives of Neurology, 44, 180-184.

Ferraro, F. R., Balota, D. A., & Connor, L. T. (1993). Implicit memory and the formation of new associations in nondemented Parkinson's disease individuals and individuals with senile dementia of the Alzheimer type: a serial reaction time (SRT) investigation. Brain and Cognition, 21, 163-180.

Filoteo, J. V., Delis, D. C., Roman, M. J., Demdura, T., Ford, E., Butters, N., Salmon, D. P., Paulsen, J., Shults, C. W., Swenson, M., & Swerdlow, N. (1995). Visual attention and perception in patients with Huntington's disease: comparisons with other subcortical and cortical dementias. Journal of Clinical and Experimental Neuropsychology, 17, 654-667.

Fimm, B., Bartl, G., Zimmermann, P., & Wallesch, C.-W. (1994). Different mechanisms underly shifting set on external and internal cues in Parkinson's disease. Brain and Cognition, 25, 287-304.

Flowers, K. A., Pearce, I., & Pearce, J. M. S. (1984). Recognition memory in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 47, 1174-1181.

Flowers, K. A. & Robertson, C. (1985). The effect of Parkinson's Disease on the ability to maintain mental set. Journal of Neurology, Neurosurgery, and Psychiatry, 48, 517-529.

Flowers, K. A. & Robertson, C. (1995). Perceptual abnormalities in Parkinson's disease: top-down or bottom-up processes. Perception, 24, 1201-1221.

Fraix, V., Pollak, P., Moro, E., Esselink, R.-A. J., Ardouin, C., Xie, J., Koudsie, A., & Benabid, A.-L. (2000). Bilateral subthalamic deep brain stimulation in parkinsonian patients previously operated in another target. Movement Disorders, 15, 56.

Freedman, M. & Oscar-Berman, M. (1989). Spatial and visual learning deficits in Alzheimer's and Parkinson's disease. Brain and Cognition, 11, 114-126.

Fuster, J. M. (1997). The Prefrontal Cortex: Anatomy, Physiololgy, and Neuropsychology of the Frontal Lobes. (3rd ed.) New York: Raven Press.

Gabrieli, J. D. E., Singh, J., Stebbins, G. T., & Goetz, C. G. (1996). Reduced working memory span in Parkinson's disease: Evidence for the role of a frontostriatal system in working strategic memory. Neuropsychology, 10, 322-332.

Germano, I. M. & Heilbrun, P. (1998). Interactive computer-assisted image-guided technology as an adjuvant to neurosurgery for movement disorders. In I.M.Germano (Ed.), Neurosurgical Treatment of Movement Disorders (pp. 219-226). Park Ridge, IL: AANS Publication Committee.

Gibb, W. R. G. & Lees, A. J. (1991). Anatomy, pigmentation, ventral and dorsal subpopulaitons of the substantia nigra, and differential cell death in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 54, 388-396.

Goetz, C. G., DeLong, M. R., Penn, R. D., & Bakay, R. A. E. (1993). Neurosurgical horizons in Parkinson's Disease. Neurology, 43, 1-7.

Golbe, L. I. & Langston, W. (1993). The etiology of Parkinson's disease. In J.Jankovic & E. Tolosa (Eds.), Parkinson's Disease and Movement Disorders (2nd ed., pp. 93-102). Baltimore: Williams and Wilkins.

Groenewegen, H. J., Berendse, H. W., Wolters, J. G., & Lohman, A. H. M. (1990). The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: Evidence for a parallel organization. In H.B.M.Uylings, C. G. VanEden, J. P. C. DeBruin, M. A. Corner, & M. G. P. Feenstra (Eds.), Progress in Brain Research (pp. 95-118). Elsevier Science Publishers.

Grossman, M., Carvell, S., Gollomp, S., Stern, M. B., Vernon, G., & Hurtig, H. I. (1991). Sentence comprehension and praxis deficits in Parkinson's disease. Neurology, 41, 1620-1626.

Gurd, J. M. & Ward, C. D. (1989). Retrieval from semantic and letter-initial categories in patients with Parkinson's disease. Neuropsychologia, 27, 743-746.

Haeske-Dewick, H. C. (1996). Are perception and memory for faces influenced by a specific age at onset factor in Parkinson's disease? Neuropsychologia, 34, 315-320.

Hamel, A. R. & Riklan, M. (1975). Cognitive and perceptual effects of long-range l-dopa therapy in parkinsonism. Journal of Clinical Psychology, 31, 321-323.

