TOWER OF CALIFORNIA PERFORMANCE EARLY IN PARKINSON'S DISEASE

APPROVED BY SUPERVISORY COMMITTEE

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DEDICATION

All glory goes to GOD and all my love and thanks to my family, past, present, and future.
This work is especially dedicated to my late maternal grandmother, Maria Socorro Arce Mendez.
And to all those running to stand still.

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ABSTRACT

Cognitive impairment associated with Parkinson's disease (PD) is widely described in the literature. Executive dysfunction has been reported even when the patients are not experiencing dementia. A significant (24% - 50+%) number of PD patients display cognitive impairment from the onset of the disease and progressively worsen. However, executive dysfunction in newly diagnosed patients often escapes clinical detection. This paper describes a study designed to test both early and late PD patients (0-5 years disease duration and 5-10 years disease duration, respectively) vs. controls on a novel tower task, the Tower of California (TOC, Delis, Kaplan, & Kramer, 2001). Use of the TOC with PD patients has not been published. The TOC is designed to be more difficult and may be more sensitive to subtle executive impairment, specifically in the areas of planning and spatial working memory. It is predicted that the early PD group will perform worse than the control group but better than the late PD group in the number of successful towers (ST) built. The early PD group is also expected to have a longer time to first move on ST built even when corrected for bradykinesia, but not as long as the late PD group, which is anticipated to be the slowest. Implications of the possible outcomes of this study are then discussed.

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CHAPTER ONE
Introduction

Parkinson's disease (PD) affects about 3% of Americans over 65 years old and more than half of the population over the age of 85 (Klockgether, 2004). PD is an idiopathic, progressive neurological disorder. As PD is essentially a disease of older people, prolongation of its course with various drug treatments and improving patient care has increased the prevalence of this disease during recent decades and is expected to more than double in the coming thirty to forty years (Yanagisawa, 2006). The cardinal symptoms of PD are rigidity, tremor and bradykinesia. Although the disease is prominently known as one of the motor system, increasing evidence points to accompanying cognitive impairment (Aarsland, Zaccai, & Brayne, 2005; Bassett, 2005; Dubois, Boller, Pillon, & Agid, 1991; Lees & Smith, 1983; Taylor, Saint-Cyr & Lang, 1986). Estimates are that between 24% – 50+% of PD patients show evidence of cognitive impairment not including those with dementia (Bassett, 2005; Muslimovic, Post, Speelman, & Schmand, 2005). This extends the common repertoire of physical symptoms to include apathy, bradyphrenia and executive dysfunction.

It is believed that some patients with PD start to experience cognitive dysfunction when the disease commences (Yanagisawa, 2006). Importantly, PD is a heterogeneous disease and there is no particular symptom profile that fits all patients, although cognitive decline is increasingly recognized as a significant consequence for many (Filoteo, Maddox, Salmon, & Song, 2007). Generally, this means that from the onset of the disease, a

considerable number of PD patients experience a decline in cognitive abilities beyond the effects of normal aging. Declining cognitive abilities in PD leaves many patients unable to perform their activities of daily living as well as unable to interact normally in social situations. PD patients who do demonstrate cognitive dysfunction continue to decline cognitively as a natural process of the disease itself. For these patients, longer disease duration has been correlated with greater motor disability, which itself is correlated with greater cognitive impairment (Locascio, Corkin, & Growdon, 2003). Other researchers have found that severity of cognitive impairment increases simultaneously with severity of movement disorder and is responsible for the increased mortality associated with PD (Zakharov & Yakhno, 2005). Cognitive dysfunction in PD continues to be a hot topic in medical science.

One of the principal reasons the topic remains an issue is that the affected cognitive abilities in PD include executive functions, which are frontal lobe type abilities (Emre, 2003). Frontal lobe abilities include planning and working memory, both of which are necessary to successfully navigate today's world. These are believed to be compromised due to the fronto-striatal loops that pass through the basal ganglia and are unable to transport a major neurotransmitter, dopamine, which is depleted as a consequence of the disease.

One executive skill in particular, the manipulation of information held in spatial working memory, has been found to be impaired in many patients with PD (Bublak, Muller, Gron, Reuter, & von Cramon, 2002). Working memory helps us to plan activities and solve everyday problems and is invaluable in an independent person's life. Spatial working memory is the mental manipulation of several pieces of spatial information to organize a

sequence of actions in a flexible way. For example, it is involved in the processes of planning and problem solving in a classic neuropsychological test, the Tower of London (TOL; Shallice, 1982). The TOL was actually first developed to work with frontal lobe patients. Because many individuals with PD tested similarly to frontal lobe patients, it became increasingly popular for research teams to test PD patients on the TOL.

