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The Effect of DBS Settings on Neuropsychological Functioning in Patients with Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is an idiopathic progressive neurological disorder. Improvement in Parkinsonian motor function has been established with subthalamic nucleus (STN) deep brain stimulation (DBS). Recently, the relationship between DBS stimulator settings and motor function has begun to be explored; however, no study to date has investigated the relationship between DBS settings and neuropsychological functioning. This study evaluated the extent to which DBS settings (i.e., amplitude, frequency, and pulse width) are associated with post-operative performances on the RBANS (Repeatable Battery for the Assessment of Neuropsychological Status). The study was a prospective clinical trial of STN DBS for the treatment of medication refractory PD. Twenty patients were identified that met study inclusion and exclusion criteria. All participants completed neuropsychological evaluations, including the RBANS. Correlations revealed significant relationships between amplitude and pulse width with RBANS indices of visuospatial/constructional ability (r =.55) and immediate memory (r = .45). Also, significant relationships were found between amplitude and line orientation (r =.45) and pulse width and delayed figure recall (r =.46). Multiple regression found DBS stimulator settings, along with symptoms of anxiety, to be significant predictors of RBANS scores. While DBS appears to be relatively benign from a neuropsychological standpoint, some patients experience more pronounced

impairments. One variable that may account for previous variability is DBS stimulation parameters.

TABLE OF CONTENTS

LIST OF TABLES

Table

CHAPTER I

INTRODUCTION

Patients with Parkinson's disease have shown a wide range of neuropsychological or cognitive impairments due to damage of critical brain circuitry, neurotransmitter systems, and neuronal pathways. In the initial phases of Parkinson’s disease, patients are effectively treated with medications. However, with time and disease progression, the drugs become less effective and their use becomes associated with increasingly disabling adverse effects. When patients reach the point where they have significant disability despite the best available medical therapy, alternate strategies must be considered. It is in this context that chronic deep brain stimulation (DBS) is becoming an important treatment for patients with Parkinson’s disease and other movement disorders.

Based on the data, DBS is now widely accepted as safe and efficacious for patients who have been diagnosed with idiopathic Parkinson's disease; idiopathic meaning of no known cause. Currently, the majority of data on the effect of DBS have focused on the reduction of involuntary motor dysfunction following surgery. However, data are lacking comparing pre to post-operative neuropsychological function in patients with Parkinson's disease. Furthermore, deep brain stimulators have an external control by which a trained health care provider is able to adjust the frequency, amplitude, and pulse

width of electrical waves that stimulate certain areas of the brain. By adjusting these parameters, patients may experience differing clinical responses that may improve or hinder their motor and cognitive behavior.

I will discuss idiopathic Parkinson's disease and the underlying neuropsychological impairments observed in attention, language, visuospatial ability, memory, and executive function. Second, the mechanisms of subthalamic nucleus (STN) deep brain stimulation will be explained in terms of treatment options for Parkinson's patients no longer responding to medication. Finally, the associations between post-surgical cognitive performance and stimulator setting are discussed. In addition, a comprehensive review of the research literature on each of these issues is presented to assess the links between stimulator setting and cognitive function.

The current literature has limited accounts of the relationship between stimulation parameters and cognition, behavior, or subjective psychotropic effects. No studies have systematically varied stimulation parameters and assessed cognition in a within-subject design. This study attempted to determine how fluctuations in amplitude, frequency, and pulse width affect neuropsychological function in patients with idiopathic Parkinson's disease. Neuropsychological measures include the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) which is a standardized psychological test used to evaluate neuropsychological function. It is hypothesized that variations in amplitude, frequency, and pulse width may cause changes in neuropsychological function post-surgery.

CHAPTER II

REVIEW OF THE RELEVANT LITERATURE

Parkinson's disease

Parkinson's disease (PD), or primary parkinsonism, is an idiopathic progressive neurological disorder that is manifested clinically by bradykinesia (or slowness in the initiation of voluntary movement), resting tremor, rigidity, and postural reflex impairment (Adams, Parsons, Culbertson, & Nixon, 1996). All individuals with PD show a moderately severe, high focal nerve-cell loss in the pars compacta of the substantia nigra (Gibb, 1992). The dopamine depletion that occurs as a result of the nerve-cell degeneration in PD reduces the concentration of this neurotransmitter along the nigro-striatal pathway, resulting in an imbalance in the activity of motor systems (Adams et al., 1996). Beyond these motor impairments, cognitive dysfunctions often occur over the course of PD. Functional disturbances of fronto-striatal loops resulting from deficient dopamine transmission due to cell loss within the substantia nigra is considered the primary neural correlate for cognitive deficits in PD (Brand et al., 2004).

Until relatively recently, the sole focus of research in Parkinson's disease was the motor symptoms associated with this neurodegenerative disorder. In the last few decades,

it has become increasingly apparent that PD involves a variety of cognitive impairments (Whittington, Podd, & Stewart-Williams, 2006). Numerous studies have reported cognitive dysfunctions in patients with Parkinson's disease relative to healthy volunteers on measures of declarative memory, working memory, visuospatial skills, language, frontal lobe capacities, and attentional processes (Locascio, Corkin, & Growdon, 2003). It is important to note that although there is some consensus that PD involves cognitive impairments, the nature of these impairments is controversial. It appears that several variables, such as severity of disease and age of onset, may be related to the observed deficits in neuropsychological functioning. Due to the age of onset of PD, it is also somewhat inconclusive and at times difficult to determine what constitutes a decline in cognitive functioning. That is, the decline may be secondary to a neurodegenerative disorder or be a consequence of the normal aging process.

Nevertheless, the most salient feature that emerges from these studies is the extensive individual variation in the patterning of the motoric and cognitive symptomology of the disease (Adams et al., 1996). Burton, Strauss, Hultsch, Moll, and Hunter (2006) observed intraindividual variability, or inconsistency, as a marker in neurological dysfunction in patients with Parkinson's disease. Intraindividual variability refers to relatively short-term, reversible changes in a person's performance within a task administered on a single occasion or the same task administered across multiple occasions over short intervals of time. Research to date indicates that intraindividual variability can be reliably measured, is substantial in magnitude, and tends to be a relatively stable characteristic of the individual (Burton et al., 2006). In this study participants were assessed on four separate occasions on two basic reaction time tasks

and two recognition memory tasks. Results showed that participants with Parkinson's disease were more variable across trials than were healthy controls on all measures of cognitive functioning. The findings suggest that there may be some specificity of the neurological mechanisms underlying intraindividual variability, such as differences in the neural structures or neural pathways affected, or the diffuseness of the damage (Burton et al., 2006). Therefore, due to the high degree of intraindividual variability amongst Parkinson's patients, it is important to question the reliability and validity of empirical findings concerning the observed neuropsychological dysfunction in Parkinson's disease.

Attention

The neuropsychology of Parkinson's disease refers to the cognitive and behavioral changes which accompany the disorder (Taylor & Saint-Cyr, 1995). Even non-demented, non-depressed PD patients are said to suffer a variable mix of specific cognitive weaknesses, which, according to the functions studied, implicate memory, language, visuospatial processes, abilities of an executive nature, and attention.

Neuropsychological research has suggested that there are many different forms and processes of attention. Studies have suggested that patients with frontal lobe damage have demonstrated deficits in tasks that require sustained, divided, and selective attention (Lee, Wild, Hollnagel, & Grafman, 1999). Lee et al. (1999) state that one approach to understanding the role of the frontal lobes in attention has viewed attention as the process of allocating resources. One specific aspect of attention allocation, termed selective attention, involves the ability to focus upon one target, while ignoring other interfering stimuli. Studies have supported the contention that patients with Parkinson's disease suffer from a disorder of attention on task-switching experiments as evidenced by

increased susceptibility to interference from distracter items as compared with controls (Lee et al., 1999).

Lee et al. (1999) examined selective attention in Parkinson patients by using the flanker task devised by Eriksen (1995). The flanker task has been employed to investigate selective attention in various patient populations. This task consists of presenting a cross on a computer monitor which indicates where a target letter will appear. Then, a letter (either S or H) appears directly above the fixation. The participant must then type the letter as quickly as possible and ignore any other letters that are presented at various distances on the monitor. The target letter was presented either without distracters (control condition) or was flanked by letters at various distances. The flanking letters could either have the same identity as the target letter (distracter compatible condition), have been a target on the previous trial (distracter incompatible condition), or were letters other than the target letters (distracter neutral condition).

Results show that patients produced results consistent with the effects originally described by Eriksen (cited in Lee et al., 1999). The patients, when compared to controls, were slower in their response times across the spatial distances and the different interference conditions. Also, as the spatial distance between the flanking letters and target letter increased, the target response times decreased across the conditions. Finally, the different conditions influenced the target response times in all of the groups, with the distracter incompatible condition producing the slowest reaction time and the compatible condition producing the fastest reaction time (Lee et al., 1999). However, the results using this task suggest that the cognitive processes underlying selective attention are spared in patients with PD.