Hariz, M. I., Johansson, F., Shamsgovara, P., Johansson, E., Hariz, G.-M., & Fagerlund, M. (2000). Bilateral subthalamic nucleus stimulation in a parkinsonian patient with preoperative deficits in speech and cognition: Persistent improvement in mobility but increased dependency: A case study. Movement Disorders, 15, 136-139.

Heck, A., Steinvorth, S., Tronnier, V., & Fogel, W. (2000). Different effects of subthalamic nucleus stimulation on motor performance and mood changes in Parkinson's disease. Movement Disorders, 15, 46.

Hoehn, M. M. & Yahr, M. D. (1967). Parkinsonism: onset, progression, and mortality. Neurology, 17, 427-442.

Hollingshead, A., (1977). A four factor index of social status. Unpublished manuscript, Yale University, New Haven, CT.

Hornykiewicz, O. (1966). Dopamine (3-hydroxytyramine) and brain function. Pharmacological Review, 18, 925-964.

Hovestadt, A., de Jong, G. J., & Meerwaldt, J. D. (1987). Spatial disorientation as an early symptom of Parkinson's disease. Neurology, 37, 485-487.

Huber, S. J., Freidenberg, D. L., Shuttleworth, E. C., Paulson, G. W., & Christy, J. A. (1989). Neuropsychological impairments associated with severity of Parkinson's disease. Journal of Neuropsychiatry, 1, 154-158.

Illes, J., Metter, E. J., Hanson, W. R., & Iritani, S. (1988). Language production in Parkinson's disease: acoustic and linguistic considerations. Brain and Language, 33, 146-160.

Inzelberg, R., Plotnik, M., Flash, t., Schechtman, E., Shahar, I., & Korczyn, A. D. (1996). Switching abilities in Parkinson's disease. Advances in Neurology, 69, 361-369.

Jahanshahi, M., Ardouin, C., Brown, R. G., Rothwell, J. C., Obeso, J., Rodriguez, M. C., Gorospe, A., Albanese, A., Moro, E., Pollak, P., & Limousin, P. (1998). The relative impact of bilateral stimulation of the subthalamic nucleus (STN) or globus pallidus (GPi) on executive function in Parkinson's disease (PD). Movement Disorders, 13, 199.

Jankovic, J. (1992). Pathophysiology and clinical assessment of motor symptoms in Parkinson's disease. In W.C.Koller (Ed.), Handbook of Parkinson's Disease (pp. 129-157). New York: Dekker.

Javoy-Agid, F. & Agid, Y. (1980). Is the mesocortical dopaminergic system involved in Parkinson's disease. Neurology, 30, 1326-1330.

Jurko, M. F. & Andy, O. J. (1973). Psychological changes correlated with thalamotomy site. Journal of Neurology, Neurosurgery, and Psychiatry, 36, 846-852.

Kaplan, E., Goodglass, H., & Weintraub, S. (1978). The Boston Naming Test. Boston: E. Kaplan & H. Goodglass.

Kopelman, M. D. (1986). The cholinergic neurotransmitter system in memory and dementia: a review. Quarterly Journal of Experimental Psychology, 38A, 535-573.

Kritchevsky, M. (1988). The elementary spatial functions of the brain. In J.Stiles-Davis, M. Kritchevsky, & U. Bellugi (Eds.), Spatial Cognition: Brain Bases and Development (pp. 111-140). Hillsdale, NJ: Lawrence Erlbaum Associates.

Lee, A. C., Harris, J. P., & Calvert, J. E. (1998). Impairments of mental rotation in Parkinson's disease. Neuropsychologia, 36, 109-114.

Levin, B. E., Llabre, M., Ansley, J., Brown, M. J., & Weiner, W. J. (1984). Do parkinsonians exhibit a visuospatial deficit? Journal of Clinical and Experimental Neuropsychology, 11, 97.

Levin, B. E., Llabre, M. M., Reisman, S., Weiner, W. J., Sanchez-Ramos, J., Singer, C., & Brown, M. C. (1991). Visuospatial impairment in Parkinson's disease. Neurology, 41, 365-369.

Levin, B. E., Tomer, R., & Rey, G. J. (1992). Cognitive impairments in Parkinson's disease. Neurologic Clinics, 10, 471-485.

Lezak, M. D. (1983). Neuropsychological Assessment, (2nd ed.) New York: Oxford University Press.