There are many versions of tower tests available, among which the Tower of London is most frequently used. The Tower tests measure the ability to plan, and depend on spatial working memory skills. Subjects are required to build a tower according to a specified stacked arrangement of doughnut-shaped, differently sized pieces on wooden pegs. The solution to the puzzle must be found in the fewest number of moves possible under such constraints as moving only one piece at a time and not placing more pieces onto a peg than can fit. Researchers have shown that on the TOL, the impairment level of PD patients may depend on their disease duration and motor symptom severity, with those patients with greater disease duration and motor symptoms performing worse (Morris, et al., 1988; Owen, et al., 1992; Owen, Sahakian, Summers, Hodges, Polkey, & Robbins, 1995; Owen, Iddon, Hodges, Summers, & Robbins, 1997).

The results of several studies suggest that PD patients of substantial disease duration (more than 10 years, i.e., late PD) display a significant deficit on the accuracy of tower construction in the TOL, while newly diagnosed patients (diagnosed within the last 5 years, or early PD) are seemingly unimpaired (Morris et al., 1988; Owen et al., 1992; 1993a). However, it is possible that the TOL is not a sensitive enough task, especially with respect to early PD patients (Culbertson, Moberg, Duda, Stern, & Weintraub, 2004;

Owen et al., 1995). It would be worthwhile to substantiate these findings by using a newer, more difficult tower task to measure planning and spatial working memory.

One of the newer tower tasks available is the Tower of California (TOC; Delis, Kaplan, & Kramer, 2001). It is a much more complex puzzle as it includes trials that require twenty-six moves to completion vs. only five for the TOL. It could potentially answer important questions. For one, it would attempt to answer whether or not early PD patients are also susceptible to executive dysfunction. This is of utmost importance in order to enable the implementation of appropriate rehabilitation at a stage of the disease when therapy is more likely to be effective. Additionally, there is evidence that subtle frontal lobe deficits may be of prognostic value in identifying PD patients at risk for dementia (Woods & Troster, 2003). Second, predicting the rate of cognitive decline in PD patients with or without dementia can have important implications for disease management and research. This is especially true because cognitive decline in PD correlates with functional declines (Sabbagh et al., 2005). Functional declines associated with PD come at a high cost, both socioeconomically as well as in terms of independence and quality of life to the patient.

The current study proposes to examine whether early PD patients have a deficit specifically in planning and the manipulation of spatial working memory that could be detected by a more complex tower task, the TOC. It would be beneficial to recognize those PD patients with cognitive impairment early in order to pursue appropriate rehabilitative efforts.

CHAPTER TWO
Review of the Literature

Introduction to PD

Parkinson's disease (PD) is a slowly progressive neurologic disorder that affects coordinated movement and balance. It is idiopathic, which means that the cause is unknown. The fact that PD is idiopathic distinguishes the primary disease from parkinsonism, which refers to the same physical symptoms occurring from a known cause. PD is not fatal but it does reduce longevity (Louis, Marder, Cote, Tang, & Mayeux, 1997). The disease progresses more quickly in older than younger people, and may eventually lead to severe incapacity. PD can seriously impair the quality of life in any age group. Additionally, the physical and emotional impact on the family should not be underestimated as the patient becomes increasingly dependent on their support network. The average age of patients at diagnosis is 55 although there are cases of early onset that can occur in the mid-thirties. These cases are believed to have a stronger genetic component than late onset PD. Multiple genetic factors may also be responsible for late-onset PD. In addition to its effects on motor control, PD is now recognized as a broader condition that can include cognitive and behavioral disturbances, sleep disorders, speech difficulties, and other problems (Klockgether, 2004).

The negative effect of overall motor impairment on daily life can be considerable in PD patients. Resting tremor is the primary symptom in 60% of cases. Both tremor and rigidity are observed in over 90% of patients (Yanagisawa, 2006). Disturbed gait and unstable posture are common and serious problems in elderly individuals with PD, since they increase the risk for falling and injury (Hoehn, & Yahr, 1967). Some studies have

suggested that the appearance of these symptoms early in the course of the disease predict a faster decline than having tremor as the predominant symptom. Motor impairment of the muscles in the throat not only impairs swallowing but it also poses a risk for aspiration pneumonia and has been associated with shorter survival times (DeLong, 1990).