In comparison with the study by Lee et al. (1999) Corbetta, Miezen, Dobmeyer, Shulman, and Petersen (1991) found that their selective attention task activated basil ganglia, the lateral orbitofrontal cortex, and the premotor cortex, which are commonly affected areas in the brains of Parkinson's patients. Furthermore, Vendrell, Punjol, Jurado, Molet, and Grafman (1995) found that PD patients with frontal lobe deficits tended to perform worse than controls on the Stroop task. However, the flanker task differs from the Stroop test in that in the flanker task, the distraction surrounds the target whereas in the Stroop test, the distraction spatially overlaps with the target stimulus shown to the subject. Therefore, task differences might account for differences in frontal lobe lesion effects upon seemingly similar attentional processes (Vendrell et al., 1995).

In another study examining subcortical attentional dysfunction by Roman et al. (1998), participants were presented with global-local figures and were instructed to focus their attention on either the global or local level. Stimuli were either consistent with the same form at the global and local levels, (a large one made up of smaller ones), or inconsistent with different forms at the global and local levels (a large one made up of smaller twos). Findings indicated that subjects responded more slowly to inconsistent than consistent stimuli; however, the results were not significant.

This study's finding that patients with PD have intact focused attention on a global-local task differs from past research (Roman et al., 1998). Several past studies have demonstrated an increased susceptibility to distraction by unattended features of stimuli in patients with PD. In addition, Maddox, Filoteo, Delis, and Salmon (1996) found that patients with PD were impaired on a perceptual decision task requiring them to attend to and classify one feature of a stimulus while ignoring another. The differences in

the findings may be explained in terms of task complexity. Task duration may also influence focused attention in that longer tasks may produce deficient performances in sustained attention in PD patients as compared to shorter tasks. Overall, these results provide further evidence for the heterogeneity of attentional dysfunction among subcortical degenerative illnesses (Roman et al., 1998).

Language

While the motor and cognitive deficits in PD have been well documented, deficits in language and language processing are also a frequently reported feature (Angwin, Chenery, Copland, Murdoch, & Silburn, 2007). The most research on PD patients has been conducted in the area of verbal fluency. Verbal fluency measures have revealed a selective deficit associated with category naming. Specifically, PD patients without dementia show significant impairment in category naming for a semantic target, such as fruit, but perform normally on tests of letter fluency (Auriacombe et al., 1993). Although several explanations have been proposed to account for this selective fluency deficit, preliminary reports by Auriacombe et al. (1993) have suggested that impaired category naming is related to the lexical retrieval impairment that has been observed in PD.

Azuma, Cruz, Bayles, Tomoeda, and Montgomery (2003) conducted a longitudinal study of neuropsychological change in individuals with PD, and reported that of the ten neuropsychological tests given, only semantic, or letter fluency, performance significantly declined by second testing two years later. Testa et al. (1998) also observed the semantic fluency performance of patients with cortical and subcortical neurodegenerative diseases. In parallel with previous data, they state that in PD, there is a marked and progressive reduction in total word output on verbal fluency tests. However,

these changes are usually attributed to retrieval failures rather than to degradation of the semantic memory stores. Studies of the patterns of responding of normal participants on semantic fluency tasks reveal that semantically related words tend to cluster together, occurring in spurts over time (Gruenewald & Lockhead, 1980). PDD patients (Parkinson's disease with dementia) exhibited reduced cluster sizes as compared to PD patients. Overall, these findings indicate that semantic cluster size reflects efficiency of access to semantic knowledge, which is similarly compromised in subcortical and cortical diseases (Testa et al., 1998).

Ho, Iansek, and Bradshaw (2002) tested both the role of attention and Parkinsonian speech control by using a dual-task paradigm. While it is well-known that skeletal motor performance is impaired when Parkinson's disease patients are required to perform two motor acts simultaneously, this has not been examined in the context of speech motor control (Ho et al., 2002). This experiment was comprised of a joystick which was placed over a visual display scale. The participant had to track a needle across the visual display scale. Moving the joystick in the opposite direction could counteract random movement of a needle. As a result, participants attempted to control the position of the needle so that it was in the middle section of the plate at all times. In addition, two different procedures were utilized in order to concurrently assess Parkinsonian speech: a numerical sequences condition in which the participants had to count forward and backward as long as possible without taking a breath while tracking the needle; or a conversation condition in which the participants had to ask and answer questions about a familiar setting, such as their house or garden, in as much detail as possible.

Results showed that instead of talking and performing the concurrent task in

parallel, patients alternately shifted attention from one task to the other, in a sequential manner. When the needle drifted from the target position, they would conveniently, and sometimes inappropriately, pause (Ho et al., 2002). Results suggest that PD patients show an additional deterioration of temporal deficits in speech when attentional resources are reduced by a distracter task. It therefore appears that this deterioration transcends motor systems, and is critically driven by the higher-order frontostriatal impairment in PD (Ho et al., 2002).

In addition to language or speaking deficits, language processing is also compromised in PD patients. For instance, researchers have reliably demonstrated that some patients with PD have poorer comprehension of sentences containing complex clauses with a noncanonical structure, such as “the girl that the boy hit dropped the parcel,” compared to sentences with simpler canonical structures, such as “the girl that hit the boy dropped the parcel” (Grossman et al., 2000). Angwin et al. (2007) studied the speed of lexical activation in Parkinson’s disease. Stimuli were presented as a continuous list of words and nonwords, with semantic priming effects being measured across intervals. The results revealed longer delays in lexical activation for PD patients with poor comprehension of noncanonical sentences, suggesting that the speed of lexical access may be compromised in PD, and this feature may contribute to certain sentence comprehension difficulties (Angwin et al., 2007).

Overall, reports of linguistic functions among PD patients indicate a relative preservation of verbal abilities. However, a proportion of PD patients suffer from speech problems, characterized by monotony of pitch and loudness, reduced stress, short

phrases, and segmented rushes of speech. These speech impairments, coupled with reduced gestural movements, compromise communication skills (Adams et al., 1996).

Visuospatial/Construction

Visuospatial dysfunction, as one of the most frequently reported cognitive deficits in PD, reveals an interesting gradient of functional decline (Adams et al., 1996). A series of studies by Levin and colleagues (Levin et al., 1991) suggested that facial recognition is one of the initial visuospatial skills to show decline in patients both with and without dementia. However, PD patients without dementia retain the ability to formulate angular judgments and are able to identify geometric figures. Tasks involving mental object assembly, such as the Hooper Visual Organization Test, show a decline as a function of disease duration and are independent of dementia (Adams et al., 1996).

In an effort to validate the observed deficits in visuo-constructional ability in PD patients, Giraduo, Gayraud, and Habib (1997) studied the visuospatial ability of PD patients and elderly adults in location memory tasks. In the more effortful task, 11 PD patients, 10 elderly control subjects, and 13 young control subjects were given 3 minutes to learn the layout of 12 places labeled on a map and then reproduce it. In the less effortful task, 9 new PD patients, 9 new elderly control subjects, and 10 new young control subjects were given 3 minutes to learn the layout of 12 black dots and then asked to reproduce it. In both cases the task was repeated twice. Results for the first task confirmed the effortful nature of the task as well as observed lower performance for PD patients with a high degree of variability. As with remembering dot locations, the PD patients also performed significantly worse, thus proving their difficulty with organizing and planning information. These results suggest deficits in the executive functions.

Pillon et al. (1997) also observed the connection between memory and spatial location in PD patients. They showed that typical, non-PDD patients have a severe memory deficit for visuospatial location of pictures, contrasting with the relative preservation of verbal memory and mild difficulties in visuospatial and executive functions. Since the patients in their study were not demented, it was proposed that their memory deficit might result from dopaminergic depletion. In the current study, the performance of 10 PD patients was compared with 14 controls on a visuospatial learning test. The task required little motor or constructive functions and was designed to allow control of encoding and comparison of free recall, cued recall, and recognition. Compared to controls, PD patients showed a lower performance in memory for visuospatial location of pictures, contrasting with relative preservation of verbal memory, perceptive visuospatial and executive functions (Pillon et al., 1997). These results confirm the deficits of visuospatial memory, even at an early stage of Parkinson's disease.

In another attempt to link executive function and visuospatial ability, Cronin-Golomb and Braun (1997) raised the question as to whether a visuospatial deficit may account for poor performance on a task of executive function, specifically on Raven's Coloured Progressive Matrices (RCPM). Fifty non-demented participants with PD and 39 age-matched healthy control participants were used in the study. The authors hypothesized that the PD group should perform deficiently not only on the B subtest of the RCPM, but also on the easy A subtest, which mainly assesses visual closure rather than logical reasoning capacities (Cronin-Golomb & Braun, 1997). Furthermore, it was

hypothesized that PD performance on the visual A (visuospatial) subtest of the RCPM would be predicted by performance on other visuospatial tests.

Results showed that the authors' first hypothesis was supported. The impairment included a small but significant group difference on subtest A, which assesses visuospatial ability. The second hypothesis was also supported in that RCPM-A performance was predicted at a significant level by the visuospatial composite score but not by the executive function or verbal memory composite scores. Overall, the PD group made significantly more errors than the control group on all RCPM subtests, including the subtest that mainly assessed visuospatial function. These results support arguments for the existence of genuine, if selective, deficits in visuospatial cognition in PD. The results also suggest that impaired PD performance on the RCPM may be due in part to deficient visuospatial function and its effect on performance subtest A (Cronin-Golomb & Braun, 1997).