Lhermitte, F. (1986). Human autonomy and the frontal lobes. Part 2: Patient behavior in complex and social situations: The "environmental dependency syndrome". Annals of Neurology, 19, 335-343.

Limousin, P., Greene, J., Pollak, P., Rothwell, J., Benabid, A. L., & Frackowiak, R. (1997). Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Annals of Neurology, 42, 283-291.

Limousin, P., Krack, P., Pollak, P., Benazzouz, A., Ardouin, C., Hoffman, D., & Benabid, A.-L. (1998). Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. New England Journal of Medicine, 339, 1105-1111.

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Brousolle, E., Perret, J. E., & Benabid, A. L. (1995). Bilateral subthalamic nucleus stimulation for severe Parkinson's disease. Movement Disorders, 10, 672-674.

Linn, M. C. & Peterson, A. C. (1985). Emergence and characterization of sex differences in spatial ability: A meta-analysis. Child Development, 56, 1479-1498.

Mack, W. J., Freed, D. M., Williams, B. W., & Henderson, V. W. (1992). Boston Naming Test: shortened versions for use in Alzheimer's disease. Journal of Gerontology Psychological Sciences, 47, 154-158.

Mahler, M. E. & Cummings, J. L. (1990). Alzheimer disease and the dementia of Parkinson disease: Comparative investigations. Alzheimer Disease and Associated Disorders, 4, 133-149.

Matison, R., Mayeux, R., Rosen, J., & Fahn, S. (1982). "Tip of the tongue" phenomenon in Parkinson's disease. Neurology, 32, 567-570.

Mattis, S. (1988). Dementia Rating Scale: Professional Manual. Odessa, FL: Psychological Assessment Resources.

Mattson, A. J. & Levin, H. S. (1990). Frontal lobe dysfunction following closed head injury: A review of the literature. Journal of Nervous and Mental Disease, 178, 282-291.

Maxwell, S. E. & Delaney, H. D. (1990). Introduction to model comparisons: one-way between-subjects designs. In Designing Experiments and Analyzing Data (pp. 63-128). Pacific Grove, California: Brooks/Cole Publishing Company.

McCarter, R. J., Walton, N. H., Rowan, A. F., Gill, S. S., & Palomo, M. (2000). Cognitive functioning after subthalamic nucleotomy for refractory Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 69, 60-66.

McDonald, C., Brown, C. C., & Gorell, J. M. (1996). Impaired set-shifting in Parkinson's disease: new evidence from a lexical decision task. Journal of Clinical and Experimental Neuropsychology, 18, 793-809.

McFie, J. (1960). Psychological effects of stereotaxic operations for the relief of Parkinsonian symptoms. Journal of Mental Science, 106, 1512-1517.

Mesulam, M. M. (1986). Frontal cortex and behavior. Annals of Neurology, 19, 320-325.

Milner, B. (1974). Hemispheric specialization: scope and limits. In F.O.Schmidt & F. G. Worden (Eds.), The Neurosciences: Third Study Program (Cambridge, MA: MIT Press.

Mishkin, M. (1982). A memory system in the monkey. Philosophical Transactions of the Royal Society of London, B, 298, 85-95.

Mohr, E., Fabbrini, G., Ruggier, S., Fedio, P., & Chase, T. N. (1987). Cognitive concomitants of dopamine system stimulation in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 50, 1192-1196.

Mohr, E., Juncos, J., Cox, C., Litvan, I., Fedio, P., & Chase, T. N. (1990). Selective deficits in cognition and memory in high-functioning Parkinsonian patients. Journal of Neurology, Neurosurger, and Psychiatry, 53, 603-606.

Money, J. (1976). Standardized Test of Direction Sense. San Rafael, CA: Academic Therapy Publications.

Montgomery, P., Silverstein, P., Wichmann, R., Fleischaker, K., & Andberg, M. (1993). Spatial updating in Parkinson's disease. Brain and Cognition, 23, 113-126.

Moro, E., Esselink, R.-A. J., Van Blercom, N., Caputo, E., Pollak, P., Limousin, P., & Hariz, M. I. (2000). Bilateral subthalamic nucleus stimulation in a parkinsonian patient with previous unilateral pallidotomy and thalamotomy. Movement Disorders, 15, 753-754.

Moro, E., Scerrati, M., Romito, L. M. A., Tonali, P., & Albanese, A. (1999). Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology, 53, 85-90.

Morrison, C. E., Borod, J. B., Brin, M. F., & Olanow, C. W. (2000a). Cognitive effects of dopamine replacement in advanced Parkinson's disease. Journal of the International Neuropsychological Society, 6, 206-207.