In fact there are a number of physical symptoms associated with PD. Constipation is a major problem and occurs both as a result of the disease and a side effect of its treatment. Laxatives, stool softeners, and other medications may be prescribed, which add to the cost of managing PD. Bladder control and urinary incontinence are also complications of PD. Speech problems occur in more than 70% of PD patients, by some estimates (Kloeckgether, 2004). Speech difficulty can be caused by rigidity of the facial muscles, loss of motor control, and impaired breath control. Tone can become monotonous, words may be repeated over and over, or the rate of speech may be abnormally fast, while other PD patients experience hypophonia, when the rate of speech is reduced (Yanagisawa, 2006).

Mood disorders are especially prevalent. Depression can affect up to 25%- 75% of the PD patient population, while anxiety affects up to 30% (A.D.A.M., 2005). The toll of these symptoms goes far beyond the cost of controlling them. Other problems that impair daily life include vision problems, sleep disorders, impaired sexuality, a decreased sense of smell, but perhaps the most costly of all, and especially pertinent here, cognitive dysfunction. Despite the plethora of symptoms, the neuropathology behind PD is relatively uniform as it attacks dopamine production within the brain (Soukrup, & Adams, 1996).

Principally, PD causes the loss of neurons within the substantia nigra pars compacta. The substantia nigra produces dopamine and has extensive projections into the striatum. The net loss of dopamine producing neurons in the substantia nigra causes a reduction in striatal functioning (DeLong, 1990). This dysfunction leads to a disruption of the indirect motor pathway in the basal ganglia and the regulation of movement. Commonly, this causes a disruption of smooth motor coordination that typically defines PD. Additionally, consistent with the pathology behind the physical symptoms, the cognitive deficits associated with PD have been attributed to the loss of the striatal and cortical dopamine necessary to uphold the functional integrity of the frontostriatal circuitry of the brain (Zgaljardic, Borod, Foldi, & Mattis, 2003). Medicinal therapies that replace or augment natural stores of dopamine have been reported to improve some cognitive tasks in PD patients, hereby suggesting that the loss of dopamine may be responsible for cognitive dysfunction. Seven frontostriatal circuits have been identified, at least one of which, the dorsolateral prefrontal circuit (DLFPC), is believed to serve executive functions. Impairment in this circuit disrupts executive functions in PD. This circuit originates in the frontal cortex, with sequential projections into the striatum (caudate, putamen, or ventral striatum), followed by the globus pallidus interna and substantia nigra, and then to designated thalamic nuclei, with final return pathways to the frontal lobes (Lichter, 2001).

The fibrous deposits known as Lewy bodies are characteristic neuropathologic signs (Yanagisawa, 2006) found widely in the PD brain. They are found in the substantia nigra, the place in the brain where dopamine is first released. It is not clear whether Lewy bodies are the major killers of the dopamine producing neurons or whether they are

merely a byproduct of the degenerative process. Lewy bodies are also present in other diseases that cause dementia, such as Lewy body disease and the Lewy Body Variant of Alzheimer's disease, and can occur in people without neurodegenerative diseases. The fact that there is shared pathology between these neurodegenerative diseases points out the subtleties that differentiate these diseases. This is important because the possibility exists that if these diseases are related, a common solution might be found for all. Medications have been developed to control the symptoms of PD yet no medicine has been produced that cures the disease. Anticholinergics were the first drugs prescribed to mask resting tremor. Levodopa, first used in 1967, was the first medication developed to artificially replenish the body's decreasing stores of dopamine in an effort to remedy the dysfunction associated with PD (Bassett, 2005). It remains the gold standard of PD treatment. It is converted to dopamine in the brain and so acts as a replacement drug. It is used in nearly all phases of the disease, once the patient has progressed to benefitting from its use. Normally, PD patients who are further along in the disease course, with greater symptom expression, are placed on dopaminergic medications to alleviate the difficulties of disabling motor symptoms. Not all patients require pharmacotherapy, although the majority eventually do as PD progressively disables them. The number of medicines to treat the expression of PD has increased since the development of Levodopa, giving more choices to tailor individual therapy. It is important that the patient and doctor work closely to tailor an individual therapy that will work best for each PD patient. Often Levodopa is prescribed with *carbodopa* (Sinemet, Atamet) to reduce nausea. A combination of entacapone, Levodopa, and *carbodopa* is now available (Stalevo) as a single pill, simplifying the drug regimen for some patients. Dopamine

agonists and Catechol-o-methyl transferace inhibitors (COMTs) are alternative medicines that augment Levodopa. Dopamine agonists make use of available natural dopamine rather than just replacing it, as Levodopa does. Treatment typically begins with low doses of several drugs versus large doses of only one or a few.