It has been shown that PD patients show deficits in facial recognition due to declines in visuospatial ability. Dujardin et al. (2004) studied deficits in decoding emotional facial expressions in PD. Eighteen PD patients participated in the study together with 18 matched control subjects. The participants' task was to rate the emotion portrayed by each face and to quantify its intensity. In order to achieve this, they had to rate each expression on seven point scales for each of seven basic emotions: happiness sadness, fear, anger, disgust, surprise, and shame. These scales were presented on a computer screen below each facial expression (Dujardin et al., 2004). Subjects also participated in an executive function task. Results showed that early in the course of the disease, untreated PD patients were significantly impaired in decoding emotional facial

expressions (EFEs), as well as in executive function. Overall, non-verbal emotional processing is disturbed in PD. These findings suggest that deficits in executive function, memory, and visuospatial ability in PD patients may contribute to their lack of facial recognition.

Memory

The prevalence and nature of memory impairments in non-demented patients with idiopathic Parkinson's disease has been the subject of considerable research effort (Ivory, Knight, Longmore, & Caradoc-Davies, 1999). However, empirical research shows that memory yields contradictory findings when exploring neuropsychological dysfunction in PD patients. Explanations for the perceived differences include differences in task complexity, differences in types of task, age of onset, and degree of impairment due to illness. Additionally, different types of memory appear to be compromised in PD which include both implicit and explicit memory, as well as several impairments with both recall and recognition tasks.

There is evidence for deficits in recall memory among non-demented PD patients. These deficits affect both verbal and nonverbal recall, and appear to be independent of anti-parkinsonian medication (Brown & Marsden, 1990). Studies have been consistent in observing memory recall dysfunction in PD patients. Demakis, Sawyer, Fritz, and Sweet (2001) studied incidental recall on the WAIS-R digit symbol task. For this task, the examinee is asked to recall, without warning, the symbols associated with each number immediately after completion of the standard subtest. The test is administered in standard fashion except that participants were not stopped after 90 seconds had expired, but completed the entire stimulus sheet. Results indicated that PD patients performed below

age-related expectations on the standard administration of the digit symbol subtest. Also, Demakis et al. (2001) found this simple incidental recall adaptation to be sensitive to memory impairment and to be related more strongly to established memory measures than were cognitive efficiency measures.

Stefanova, Kostic, Ziropadja, Ocic, and Markovic (2001) also observed memory recall in patients with early PD by examining the serial positioning effects of word list learning across five successive trials. Cued, both verbal and visual paired associate learning from the Wechsler Memory Scale-Revised, and uncued, free recall memory tasks, such as the RAVLT and ROCFT, were used. Results indicated that impairments were found on the uncued memory tasks, in which the PD group performed significantly worse than their matched controls. Stefanova et al. (2001) assume that the memory problems of the PD group are secondary to frontal system dysfunction. However, they state that the serial positioning analyses of the word list, and their dynamic changes over five trials in the PD group, could not be entirely explained in terms of frontal dysfunction. Therefore, deficits in specific types of memory, such as free recall, may be attributable to other underlying cognitive processes.

In another attempt to confirm recall deficits in PD patients, Ivory et al. (1999) assessed the verbal memory functions of 20 patients with idiopathic PD. Performance was compared on tests of immediate recall, word list learning, word completion priming, and remote memory. Taken together, results showed the memory impairments present in this group of non-demented patients with PD were rather mild. The only specific deficit to emerge was that the PD subjects exhibited impairment on a free recall memory test when no specific orienting instructions were provided (Ivory et al., 1999). Therefore, it

appears that task conditions such as the presence of orienting instructions and retrieval cues may determine whether PD patients will experience difficulties on tests of verbal and working memory.

It has often been reported that PD impairs free recall, but not recognition (Arroyo-Anllo, Ingrand, Neau, Aireault, & Gil, 2004). The research concerning recognition memory is inconsistent, with various studies reporting some form of impaired recognition in non-demented PD participants (Whittington et al., 2006). Older research supports the notion that recognition in Parkinson's disease patients remains relatively intact and is largely independent of impairments in free recall tasks. However, recent attempts have found significant differences between PD patients and matched controls on recognition memory tasks. For example, Stebbins, Gabrrrieli, Masciari, Monti, and Goetz (1999) found that PD patients, relative to control participants, had intact immediate but impaired delayed recognition memory performance.

Furthermore, Higginson, Wheelock, Carroll, and Sigvardt (2003) set out to provide evidence that recognition and cued recall are not intact in PD patients. They hypothesized that PD patients would perform below expectations on measures of a cued recall and recognition as well as free recall task, suggesting that memory deficits in PD are not solely due to retrieval problems. PD patients were administered the California Verbal Learning Test and their performance was compared to a well-matched normative sample. A profile analysis revealed that non-demented PD patients exhibited deficits on measures of cued recall and delayed recognition that were similar in magnitude to that of free recall (Higginson et al., 2005). This was also the case for cued recall deficits exhibited by demented patients; however, in this group, recognition was worse than free

recall. In both groups, poor recognition appeared due to an elevated number of false positive errors (Higginson et al., 2005).

Whittington et al. (2006) further investigated deficits in recognition, recall, and prospective memory among PD patients, while also observing how task difficulty and disease severity moderate these deficits. The comparisons were made between 41 non-demented PD participants, divided into early-stage and advanced-stage groups, and 41 matched controls. PD participants exhibited deficits in recognition, recall, and prospective memory. The advanced-stage group produced greater deficits than the early-stage PD group in all tasks, suggesting that these deficits increase in step with overall disease severity (Whittington et al., 2006). In addition, the results of three previous studies examining recognition memory in PD with the CVLT are consistent with those reported here: poor recall and recognition errors with an elevated number of false positives. Thus, it appears that evidence of recognition memory impairment is more consistently found with the CVLT than with other measures (Higginson et al., 2005). This is likely due to the fact that the task involves conceptual ability as well as verbal memory and requires examinees to internally generate a problem solving plan or strategy (Higginson et al., 2005).

In an effort to resolve the recognition debate amongst Parkinson patients, Whittington, Podd, and Kan (2000) conducted an analysis of the statistical power of studies investigating PD-related recognition memory deficits. They discovered that the power of the relevant research has generally been too low to reliably detect small-to medium-size effects. For example, in 48 studies investigating memory functioning in PD, the mean power to detect small effects was just 20% (Whittington et al., 2000).

Underpowered studies increase the likelihood that researchers will conclude that there is no population effect when in fact there is one. Wittington et al. (2000) also ran a meta-analysis of studies investigating recognition deficits in PD. They found that small deficits in recognition memory do occur in non-demented PD patients. Thus, the view that PD involves relatively intact recognition memory may largely be an artifact of underpowered studies. Overall, it is clear that Parkinson patients display a wide range of neuropsychological dysfunction in the area of verbal and nonverbal recall and recognition memory tasks.

Executive Function

Research over the last two decades has provided an extensive body of evidence associating frontal lobe type cognitive deficits with Parkinson's disease (Berry, Nicolson, Foster, Behrmann, & Sagar 1999). Traditionally, dysfunction of the complex loop between the caudate nucleus and the prefrontal cortex resulting from dopamine deficiency is presumed to underlie the cognitive deficits of PD. However, depletion of dopamine in the mesocorticolimbic system, which also projects to the prefrontal cortex, has led some investigators to suggest that it is the degeneration of this system that causes the observed deficits (Berry et al., 1999). Moreover, there is dysfunction of non-dopaminergic neurotransmitter pathways innervating the frontal cortex in PD. Therefore, dysfunction of any one of the major neurotransmitter systems in subcortical-cortical pathways may alter cognitive behaviors that are mediated by the frontal lobes (Berry et al., 1999).

Some of the most prominent cognitive deficits of PD patients that comprise disturbances of the executive functions include cognitive flexibility, strategy learning and

application, working memory, and different forms of higher order attention and susceptibility to interferences. Category formation, abstract reasoning, mental planning, set shifting and set maintaining are other dysfunctional areas observed in PD patients, which further suggest the role of the frontal lobes (Farina et al., 2000). It has been hypothesized that neuropsychological decline in PD is secondary to executive dysfunction. Early in the course of the illness, cognitive symptoms are predominantly "frontal like" and involve set shifting, planning, problem solving, and organization (Higginson et al., 2003).

Higginson et al. (2003) examined the relationship between executive dysfunction and working memory in PD patients. They state that working memory is an aspect of executive functioning which involves the active manipulation of information in a temporary store, thus including processes that may be necessary for other cognitive tasks (Higginson et. al, 2003). Additionally, they hypothesized that working memory would be predictive of recall, due to the correlation between working memory and executive function. Thirty-two idiopathic PD patients were tested using the CVLT, the letter-number sequencing task, digit span, similarities, comprehension, and matrix reasoning from the WAIS III, the Stroop test, and the Wisconsin Card Sorting Task. Working memory predicted 50% of variability in recall (Higginson et. al, 2003). The results corroborate previous literature. For example, Cooper, Sagar, and Sullivan (1993) found significant correlations between memory and attention and other aspects of executive function, suggesting that deficits in the frontal lobes may cause further cognitive decline for patients with PD.

Farina et al. (2000) also researched the differential impairment of frontal functions and explicit memory in early Parkinson's disease. Results showed that the greatest impairment was seen with the Wisconsin card sorting task (WCST) and the odd-man-out test. The WCST and the odd-man-out test are widely used tests that assess abstract behavior and shifting ability. The group of mild PD patients showed a reduced number of correct responses on the WCST and a higher error score on the odd-man-out test. This finding confirms the previous reports of impaired set shifting and maintaining being the first executive ability to be lost in the early stages of PD (Farina et al., 2000).