Morrison, C. E., Borod, J. B., Brin, M. F., Raskin, S. A., Germano, I. M., Weisz, D. J., & Olanow, C. W. (2000b). A program for neuropsychological investigation of deep brain stimulation (PNIDBS) in movement disorders patients: development, feasibility, and preliminary data. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 13, 204-219.

Mortimer, J. A. (1996). The mysterious cognitive disorder of Parkinson Disease. Alzheimer Disease and Associated Disorders, 4, 129-132.

Natsopoulos, D., Bostantzopoulou, M.-S., Katsarou, Z., Grouios, G., & Mentenopoulos, G. (1993). Space deficits in Parkinson's disease patients: quantitative or qualittive differences from normal controls. Behavioral Neurology, 6, 193-206.

Natsopoulos, D., Katsarou, Z., Alevriadou, A., Grouios, G., Botantzopoulou, S., & Mentenopoulos, G. (1997). Deductive and inductive reasoning in Parkinson's disease patients and normal controls: review and experimental evidence. Cortex, 33, 463-481.

Newcombe, F. (1969). Missile Wounds to the Brain. London: Oxford University Press.

Olanow, C. W., Germano, I. M., Brin, M. F., Swope, D., & Weisz, D. (1996). Deep brain stimulation of the subthalamic nucleus for Parkinson's disease. Movement Disorders, 11, 598-599.

Olanow, C. W. & Koller, W. C. (1998). An algorithm (decision tree) for the management of Parkinson's disease. Neurology, 50(Suppl 3), S1-S57.

Olichney, J. M., Galasko, D., Corey-Bloom, J., & Thal, L. J. (1995). The spectrum of diseases with diffuse lewy bodies. Advances in Neurology, 65, 159-170.

Owen, A. M., Iddon, J. L., Hodges, J. R., Summers, B. A., & Robbins, T. W. (1997). Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia, 35, 519-532.

Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., Lange, K. W., & Robbins, T. W. (1992). Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain, 115, 1727-1751.

Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. Brain, 116, 1159-1175.

Owen, A. M., Sahakian, B. J., Hodges, J. R., Summers, B. A., Polkey, C. E., & Robbins, T. W. (1995). Dopamine-dependent frontostriatal planning deficits in early Parkinson's Disease. Neuropsychology, 9, 126-140.

Parent, A. & Hazrati, L.-N. (1995). Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Research Reviews, 20, 128-154.

Parkinson, J. (1938). An essay on the shaking palsy. Medical Classics, 2, 964-997.

Perecman, E. (1987). Consciousness and the meta-functions of the frontal lobes. In E.Perecman (Ed.), The Frontal Lobes Revisited (pp. 1-10). Hillsdale, NJ: Lawrence Erlbaum and Associates.

Pirozzolo, F. J., Hansch, E. C., Mortimer, J. A., Webster, D. D., & Kuskowski, M. A. (1982). Dementia in Parkinson disease: a neuropsychological analysis. Brain and Cognition, 1, 71-83.

Pollak, P., Benabid, A. L., Limousin, P., Benazzouz, A., Hoffmann, D., Le Bas, J. F., & Perret, J. (1996). Subthalamic nucleus stimulation alleviates akinesia and rigidity in parkinsonian patients. Advances in Neurology, 69, 591-594.

Portin, R. & Rinne, U. K. (1980). Neuropsychological responses of parkinsonian patient to long- term levodopa treatment. In U.K.Rinne, M. Klingler, & G. Stamm (Eds.), Parkinson's Disease: Current Progress, Problems, and Management (pp. 271-312). New York: Elsevier.

Posner, M. I. (1980). Orienting of attention. Quarterly Journal of Expermental Psychology, 32, 3-25.

Posner, M. I. & Peterson, S. E. (1990). The attention system of the human brain. Annual Review of Neuroscience, 13, 25-42.

Randolph, C., Braun, A. R., Goldberg, T. E., & Chase, T. N. (1993). Semantic fluency in Alzheimer's, Parkinson's, and Huntington's disease: dissociation of storage and retrieval failures. Neuropsychology, 7, 82-88.

Randt, C. T. & Brown, E. R. (1984). Randt Memory Test. Bayport, NY: Life Science Associates.

Raskin, S. A., Borod, J. B., & Tweedy, J. (1990). Neuropsychological aspects of Parkinson's disease. Neuropsychology Review, 1, 185-221.