Normally, with the onset of symptoms, the patient may be prescribed several therapies, including any combination of exercise, diet, and anticholinergics. With the onset of moderate symptoms, Levodopa is most commonly used in combination with dopamine agonists and COMT's. For long term use, in combination with Levodopa, dopamine agonists tend to be most effective. In the most advanced cases, when Levodopa is no longer effective, experimental drugs are being studied as well as the option of some surgical procedures, including deep brain stimulation which uses electric pulse generators implanted in the brain to control symptoms. The benefit is that it does not require removal of brain tissue and is reversible. Pallidotomy (an implanted electrode generates a current and heat to destroy small amounts of tissue in the globus pallidus) and thalamotomy (the same technique as pallidotomy – only it is performed on the thalamus) are also surgical treatment options that reduce PD motor symptoms. The number of patients who are good candidates for surgery are few, however, so medicinal therapies such as Levodopa are more commonly used.

With such an abundant history of clinical use, it is well documented that Levodopa eventually outlasts its usefulness. Eventually, the continued use of Levodopa may cause dyskinesias which can be painful and mimic the rigidity and uncontrollable tremors of PD (Cooper, Sagar, Doherty, Jordan, Tidswell, & Sullivan, 1992). Levodopa- related motor fluctuations or dyskinesias are seen in approximately 40% of patients after five

years of Levodopa therapy (Bhat & Weiner, 2005). Amantadine is an example of drug that can relieve dyskinesias. As with any chronic medical condition, prolonged pharmacological therapies can come at several costs.

Cognitive dysfunction in PD

It is well known that some 24% to 31% of PD patients develop dementia with an incidence of 10% per year (Aarsland, Zaccai, & Brayne, 2005). "However, dissociation in the time and prevalence of clinical manifestation between cognitive dysfunction and dementia exists (Yanagisawa, 2006; p. S44)." Between 24% to more than 50% of patients with PD experience cognitive symptoms, although debate exists regarding the frequency and severity of such deficits (Bassett, 2005; Muslimovich, et al., 2005). Inconsistent results in the literature surrounding the presence or prevalence of cognitive impairments may reflect the heterogeneity among patients with PD as well as differing methodologies. Several researchers posit that loss of attentional control may underlie many of cognitive deficits associated with PD (Bhat & Weiner, 2005; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991). In 1988, Brown and Marsden showed that PD patients were significantly different from normal controls when it came to trials which required internal attentional control. Basically PD patients can perform just as well as normal controls provided the demands of the task are within the patients' available attentional resources (Bublak, et al., 2002). On visual attention tasks, Sharpe (1990) found that patients with PD were more prone to interference in the presence of distracter items than in normal control subjects. Dysfunction of the complex loop between the caudate nucleus and the prefrontal cortex resulting from striatal dopamine deficiency is presumed to underlie such

dysfunction. This is at least partially responsible for the cognitive deficits seen in PD (Galvin, 2006).

> These deficits, better demonstrated in nondemented PD patients using several different paradigms, include… problem solving… and planning…Patients have more difficulties with internally cued behavior and benefit from external cues; difficulties are rather due to shifting attention to novel stimuli (Emre, 2003, p. 65).

Speed of cognitive processing has been reported as a common problem (Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002). Goldman, Baty, Buckles, Sahrman, and Morris (1998) found that PD subjects without clinical indication of dementia performed more poorly than healthy elderly controls on a wide range of tasks, measuring declarative memory, visuospatial skills, speed of cognitive processing, and attentional processes (Locascio, Corkin, & Growdon, 2003). Subjects with PD but without dementia are often subtly impaired even on cognitive tasks with no motor component. One study concluded that the motor slowing known as bradykinesia appears to be attributable primarily to a deficit in cognitive motor control (i.e., an ability to arrange complex movement) rather than simply an impairment in motor initiation and execution (Sawamoto, et al., 2002). Overall, PD is now widely recognized to be associated with some degree of cognitive compromise.