In another attempt to investigate possible associations between decision-making and executive functions in PD, Brand et al. (2004) examined 20 non-demented PD patients and 20 healthy control subjects with a neuropsychological test battery and the Game of Dice Task. The neurological test battery consisted of the Mini Mental State Examination (MMSE), the Modified Card Sorting Task (MCST), the Controlled Oral Word Association Test (COWAT) of verbal fluency, and a word recall task. The Game of Dice Task examines decision-making ability in a gambling situation in which explicit rules for gains and losses as well as winning probabilities are explained to the participant. Results showed that patients with PD were impaired in decision-making tasks with explicit rules for gains and losses (Brand et al., 2004). Also, the frequency of disadvantageous choices correlated with both executive functions and feedback processing. These results further implicate the dysfunction of the prefrontal-striatal loop involved in the executive functions of PD patients.

In order to distinguish impairment in set-shifting in PD from inability to inhibit distraction by stimuli that compete for attention, Richards, Cote, and Stern (1993)

compared 18 non-demented patients with PD to 13 normal controls on the odd-man-out test (OMO) and the Stroop Color-Word Test. PD patients were significantly impaired on the OMO, but results were not significant for the Stroop test. Analysis of error patterns during the OMO test indicated that the requirement to repeatedly switch rules, rather than the requirement to maintain steady responding between rule switches, was responsible for impaired OMO performance (Richards et al., 1993). It was concluded that the OMO test is fundamentally a test of set shifting, rather than a test of set maintenance in PD. These results suggest that impairment in set-shifting function in PD may arise from pathology of the fronto-striatal system independently of changes in cognitive ability.

Deep Brain Stimulation

In the initial phases of Parkinson's disease, patients are effectively treated with medications. With time and disease progression, however, the drugs become less effective and their use becomes associated with increasingly disabling adverse effects. Among the problems that arise are the appearances of motor fluctuations and of drug-induced involuntary movements or dyskinesias. When patients reach the point where they have significant disability despite the best available medication therapy, alternate strategies must to be considered. It is in this context that chronic DBS is becoming an important treatment for patients with Parkinson's disease and other movement disorders (Lozano, 2001).

Deep brain stimulators, often called "pacemakers for the brain," are implantable devices that continuously deliver impulse stimulation to specific targeted nuclei of deep brain structure. The deep brain stimulator has four contact electrodes which are stereotactically placed into the targeted nucleus of the basil ganglia or thalamus (Gang,

Chao, Ling, & Lu, 2005). The electrodes are connected to a pulse generator by a wire that is tunneled down to the pulse generator from the brain. The pulse generator typically is placed in subcutaneous tissue of the chest, much the same as a cardiac pacemaker. Stimulation parameters include electrode selection, stimulation pulse amplitude (mV), frequency (Hz), and pulse width (μs). These can be adjusted or altered in order to achieve maximum clinical effect and minimize side effects (Gang et al., 2005).

Evidence gathered from experimental models of Parkinsonism in non-human primates has shown that the parkinsonian state is characterized by pathological neural activity in several relays in the motor system including the thalamus, the internal segment of the globus pallidus (Gpi), and the subthalamic nucleus (Lozano, 2001). The suppression of this abnormal activity by lesions or through the use of chronic electrical stimulation can produce important benefits in experimental models of parkinsonsim and in patients with PD. The three main targets in current usage for the treatment of PD are the thalamus for tremor and Gpi or STN for bradykinesia, rigidity, tremor, postural gait disturbances, and drug-induced involuntary movements in addition to tremor (Lozano, 2001). However, only STN DBS is pertinent to this review.

It is plausible that DBS disrupts not only the motor circuits, but also the circuits needed for efficient cognitive processing (Gironell et al., 2003). Therefore, post-operative programming or adjusting the deep brain stimulator for amplitude, pulse width, or frequency becomes crucial to achieve clinically significant improvements in both motor control and cognitive function. While pulse width and frequency are usually kept at a constant, amplitude varies depending on clinical response and side effects (Volkmann, Moro, & Pahwa, 2006). Although it is well-known how stimulator setting is related to the

decreased involuntary motor movements of PD, only a few studies have correlated stimulator setting and cognitive functioning. Based on the sparse research that has been conducted, it is hypothesized that differential variations in amplitude, frequency, and pulse width may lead to significant changes in the neuropsychological functioning of PD patients.

Fundamental knowledge regarding the application of electrical currents to deep brain structures is far from complete (Temel et al., 2005). One of the more popular hypotheses is that DBS causes a reduction of neuronal activity, meaning that the stimulation reduces or inactivates neurons in the vicinity of the electrical stimulation. Another assumption is that the electrical stimulation causes disruption of basil ganglia circuitry, possibly allowing a re-setting function or re-programming of motor control (Saint-Cyr et al., 2000). However, Saint-Cyr et al. (2000) state there are many reasons to believe that these hypothesized mechanisms may be too simplistic or may not be uniformly applied to all structures treated with DBS. Therefore, future studies directed at improving the understanding of the mechanism underlying the effect of deep brain stimulation will be important for the continued development and application of DBS treatment of neurological disease (Gang et al., 2005).

DBS and Neuropsychological Function

Although the motor symptoms of PD are not the focus of this review, it is important to note that improvements in Parkinsonian motor function have been well established with STN DBS. Several studies have found significant reductions in bradykinesia, tremor, rigidity, postural reflex, and freezing of gait. Recently, the relationship between DBS settings and motor function has begun to be explored. Results

have shown that fluctuations in amplitude are strong predictors of the consequent improvements of the motoric functioning in PD patients. However, due to small sample sizes and the relatively new interest in the area, all results relating specific stimulator settings and motor functioning should be taken as preliminary.

Conversely, the effects of DBS on these non-motor cognitive and psychiatric symptoms are less clear (Voon, Kubu, Krack, Houeto, & Troster, 2006). Most studies report that cognitive functions do not change significantly upon stimulation. However, some authors have noted a trend towards improved executive functions, attention, and working memory, whereas other works report cognitive declines in individual cases (Perriol et al., 2006). Given these discordant results, it is now generally acknowledged that cognitive decline and psychiatric disorders should be evaluated extensively in patients applying for surgery. However, despite rigorous selection, some individuals nevertheless develop cognitive decline and behavioral disorders after STN stimulation (Perriol et al., 2006). To date, no clear explanation has been found.

Looking at short-term (3-6 months post surgery) cognitive effects of STN DBS, Morrison et al. (2004) reported on a series of PD patients who had undergone bilateral STN electrode placement. By comparing the pre-surgical baseline to the post-surgical stimulation-*on* condition, investigators found a decline in verbal fluency and improvements on the Trail Making Test (TMT) parts A and B. In another study, Hariz et al. (2000) reported the case of a man who had moderate memory deficits pre-surgically and demonstrated cognitive deterioration post-operatively. Finally, in a small sample of PD patients who underwent unilateral STN DBS, two of three subjects demonstrated

minimal cognitive change whereas the third subject declined in verbal fluency, verbal learning and memory, and executive functioning (Morrison et al., 2004).

Assessment of cognitive functioning at longer follow-up intervals (9-12 months post surgery) has revealed more mixed findings. Some authors report no cognitive decline or only isolated reductions in verbal fluency following bilateral STN DBS (Morrison et al., 2004). For example, in some studies learning ability recovered somewhat, whereas performance on frontal lobe tasks either did not improve or continued to decline. It could be argued that the persistent deficits observed at long-term follow-up were related to Parkinson's disease progression, rather than to the DBS per se. However, if this were the case, all studies with long-term follow-up data would note a similar decline in cognitive performance (Morrison et al., 2004). As indicated before, other studies have not observed this pattern, suggesting that disease progression may not be the primary reason for the persistent reduction in performance following DBS surgery (Saint-Cyr et al., 2000).

Although no clear link exists between DBS and cognitive function, research has examined correlations between pre and post-operative neuropsychological function of PD patients, only to find contradictory results. Saint-Cyr et al. (2000) examined the possible neuropsychological changes in patients with advanced idiopathic Parkinson's disease treated with bilateral deep brain stimulation of the subthalamic nucleus. Eleven patients were assessed using a full neuropsychological test battery, which consisted of tasks of attention and working memory, executive functioning, language, and verbal and visual learning, at 3-6 months and 9-12 months post-operatively. Results showed that various aspects of frontal striatal functioning were further compromised with bilateral STN DBS.

Cognitive processes involving executive functioning, such as working memory, phonemic fluency, encoding efficiency, susceptibility to interference, and associative learning were all impaired following electrode implantation (Saint-Cyr et al., 2000). Participants over the age of 69 also performed significantly worse post-operatively as compared to some of the younger participants who nevertheless were also vulnerable to cognitive decline. This is in line with previous research which states that patients with cognitive impairment before surgery or older than 69 are at risk of worsening after surgery (Dowsey-Limousin & Pollak, 2001).