Raskin, S. A., Borod, J. C., & Tweedy, J. R. (1992a). Set-shifting and spatial orientation in patients with Parkinson's Disease. Journal of Clinical and Experimental Neuropsychology, 14, 801-821.

Raskin, S. A., Borod, J. C., Wasserstein, J., Bodis-Wollner, I., Coscia, L., & Yahr, M. D. (1990). Visuospatial orientation in Parkinson's Disease. International Journal of Neuroscience, 51, 9-18.

Raskin, S. A., Sliwinski, M., & Borod, J. C. (1992b). Clustering strategies on tasks of verbal fluency in Parkinson's Disease. Neuropsychologia, 30, 95-99.

Reid, W. G. J., Broe, G. A., Morris, J. G. L., Hely, M. A., Genge, S. A., O'Sullivan, D. J., & Williamson, P. M. (1992). The role of cholinergic deficiency in neuropsychological deficits in idiopathic Parkinson's disease. Dementia, 2, 114-120.

Reus, V. I. (1986). A neuroanatomic perspective on state-dependent learning: The role of the striatum. Acta Neurologica Scandinavica, Suppl 109, 31-36.

Richards, M., Cote, L. J., & Stern, Y. (1993). Executive function in Parkinson's disease: Set-shifting or set-maintenance. Journal of Clinical and Experimental Neuropsychology, 15, 266-279.

Riklan, M., Diller, L., Weiner, H., & Cooper, I. S. (1960). Psychological studies on effects of chemosurgery of the basal ganglia in parkinsonism. Archives of General Psychiatry, 2, 22-32.

Rodriguez, M. C., Guridi, O. J., Alvarez, L., Mewes, K., Macias, R., Vitek, J. L., DeLong, M. R., & Obeso, J. A. (1998). The subthalamic nucleus and tremor in Parkinson's disease. Movement Disorders, 13, 111-118.

Sager, H. J., Sullivan, E. V., Gabrieli, J. D. E., Corkin, S., & Growdon, J. H. (1988). Temporal ordering and short-term memory deficits in Parkinson's disease. Brain, 111, 525-539.

Saint-Cyr, J. A., Taylor, A. E., & Lang, A. E. (1993). Neuropsychological and psychiatric side effects in the treatment of Parkinson's disease. Neurology, 43, S47-S52.

Schretlen, D. (1989). Brief Test of Attention. Odessa, FL: Psychological Assessment Resources.

Sharpe, M. H. (1996). Is there a divided attention deficit in patients with early Parkinson's disease? Cortex, 32, 747-753.

Small, J. A., Lyons, K., & Kemper, S. (1997). Grammatical abilities in Parkinson's disease: Evidence from written sentences. Neuropsychologia, 35, 1571-1576.

Soukup, V. M., Ingram, F., Schiess, M. C., Bonnen, J. G., Nauta, H. J. W., & Calverley, J. R. (1997). Cognitive sequelae of unilateral posteroventral pallidotomy. Archives of Neurology, 54, 947-950.

Starkstein, S. E., Bolduc, P. L., Preziosi, T. J., & Robinson, R. G. (1989). Cognitive impairments in different stages of Parkinson's disease. Journal of Neurospychiatry and Clinical Neurosciences, 1, 243-248.

Stern, Y., Mayeux, R., & Cote, L. (1984). Reaction time and vigilance in Parkinson's disease. Archives of Neurology, 41, 1086-1089.

Stern, Y., Mayeux, R., Ilson, J., Fahn, S., & Cote, L. (1984). Pergolide therapy for Parkinson's disease: neurobehavioral changes. Neurology, 34, 201-204.

Stroop, J. (1935). Studies of interference in serial verbal reactions. Journal of Experimental Psychology, 18, 643-662.

Stuss, D. T. & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. Psychological Bulletin, 95, 3-28.

Sullivan, E. V. & Sagar, H. J. (1991). Double dissociation of short-term and long-term memory for nonverbal material in Parkinson's disease and global amnesia. Brain, 114, 893-906.

Sullivan, E. V., Sagar, H. J., Cooper, J. A., & Jordan, N. (1993). Verbal and nonverbal short-term memory impairment in untreated Parkinson's disease. Neuropsychology, 7, 396-405.

Svennilson, E., Torvik, A., Lowe, R., & Leksell, L. (1960). Treatment of parkinsonism by stereotactic thermolesions in the palidal region. Acta Psychiatr Neural Scand, 35, 358-377.