Gironell et al. (2003) also examined the consequences on STN DBS on cognitive function in a controlled comparison design. Sixteen patients were evaluated 1 month before surgery and again at 6 months post-surgery. The same assessments were performed in a control group of eight matched PD patients recruited from surgery candidates who refused the operation. The neuropsychological battery consisted of tests measuring memory, attention, arithmetic, problem solving and language, as well as visuospatial ability and executive function. The main finding was that bilateral STN DBS did not result in global neuropsychological impairment relative to pre-surgical baseline. However, a slight effect was found for a selective decrease in verbal fluency (Gironell et al., 2003).

Significantly decreased verbal fluency is one of the most consistent findings across studies (Gironell et al., 2003). Verbal fluency is a composite task, with multiple cognitive subcomponents (e.g. conceiving and application of a retrieval strategy, shifting between subcategories, vocabulary access, semantic processing), which may be classified as either executive or semantic in nature (Gaspari et al., 2006). Qualitative analysis of

verbal fluency performance from both brain damaged patients and normal subjects has revealed a consistent pattern of task execution based on the generation of phonological or semantic subcategories, i.e. clusters (Chertkow & Bub, 1990). Cluster size and number of switches between clusters provide specific information about two distinct cognitive underpinnings of the task, i.e. the integrity of the lexical-semantic store and the ability to shift from an exhausted cluster to a new one (Gaspari et al., 2006). Gaspari et al. (2006) state that a decrease in the number of switches has consistently been shown to be associated with frontal or subcortical pathology.

Gaspari et al. (2006) hypothesized that there would be a post-surgical decrease in both total verbal production and in switching rate. The sample consisted of twenty-six patients suffering from idiopathic PD. Pre and post-surgery neurological evaluations were preformed using a version of the FAS test along with some other tests of executive function and motor ability. Results showed that comparisons between pre and post-surgical general neuropsychological evaluations showed worsening at both raw global fluency scores (Gaspari et al., 2006). Additionally, number of total words and switches were both significantly reduced after surgery. Therefore, Gaspari et al. (2006) confirmed previous literature findings showing a significant, long-lasting decline in verbal fluency after surgery for DBS in Parkinson's disease.

Only a handful of studies have systematically examined the role of stimulation and/or medications on neuropsychological performance. Morrison et al. (2004) examined the neuropsychological function of 17 PD patients following bilateral STN stimulator implantation. However, their objective was to compare patients post-operatively both *on* and *off* stimulation. Eleven matched PD controls were administered the same repeatable

neuropsychological test battery twice. The STN DBS procedure as a whole resulted in a mild decline in delayed verbal recall and language functions. One patient in particular demonstrated significant cognitive decline on all measures following surgery. However, these conclusions must be viewed as preliminary because the sample size was somewhat small and may have limited the power of the data analyses. Additionally, the issue of differential practice effects as a result of the DBS surgical group having been tested one more time than the control group and shorter inter-test interval in the post-operative conditions for the surgical group, as compared to that for the control group, may have also influenced the results of this study (Morrison et al., 2004).

In addition to the study conducted by Morrison et al., Voon et al. (2006) reported that systematic assessment *on* and *off* STN stimulation demonstrated either no significant cognitive effects or improvements in processing speed, random number generation, and problem solving with stimulation. Conversely, performances on working memory and response inhibition measures under high cognitive demand conditions were shown to decline with STN stimulation. Also, systematic assessments *on* and *off* medications during STN stimulation were not associated with cognitive changes on a variety of neuropsychological measures, including tests sensitive to frontostriatal dysfunction (Voon et al., 2006). Jahanshahi et al. (2000) also observed the impact of DBS on executive function in Parkinson's disease by controlling for stimulation *on*, *off*, and then *on* again. Results showed that participants showed mild improvements on tasks which were executive in nature.

Perozzo et al. (2001) also examined twenty PD patients before and after bilateral STN DBS surgery. Four conditions were assessed: medication on and medication off

during the preoperative period, and medication on/stimulation *on* and medication off/stimulation *on* during the post-operative period. The most relevant finding of this study concerns the absence of an overall cognitive decline after the surgical procedure. Also, there was no significant worsening in literal and category verbal fluency after surgery. However, it is possible that this difference in comparison to previous studies depends on the different angles of the electrode placement. Finally, disease severity did not produce any significant differences between the conditions (Perozzo et al., 2001).

In regards to Parkinson's disease and postoperative neuropsychological function, numerous methodological issues may be to blame for contradictory and conflicting results. The greatest methodological issues in the current literature are the small sample sizes and the general absence of control groups (Voon et al., 2006). Modest sample sizes limit the power of a study to detect the effects of DBS on cognition and behavior and also limit the reliability and generalizability of findings. For example, Voon et al. (2006) reviewed 30 neuropsychological studies of extremely small sample sizes of STN DBS and found that only 2 of 30 studies had adequate power to detect large effect sizes and none had the power to detect small or medium effects.

Additionally, the absence of control groups makes it difficult to determine whether a change occurring after DBS might also have occurred in a non-operated control group, thus reflecting non-DBS factors (e.g., disease progression, medication, test-retest practice effects, or some other extraneous variable) (Voon et al., 2006). Fields and Troster (2000) state that what remains an unresolved issue is what type of control group should be included in DBS studies. Given the now widespread availability of DBS, it is increasingly difficult to recruit the most relevant control for DBS: a surgical wait list

control group (Voon et al., 2006). However, even the use of a wait list control group is not without potential interpretative pitfalls. Since medication dosage is often greatly reduced after STN DBS, neurobehavioral changes, when they occur in the surgical but not the control group, cannot confidently be interpreted as effects of DBS. Therefore, existing empirical evidence appears to show biases through which conclusions can only confidently be drawn by using within subjects designs.

The last methodological issue is that of test-retest effects. For example, scores may improve simply due to experience with the test rather than improvement of the function being evaluated. Strategies to minimize practice effects include employing multiple versions of the test that differ in specific content but not in difficulty, maximizing the test-retest interval, or utilizing statistical techniques. Notably, a familiarity or "test wise" effect may occur even when alternate forms are used (Voon et al., 2006). However, it is important to note that if practice effects do occur in PD patients, then a lack of gain may represent a decline. Furthermore, if practice effects occur, then small declines in scores may actually represent a sizable deterioration in function, and a score gain would have to exceed the practice effect before it is considered an improvement (Voon et al., 2006). Therefore, researchers should always address and be aware of the methodological issues when comparing pre and post-operative neuropsychological function of patients with idiopathic Parkinson's disease.

Stimulation Parameters and Cognitive Function

Very few studies have examined the relationship between stimulation parameters and cognition, behavior, or subjective psychotropic effects. No studies have systematically varied stimulation parameters and assessed cognition in a within-subject

design (Voon et al., 2006). However, one problem that has been noted is a developed tolerance to certain stimulation parameters (Benabid et al., 1998). If tolerance to stimulation does occur, then higher stimulation intensities may be necessary to sustain adequate motor benefit. The degree to which stimulation intensities can be increased before cognitive side effects become clinically remarkable is unknown (Fields & Troster, 2000).

A recent study conducted by Tornqvist, Schalen, and Rehncrona (2005) evaluated the effects of different electrical parameter settings on the intelligibility of speech in patients with Parkinson's disease bilaterally treated with deep brain stimulation in the subthalamic nucleus. Amplitude and frequency were varied as ten PD patients read a standard running text and five nonsense sentences per setting. Results showed that with the patients' normally used settings, there were no significant group differences between DBS *off* and *on*, but in four patients the intelligibility of speech deteriorated with DBS *on*. However, the higher frequencies or increased amplitude caused significant impairments of intelligibility. Therefore, careful individual programming of the DBS treatment is needed to achieve a clinically optimal balance between satisfactory motor function and intelligibility of speech (Tornqvist et al., 2005).

Research Questions

It has been established that deep brain stimulation is now widely accepted as one of the favored treatments with patients whom have Parkinson's disease. While the relationship between DBS of the STN and post-surgical neuropsychological function in PD patients has been established with varying results, no study to date has investigated the relationship between DBS settings and neuropsychological function. This study

evaluated the extent to which DBS settings (i.e., amplitude, frequency, and pulse width) are associated with post-operative performances on the RBANS. This study was designed to answer these research questions:

Question 1: What are the neuropsychological effects on Parkinson's patients from baseline to post DBS surgery?

Question 2: What is the nature of the relationship between amplitude, frequency, and pulse width and consequent performance on measures of memory, language, attention, and visuospatial/constructional ability?

Questions 3: Can the stimulation parameters predict subsequent performance on neuropsychological tests?

CHAPTER III

METHOD

Research Subjects

20 PD participants, both male (N=10) and female (N= 10), underwent bilateral deep brain stimulation of the STN. The mean age of the DBS Parkinson's sample was 66.7 (SD= 9.38) with 13.4 years of education. Disease duration was 9.4 years (SD= 5.1). All participants were recruited through the Oklahoma University Medical Center Departments of Neurology and Neurosurgery. All subjects were diagnosed with PD by a board certified neurologist who also stated the participants' disease severity using the Hoehn and Yahr scale. All Hoehn and Yahr ratings were performed while the participants were taking medication. Medications used to treat Parkinson's disease were converted to dopamine equivalents. All DBS participants had significant PD related motor symptoms which interfered with activities of daily living and were no longer adequately relieved by medications. No participants had a previous history of another suspected or known central nervous system disease or injury besides PD or a history of major psychiatric disturbance or dementia.