Tang, C. & Liu, Y. (1993). Impairment of visual form discrimination in Parkinson's disease. Acta Psychologica Sinica, 25, 258-263.

Taylor, A. E. & Saint-Cyr, J. A. (1995). The neuropsychology of Parkinson's disease. Brain and Cognition, 28, 281-296.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Frontal lobe dysfunction in Parkinson's disease. Brain, 109, 845-883.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1987). Cognitive changes in relation to treatment response. Brain, 110, 35-51.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1990). Memory and learning in early Parkinson's disease: evidence for a "frontal lobe syndrome". Brain and Cognition, 13, 211-232.

Tweedy, J. R., Langer, K. G., & McDowell, F. H. (1982). The effect of semantic relations on the memory deficit associated with Parkinson's Disease. Journal of Clinical Neuropsychology, 4, 235-247.

Van Blercom, N., Charles, D., Limousin, P., Krack, P., Benazzouz, A., Ardouin, C., Koudsie, A., Xie, J., Benabid, A.-L., & Pollak, P. (1999). Long-term bilateral

subthalamic nucleus stimulation for the treatment of Parkinson's disease. Neurology, 52, A271.

Van Spaendonck, K. P. M., Berger, H. J. C., Horstink, M. W. I., Buytenhuijs, E. L., & Cools, A. R. (1993). Impaired cognitive shifting in parkinsonian patients on anticholinergic therapy. Neuropsychologia, 31, 407-411.

Van Spaendonck, K. P. M., Berger, H. J. C., Horstink, M. W. I. M., Borm, G. F., & Cools, A. R. (1995). Card sorting performance in Parkinson's disease: a comparison between acquisition and shifting performance. Journal of Clinical and Experimental Neuropsychology, 17, 918-925.

VanSpaendonck, K. P. M., Berger, H. J. C., Horstink, M. W. I. M., Borm, G. F., & Cools, A. R. (1996a). Memory performance under varying cueing conditions in patients with Parkinson's disease. Neuropsychologia, 34, 1159-1164.

VanSpaendonck, K. P. M., Berger, H. J. C., Horstink, M. W. I. M., Buytenhuijs, E. L., & Cools, A. R. (1996b). Executive functions and disease characteristics in Parkinson's disease. Neuropsychologia, 34, 617-626.

Veldman, B. A., Wijn, A. M., Knoers, N., Praamstra, P., & Horstink, M. W. (1998). Genetic and environmental risk factors in Parkinson's disease. Clinical Neurology and Neurosurgery, 100, 15-26.

Walkup, J. (1991). Increased anticholinergic levels, memory and judgement. Human Psychopharmacology, 6, 189-196.

Weisz, D. J. & Yang, B. Y. (1998). Intraoperative electrophysiological recording techniques. In I.M.Germano (Ed.), Neurosurgical Treatment of Movement Disorders (pp. 207-218). Park Ridge, IL: AANS Publication Committee.

Wichmann, T. & DeLong, M. (1993). Pathophysiology of parkinsonian motor abnormalities. Advances in Neurology, 60, 53-61.

Woodard, J. L., Benedict, R. H. B., Roberts, V. J., Goldstein, F. C., Kinner, K. M., Capruso, D. X., & Clark, A. N. (1997). Short-Form Alternatives to the Judgment of Line Orientation Test. Journal of Clinical and Experimental Neuropsychology, 18, 898-904.

Wright, M. J., Burns, R. J., Geffen, G. M., & Geffen, L. B. (1990). Covert orientation of visual attention in Parkinson's disease: an impairment in the maintenance of attention. Neuropsychologia, 28, 151-159.

Yahr, M. (1993). Parkinson's disease: The L-DOPA era. Advances in Neurology, 60, 11-17.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. (1983). Development and validation of a geriatric depression screening scale: a preliminary report. Journal of Psychiatric Research, 17, 37-49.

Yokoyama, T., Sugiyama, K., Nishizawa, S., Tanaka, T., Yokota, N., Ohta, S., & Uemura, K. (1998). Neural activity of the subthalamic nucleus in Parkinson's disease patients. Acta Neurochirurgica, 140, 1287-1290.

Young, A. B. & Penney, J. B. (1993). Biochemical and Functional Organization of the Basal Ganglia. In J.Jankovic & E. Tolosa (Eds.), Parkinson's Disease and Movement Disorders (pp. 1-12). Baltimore: Williams and Wilkins.