Procedure

The records of 20 idiopathic PD patients admitted to the Oklahoma University

Medical Center Departments of Neurology and Neurosurgery were evaluated. DBS participants were evaluated approximately 1 month before surgery and 5-6 months after surgery. Demographic data were collected for each subject and included age, education, gender, and test-retest interval. All participants completed extensive neuropsychological evaluations that included: the Hoehn and Yahr rating scale, the Unified Parkinson Disease Rating Scale (UPDRS), the Mini Mental Status Exam (MMSE), the State Trait Anxiety Inventory (STAI), California Card Sorting Task, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). However, for the purposes of this study, only the RBANS was used in the primary analysis.

Surgical Procedures

Cranial MRI and stereotactic procedures were used to target the STN nucleus on each side of the brain. A four pole Medtronic DBS electrode was positioned at the target site where stimulation resulted in good motor symptom control. Next, the generator was placed in the chest and connected to the electrodes. Stimulation parameters were programmed by a trained health care professional after the patient recovered from surgery.

Measures

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS (Randolph, 1998) is a brief, individually administered test measuring attention, language, visuospatial/constructional abilities, and immediate and delayed memory. The test is comprised of 12 subtests, which yield five index scores (Attention, Language, Visuospatial/Constructional, Immediate Memory, and Delayed Memory) and a Total Scale score. Normative scores were developed using a stratified, nationally

representative sample of 540 healthy, primarily Caucasian adults aged 20-89 years. The normative data of Randolph (1998) were employed for the current study. All subtests were administered and scored as defined in the manual. In the present study, Form A of the RBANS was utilized at each assessment.

Hoehn and Yahr Scale

The Hoehn and Yahr scale (Hoehn, & Yahr, 1967) is a commonly used system for describing how the symptoms of Parkinson's disease progress. Because of the variability with which the syndrome evolves, it is essential to consider the extent of disability at the time of treatment and the rate of progression before and after treatment. Each case is rated on an arbitrary scale (I-V) based on the level of clinical disability. Stage I consists of unilateral involvement only, usually with minimal or no functional impairment. Stage II consists of bilateral or midline involvement, without impairment of balance. Stage III is the first sign of impaired reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he or she is pushed from standing equilibrium with the feet together and eyes closed. Overall, their disability is mild to moderate. Stage IV means the patient has fully developed the severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated. In the final stage, Stage V, the patient is confined to a bed or wheelchair unless aided. This method of staging is practical and allows for reproducible assessments by independent examiners of the general functional level of the patient (Hoehn and Yahr, 1967).

State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (Spielberger, 1983) has been used extensively

both in clinical practice and in research. It comprises separate self-report scales for measuring state and trait anxiety. The S-Anxiety scale (STAI Form Y-1) consists of twenty statements that evaluate how respondents feel “right now, at this moment”. The T-Anxiety scale (STAI Form Y-2) consists of twenty statements that assess how people generally feel. The essential qualities evaluated by the STAI-S Anxiety scale are feelings of apprehension, tension, nervousness, and worry. In addition to assessing how people feel right now, the scale is also used to see how people anticipate they will feel in future situations. The STAI-T Anxiety scale has been widely used in assessing clinical anxiety in medical, surgical, psychosomatic, and psychiatric patients (Spielberger, 1983). It is also used for screening high school, college students, and military recruits for anxiety problems, and for evaluating the immediate and long-term outcome of psychotherapy and counseling. With both scales, higher scores yield increased levels of anxiety and worry.

Unified Parkinson Disease Rating Scale (UPDRS)

The Unified Parkinson Disease Rating Scale is a rating tool to follow the longitudinal course of Parkinson’s disease. It is made up of the following scales: Mentation, behavior, and mood scale, activities of daily living scale, and motor sections. All ratings are evaluated by interview by a trained healthcare professional. Some sections require multiple grades assigned to each extremity. A total of 199 points are possible, with 199 representing total disability and 0 being equal to no disability. Clinicians and researchers alike use the UPDRS and motor section in particular to follow the progression of PD. The motor section consists of 14 questions based on the areas of posture, speech, gait, tremor, rigidity, and bradykinesia, among others. These areas are rated on a 4-point likert scale, with 0 being normal and 4 meaning that the patient can

barely perform the task. For the purposes of this paper, only the motor section of this scale was used.

Analyses

The DBS group's pre and post-surgical z scores were compared for all RBANS index and individual subtests using paired samples t-tests. No significant differences between pre and post surgery were found. Additionally, the group's pre and post-surgical motor function was compared using the motor section of the UPDRS. There was a significant difference between pre and post-surgery, thereby validating improvement in motor function following DBS surgery. In the primary analysis, a Pearson product moment correlation was performed to determine the relationship between RBANS index and subtest scores with stimulation parameters (amplitude, frequency, and pulse width). Additionally, a partial correlation was conducted in order to examine the relationship between the RBANS and stimulation parameters while controlling for motor impairment, dopamine use, and level of anxiety. In order to determine the best predictors for the RBANS index and subtest scores, stepwise and hierarchal multiple regression analyses were performed.

CHAPTER IV

RESULTS

Demographics

A total of 20 participants were administered the RBANS along with other neuropsychological measures. The participant's average age was 66.65 and the average education level was 13.35. Disease duration in years was an average of 9.40 (see Table I).

Table I.

Descriptive statistics for the sample population (N=20)

	Mean	Std. Deviation	Range
Age	66.65	9.38	48-79
Education	13.35	2.28	9-18
Disease Duration (years)	9.40	5.11	5-18

Research Questions

Question 1: What are the neuropsychological effects on Parkinson's patients from baseline to 6 months post DBS surgery?

A Paired samples T-Test was conducted to determine whether there was a significant difference between the pre and post surgical neuropsychological function of Parkinson's patients. The goal was to determine whether this group differed with regard

to the 5 index scores and 12 individual subtest scores on the RBANS. The means, standard deviations, and ranges of the DBS group and their scores from baseline to 6 months post surgery can be found in Tables 1 and 2 in the Appendix. Z scores indicate that taken overall, neuropsychological function improved, but not significantly, from baseline to post surgery. Table II displays the mean differences in scores between baseline and follow-up using the RBANS index scores. Although no significant differences were found, the visuospatial/constructional index approached significance at .06 ($p < .05$). A Paired samples T-Test was also conducted to confirm the common findings of increases in motor function post DBS surgery. Results using the UPDRS motor section were significant and can be found in Table II.

Table II.

Differences in z-scores between baseline and follow-up on the RBANS and UPDRS (N= 20)

	Paired Differences					
	Mean	SD	Std. Error Mean	t	df	Sig. (2-tailed)
Total Score	-.19	.93	.21	-.90	19	.38
Attention	-.06	1.13	.25	-.23	19	.81
Language	-.10	1.08	.24	-.42	19	.67
Visuospatial/Constructional	-.46	1.01	.23	-2.03	19	.06
Immediate Memory	-.44	1.54	.34	-1.29	19	.21
Delayed Memory	-.46	1.56	.35	-.92	19	.37
UPDRS- Motor section	8.85	8.34	2.31	3.83	19	.002*

Significant at p< .05.

Question 2: What is the nature of the relationship between amplitude, frequency, and pulse width and consequent performance on measures of memory, language,

attention, and visuospatial/constructional ability?

Pearson product moment correlations were computed to investigate the relationship between stimulation parameters and performance on measures of attention, language, memory, and visuospatial/constructional ability (see Table III). Descriptive statistics for the stimulation parameters can be found in Table 3 in the Appendix. Results indicated that amplitude was positively related to the visuospatial/constructional index (r = .545, p< .05) and pulse width was positively related to the immediate memory index (r = .448, p< .05). Therefore, as amplitude and pulse width increase, there is an increase in performance on memory and visuospatial/constructional tasks. Results also indicated that amplitude and the line orientation subtest were correlated (r = .449, p< .05) along with pulse width and the delayed figure recall (r = .455, p< .05). Although other relationships were found to be moderately correlated, they were not found to be significant.

Table III.

Correlation Coefficients between Follow- up RBANS Index and Subtest Scores and Stimulation Parameters

RBANS Index and Subtest Scores	Amplitude	Frequency	Pulse Width
Attention Index	.003	-.104	.112
Digit Span	-.242	-.166	.010
Coding	.257	-.091	.107
Language Index	-.231	.127	.078
Picture Naming	.352	.174	.025
Semantic Fluency	-.190	.057	.109
Immediate Memory Index	.386	.213	.448*

RBANS Index and Subtest Scores	Amplitude	Frequency	Pulse Width
List Learning	.182	.225	.337
Story Memory	.426	.202	.363
Delayed Memory Index	.320	.202	.347
Delayed List Recall	.271	.125	.368
Delayed List Recog.	.150	.089	.242
Delayed Story Recall	.120	.261	.096
Delayed Figure Recall	.400	.278	.455*
Visuospatial/Construction Index	.545*	.283	.322
Figure Copy	.428	.345	.433
Line Orientation	.449*	.172	.048

**Correlation is significant (p< .05)*

Incidental Findings

In order to further validate the relationship between the stimulation parameters and neuropsychological function post-DBS surgery, a partial correlation was performed in order to assess whether disease severity, motor symptoms, and symptoms of anxiety were contributing factors to the changes observed at 6 months post surgery. In order to assess the role of disease severity and the motor components of Parkinson's disease, the Hoehn and Yahr scale and dopamine medication daily dosage were used as co-variates for the previous analysis For the anxiety component, the State-Trait Anxiety Inventory was also co-varied. Descriptive statistics for the dopamine medication daily dosage and State-Trait Anxiety Inventory can be found in Table IV.

Table IV.

Descriptive Statistics for Dopamine Dosage and Anxiety Symptoms

	Mean	Std. Deviation	Range
Baseline dopamine equivalent med. dose	716.27	334.85	25.46-1368.00
Follow up dopamine equivalent med. dose	690.52	362.47	0.00-1368.00
Baseline STAI-S anxiety score	1.16	1.45	-1.41-3.78
Follow up STAI-S anxiety score	1.17	1.26	-1.13-3.90
Baseline STAI-T anxiety score	1.33	1.53	-1.52-3.63
Follow up STAI-T anxiety score	1.04	1.59	-1.39-4.91

In using the Hoehn and Yahr Scale as a covariate for the above analysis, no significant relationships were found because not all participants were given this measure at follow-up. Therefore, disease severity was excluded from all further analyses. However, when controlling for dopamine daily dosage, significant correlations were found between the stimulation parameters and RBANS scores (see Table V). Results indicated that pulse width was positively related to the immediate memory index (r = .483, $p < .05$) and amplitude was correlated with the visuospatial/constructional index (r = .537, $p < .05$). When looking at individual subtest scores of the RBANS while controlling for dopamine daily dosage, similar results were found. There was a positive correlation between pulse width and both the figure copy subtest (r = .492, $p < .05$) and the delayed

figure recall (r = .518, p< .05). These relationships were similar to the ones found above, which indicates that dopamine does not play a role post surgically in enhancing the neuropsychological functioning of Parkinson's patients. Moderate correlations were found between amplitude and story recall, figure copy, and line orientation, as well as with pulse width and list delayed recall.

Table V.

Correlation Coefficients between RBANS Scores and Stimulation Parameters when Controlling for Dopamine Daily Dosage

RBANS Index and Subtest Scores	Amplitude	Frequency	Pulse Width
Attention Index	-.032	-.070	.187
Digit Span	-.271	-.145	.053
Coding	.235	-.047	.207
Language Index	-.209	.094	.017
Picture Naming	.339	.205	.069
Semantic Fluency	-.173	.035	.074
Immediate Memory Index	.379	.230	.483*
List Learning	.166	.251	.385
Story Memory	.419	.218	.395
Delayed Memory Index	.313	.215	.374
Delayed List Recall	.263	.140	.400
Delayed List Recognition	.165	.076	.225
Delayed Story Recall	.098	.300	.150
Delayed Figure Recall	.388	.311	.518*

RBANS Index and Subtest Scores	Amplitude	Frequency	Pulse Width
Visuospatial/Constructional Index	.537*	.325	.390
Figure Copy	.417	.380	.492*
Line Orientation	.439	.215	.110

**Correlation is significant (p< .05)*

When anxiety was co-varied, significant correlations were also found (see Table VI). Results showed that pulse width was significantly related to both the immediate memory index (r = .552, p<.05) and the delayed memory index (r = .567, p<.05). Results also showed a significant relationship between amplitude and the immediate memory index (r = .489, p< .05) and the visuospatial/construction index (r = .567, p< .05). When looking at the individual subtests, significant correlations were found between pulse width and story recall (r = .549, p< .05), figure copy (r = .514, p< .05), list delayed recall (r = .494, p< .05), and delayed figure recall (r = .553, p< .05). Correlations were also found between amplitude and story recall (r = .489, p< .05). Moderate correlations were found between amplitude and pulse width with other measures of the RBANS, but lacked significance. Therefore, it appears as though amplitude and pulse width also have a direct relationship with memory and visuospatial/constructional ability when medication dosage and anxiety are controlled.

Table VI.

Correlation Coefficients between RBANS Scores and Stimulation Parameters when Controlling for Anxiety

RBANS Index and Subtest Scores	Amplitude	Frequency	Pulse Width
Attention Index	.003	.201	.268

RBANS Index and Subtest Scores	Amplitude	Frequency	Pulse Width
Digit Span	-.161	-.327	.072
Coding	.164	-.088	.333
Language Index	-.192	.100	.056
Picture Naming	.380	.151	.230
Semantic Fluency	-.171	.046	.090
Immediate Memory Index	.489*	.148	.552*
List Learning	.289	.156	.393
Story Memory	.489*	.159	.549*
Delayed Memory Index	.399	.140	.470*
Delayed List Recall	.316	.075	.494*
Delayed List Recognition	.224	.038	.268
Delayed Story Recall	.198	.181	.251
Delayed Figure Recall	.382	.312	.553*
Visuospatial/Constructional Index	.567*	.294	.463
Figure Copy	.414	.386	.514*
Line Orientation	.437	.192	.179

**Correlation is significant (p< .05)*

Question 3: Can the stimulation parameters predict subsequent performance on neuropsychological tests?

A stepwise multiple regression analysis was performed in order to assess whether amplitude, frequency, pulse width, the STAI, and dopamine daily dosage best predicted performance on tasks on attention, language, memory, and visuospatial/constructional

ability (see Table 7). The State-Trait Anxiety Inventory predicted performance on the picture naming subtest (R^2= .24) and together with pulse width on the coding subtest of the RBANS (R^2= .38). The RBANS immediate memory index score was best predicted by pulse width, which accounted for 20% of the variance (R^2= .20), along with the State-Trait Anxiety questionnaire, which predicted 16% of the total variance (R^2= .16). Story memory was significantly predicted by pulse width and the State-Trait Anxiety Inventory. The delayed list recall was predicted by both pulse width (R^2= .14) and the STAI (R^2= .15), while the RBANS delayed story recall score was best predicted by the State-Trait Anxiety Inventory alone (R^2= .20). The delayed figure recall subtest was best predicted by pulse width (R^2= .21) along with the State-Trait Anxiety Inventory (R^2= .13). Finally, amplitude and the STAI were found to significantly predict RBANS visuospatial/constructional index scores, accounting for 39% of the total variance.

Table VII.

Stepwise Regression Analysis of Stimulation Parameters, the STAI, and Dopamine Equivalents with Scores on the RBANS

	Predictor Standardized Beta Weights						
	Amplitude	Freq.	Pulse Width	STAI	Dop. Eq.	F	R^2
RBANS Variables							
Attention Index				-.389		3.22	.15
Digit Span				-.317		2.01	.10
Coding			.298	-.634		5.15*	.38
Language Index					-.307	1.87	.09
Picture Naming				-.493		5.80*	.24

	Predictor Standardized Beta Weights						
	Amplitude	Freq.	Pulse Width	STAI	Dop. Eq.	F	R^2
RBANS Variables							
Semantic Fluency							
Imm. Memory Index			.559	-.408		4.68*	.36
List Learning			.419	-.303		2.10	.20
Story Memory	.278		.338	-.488		3.90*	.42
Delayed Memory Index			.463	-.426		3.45	.29
Del. List Recall			.480	-.410		3.49*	.29
Del. List Recog.							
Del. Story Recall				-.443		4.39*	.20
Del. Figure Recall			.568	-.376		4.30*	.34
VS/Construction Index	.571			-.299		5.33*	.39
Figure Copy			.533	-.332		3.43	.29
Line Orientation	.476			-.296		3.45	.29

**Significant at p< .05*

A hierarchal multiple regression was conducted in order to ensure that other variables were not confounding the relationship between dopamine daily dosage and the STAI with RBANS index and subtest scores. However, no significant relationships were found for dopamine, thus supporting the previous analyses in that dopamine daily dosage is not a factor in measuring the neuropsychological function of Parkinson's patients 6

months post DBS surgery. The only significant relationships found using the STAI were picture naming and delayed story recall, which was also found in the above analyses.

CHAPTER V

DISCUSSION

The goal of this study was to answer the following research questions: what are the neuropsychological effects on Parkinson's patients from baseline to post DBS surgery; what is the nature of the relationship between amplitude, frequency, and pulse width and consequent performance on measures of memory, language, attention, and visuospatial/constructional ability; and can the stimulation parameters predict subsequent performance on neuropsychological tests. Overall, neuropsychological performance improved slightly from pre to post DBS implantation, though results were not significant. Memory, both immediate and delayed, and visuospatial/constructional ability were the two areas where patients showed the most improvement, as compared to language and attention in which patients showed a mild to moderate decline or no change at all. However, it is important to note that when comparing the indices from pre to 6 months post surgery, no significant differences were found.

These results indicate that DBS surgery tends to be a relatively benign procedure from a neuropsychological standpoint. That is, this particular sample showed some improvements in the areas of memory and visuospatial/constructional ability, while other areas, such as language and attention, showed mild to moderate declines. Thus, the

results appear to be mixed. That is, some of the data support the literature on the pre and post surgical neuropsychological function of PD patients. Data comparing the current study with other research in the field can be found in Table 4 in the appendix.

Currently, the data suggests that attention, both divided and sustained, tends to be relatively impaired in PD patients. In the sample used in this study, PD patients showed a decline in digit span, which is an attention task that is also used to assess concentration, sequencing, and auditory short-term memory. Furthermore, PD patients showed a marked decline in a coding task, which measures not only visual motor coordination and mental speed, but also requires executive control of attention and sustained effort in order to complete the task. These results are consistent with current research (Saint-Cyr et al.; Gironell et al.). Therefore, it appears as though DBS implantation has a relatively small effect on improving the attention of PD patients.

Language is another area of impairment among PD patients that is marked by a progressive decrease in total word output. This sample of PD patients showed a rather large decline in verbal fluency post surgery which is consistent with current findings (Morrison et al.; Saint-Cyr et al.; Gironell et al.; Gaspari et al.; Perozzo et al.). The explanation for language decline consistently points to retrieval failures. That is, PD patients, among others with subcortical and cortical neurodegenerative diseases, tend to have impaired lexical retrieval which is largely independent of memory stores. Taken together, these data suggest that deep brain stimulator surgery may actually be a confounding variable to the reported decrease in verbal fluency following surgery.

Although memory and visuospatial/constructional ability are typically considered to be areas showing a pronounced cognitive decline in PD patients (Morrison et al.;

Saint-Cyr et al.; Gironell et al.; Voon et al.), this sample found opposite results. On visuospatial/constructional tasks of an executive nature, PD patients showed a rather marked improvement in the drawing a complex figure and a problem solving task of frontal lobe functioning. Additionally, patients also showed improvements in both immediate and delayed recall. Recent studies have shown that PD patients tend to show a decline in recall and an improvement in recognition. However, with this sample, the opposite was true. That is, when patients were asked to recall a list of words after a short delay, they slightly improved. Conversely, when patients were asked to recognize words out of a longer word list, their performance declined.

When examining the relationship between the stimulation parameters and neuropsychological function, significant correlations were found between pulse width and the immediate memory index score and figure recall. Significant correlations were also found between amplitude and the visuospatial/constructional index score and line orientation. Due to the influence of anxiety and dopamine medication dosage on PD patients, partial correlations were conducted which showed that relationships were still significant between amplitude and pulse width with measures of memory, both immediate and delayed, and visuospatial/constructional ability. This implies that increases in the stimulation parameters of amplitude and pulse width may be the cause of enhanced neuropsychological performance post DBS surgery.

To assess whether or not the stimulation parameters, along with the State-Trait Anxiety Inventory and dopamine daily dosage, would be able to predict subsequent neuropsychological performance and account for the variance in the test scores, a linear stepwise multiple regression was conducted. Results showed that the STAI, pulse width,

and amplitude were able to predict performance on measures of attention, language, immediate memory, delayed memory, and visuospatial/constructional ability. It is important to note that amplitude, pulse width, and the STAI almost reached significance with other measures of the RBANS; specifically with the attention index score, delayed memory index score, figure copy subtest score, and line orientation subtest score. A probable explanation for why they did not reach significance may be due to the small sample size. As with other studies, the current study is underpowered as it only consisted of twenty participants. Underpowered studies increase the likelihood of producing a false negative, which may pose an explanation as to why no significant differences were found amongst other subtests or indices of the RBANS. Therefore, because the effect size was so small, the probability of finding statistically significant differences was also small.

Clinical Implications

In putting these results in a clinical context, it appears that the DBS settings used in this study had a mild effect on neuropsychological function. It is important to note that patients reported increased motor function post-surgery which lead to an increased quality of life. Taken together, the non-significant findings should not necessary be viewed as negative because there were no substantial decreases in function. On the other hand, the significant findings pose considerable clinical benefits. The fact that aspects of memory, both immediate and delayed, and visuospatial/constructional ability increased slightly and were correlated with the stimulation parameters of amplitude and pulse width is a new finding in the literature. Therefore, the stimulator settings used in the current study appear to have both neuropsychological and motor benefits. Overall, the study

confirms that DBS surgery does not carry large risks for dramatic decreases in neuropsychological functioning post surgery.

An additional finding in this study that carries large clinical impacts was the presence of anxiety. High levels of anxiety were reported from participants both before and after surgery. Although levels of anxiety decreased from pre to post surgery, anxiety was still a significant factor in predicting neuropsychological outcome. Therefore, it would be fair to conclude that decreases in anxiety post-surgery may have a significant effect on attention, language, memory, and visuospatial/constructional ability in PD patients. In the sense of applying this information clinically, perhaps health care professionals should turn more to psychological treatments of anxiety, whether it is talk therapy or medical therapy, following DBS surgery in order to improve the cognitive function in PD patients. While it has been proposed that depression and anxiety are highly correlated, future research may focus on aspects of mood in treating PD patients post-surgery.

Due to the amount of intraindividual variability found within the previous literature and the current study, it is important to note that some patients may exhibit more pronounced impairments. Additionally, different stimulation settings may affect patients differently. It has been noted that increases in amplitude and frequency may have a more positive effect on the neuropsychological function of the patient, but may cause an increase in the motor symptoms of the disease. Therefore, there appears to be a trade-off to what patients would more likely value. That is, would they rather have increased motor function or increased neuropsychological function. As was demonstrated by this study, frequency, or the rate of stimulation, had no effect on the neuropsychological

function of PD patients. Due to that variability, these results should be taken with caution and should be used only as a guideline on which to base future studies.

CHAPTER VI

CONCLUSION

Overall, it appears that the DBS settings of amplitude and pulse width are positively correlated with aspects of memory and visuospatial/constructional ability in PD patients as was measured using the RBANS. Additionally, pulse width, amplitude, and the STAI were found to be significant predictors accounting for a rather large amount of the variance for the memory and visuospatial/constructional tasks. While this study has some limitations, a follow-up study might investigate the performance of a larger group on a similar, if not the same task, to assess neuropsychological function. Also, one may want to use similar but equivalent tasks in order to eliminate test-retest effects. Additional studies might compare groups of PD patients whom have all undergone DBS surgery to evaluate the differences in the stimulator settings and compare those to scores on tasks assessing memory, attention, language, and visuospatial/constructional ability. From there, one may be able to better differentiate which settings lead to the most improvement in neuropsychological function post-surgery.

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APPENDIX

Table 1

Descriptive Statistics for RBANS Index Z-Scores Pre to Post Surgery (N=20)

	Pre-Surgery			Post-Surgery		
RBANS Index Scores	Mean	Std. Deviation	Range	Mean	Std. Deviation	Range
Total Score	-1.23	.94	(-2.80)-(.20)	-1.05	1.14	(-3.00)-(1.27)
Attention	-1.38	1.23	(-5.20)-(.20)	-1.32	1.12	(-3.13)-(.40)
Language	-.76	1.25	(-5.27)-(.53)	-.66	.41	(-1.33)-(.33)
Visuospatial/ Constructional	-1.02	1.57	(-5.33)-(1.40)	-.56	1.28	(-3.13)-(2.07)
Immediate Memory	-1.21	1.55	(-5.07)-(.93)	-.77	1.19	(-2.87)-(1.13)
Delayed Memory	-1.12	1.46	(-5.27)-(.67)	-.80	1.29	(-3.20)-(.87)

Table 2

Descriptive Statistics for RBANS Subtest Z-Scores Pre to Post Surgery (N=20)

	Pre Surgery			Post Surgery		
RBANS Subtest scores	Mean	Std. Deviation	Range	Mean	Std. Deviation	Range
List learning	-1.05	1.23	(-2.67)-(.88)	-.78	1.18	(-3.11)-(1.28)
Story Memory	-1.25	1.39	(-4.28)-(1.00)	-.77	1.29	(-3.44)-(1.28)
Figure Copy	-.71	1.65	(-3.78)-(1.29)	-.45	1.43	(-3.78)-(1.29)
Line Orientation	-1.02	1.47	(-3.36)-(.93)	-.71	1.63	(-4.00)-(1.29)
Picture Naming	.15	.83	(-2.29)-(.67)	-.34	.86	(-1.40)-(.90)
Semantic Fluency	-.77	.95	(-2.61)-(.81)	-1.11	.75	(-2.39)-(.80)
Digit Span	-.23	.88	(-2.00)-(1.09)	-.39	.87	(-2.16)-(.86)
Coding	-1.91	1.02	(-3.68)-(-.03)	-2.01	1.45	(-4.70)-(.08)
List Delayed Recall	-.85	1.38	(-3.32)-(1.24)	-.69	1.30	(-2.73)-(2.04)
List Recognition	-.62	1.58	(-6)-(1)	-.92	1.61	(-4.50)-(.67)
Story Delayed Recall	-1.40	1.60	(-4.94)-(.91)	-.64	1.25	(-2.73)-(1.17)
Delayed figure recall	-1.19	.78	(-2.74)-(.45)	-.60	1.35	(-3.40)-(1.31)

Table 3

Descriptive Statistics for the Stimulation Parameters

	Mean	Std. Deviation	Range
Frequency (Hz)	149.25	19.75	130.00-185.00
Amplitude (mV)	1.72	.63	0.80-3.70
Pulse Width (μs)	82.50	25.52	60.00-150.00

Table 4

Comparison of Studies of Neuropsychological Function Following DBS Implantation

Cognitive Function	Increase, Decrease, or No Change		
	+	-	0
Memory		1 2 5	3 7*
Language		1 2 3 4 6 7*	
Attention		2 7*	3
Visuospatial/Construction			3 7*

1= Morrison et al.
2= Saint-Cyr et al.
3= Gironell et al.
4= Gaspari et al.
5= Voon et al.
6= Perozzo et al.
*7= Current Study