Simultaneously, PD patients will typically demonstrate preserved abilities such as implicit memory (an automatic or unconscious form of memory), prospective memory (the ability to remember a future intention), and recognition memory. It is apparent that aphasia (the loss of a previously held ability to understand or use spoken or written

language), agnosia (partial or total loss of the ability to recognize objects by use of the senses) and apraxia (the inability to perform purposeful movements, but not accompanied by a loss of sensory function or paralysis) do not manifest in PD (Yanagisawa, 2006). As a testament to the heterogeneity of the PD population, while some researchers have reported preserved verbal fluency (Kuzis, Sabe, Tiberti, Leiguarda, & Starkstein, 1997) most have found that verbal fluency is compromised in PD (Auriacombe, Grossman, Carvell, Gollomp, Stern, & Hurtig, 1993; Flowers, Robertson, & Sheridan, 1996; Huberman, Moscovitch, & Freedman (1994).

Recently, the question has not been whether or not PD patients express cognitive impairment, but which specific abilities are compromised. While it has been found that cognitive dysfunction is often present several years after PD is diagnosed, the model of cognitive impairment is different when we look at patients diagnosed within the last five years (Williams-Gray, Foltynie, Brayne, Robbins,& Barker, 2007). It is clear, however, that the number and severity of cognitive impairments are less in early PD patients than in late PD. The exact pattern of impairment in early PD is still the subject of considerable controversy. As stated previously, isolated cognitive deficits have been found in early PD that have been thought to be related to frontal lobe dysfunction (Lees & Smith, 1983; Owen, et al., 1992; Yanagisawa, 2006). Other studies, however, have found a more generalized pattern of cognitive impairment (Bassett, 2005; Levin, Llabre, & Weiner, 1989). Furthermore, some investigators have reported no evidence of frontal deficits (Growdon, Corkin, & Rosen, 1990), suggesting that such an impairment is not a universal cognitive feature of early PD. This is understandable considering the heterogeneity of PD patients, as patients typically vary along multiple dimensions including disease severity,

dominant motor symptom, and age at onset (Lewis et al., 2003). Generally, PD patients are categorized by their dominant motor symptom (usually resting tremor) and the possible presence of cognitive deficits. Executive dysfunction is often a characteristic of PD (Goldberg & Bougakov, 2005).

A study of 126 consecutive PD patients diagnosed within the last three years found that 36% displayed evidence of frontal cognitive impairment based upon a battery of tests that included the TOL, Mini Mental State Examination (Fostein, Folstein, & McHugh, 1975), and a pattern recognition task (Foltynie, Brayne, Robbins, & Barker, 2004). Subjects were re-tested three and a half years later and the percentage of cognitive impairment rose to 57%. Thus, even though the cognitive dysfunction of PD encompasses a wide range of deficits, perhaps the most well defined are executive in nature, affecting the ability to plan, organize and regulate goal-directed behavior. Such deficits are demonstrable on tasks of working memory and planning (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007).

Executive dysfunction in PD

Impairment of executive functions constitutes one of the core features of neuropsychological deficits in PD patients (Emre, 2003). Executive function refers to a group of cognitive skills involved in the initiation, planning and monitoring of goal-directed behaviors (Levin, Llabre, & Weiner, 1989) and are largely mediated by frontal lobe systems. The cognitive impairments seen in the early stages of PD include deficits in planning and working memory (Lewis, Cools, Robbins, Dove, Barker, &Owen, 2003). Early impairment of executive function has been reported in many patients with PD (Foti & Cummings, 1997). As described above, dysfunction within the basal ganglia can have

disruptive effects on the proper functioning of the fronto-striatal loops that course the length of the brain and affect the function of the frontal lobes. Executive dysfunction can render a previously independent and well functioning individual dependent upon others, and may prevent him/her from performing daily routines. Executive dysfunction in PD has been posited as the leading cause for loss of employment and serious difficulties at home (Bassett, 2005).

Classically, the frontal lobes are associated with executive functions. In fact, the highest cognitive functions, such as planning, decision-making, problem solving, and logical analysis have been consistently associated with the largest and most enigmatic brain region, the frontal lobes (Luria, 1966; Reitan & Wolfson, 1994). Even before systematic neuropsychological studies were done on the functions of the frontal lobes, higher level cognitive abilities were attributed to the anterior brain regions because neurological studies had already mapped the majority of lower level functions onto posterior brain areas (Reitan & Wolfson, 1994). More recently, advanced imaging techniques, such as functional magnetic resonance imaging, have confirmed the association of the frontal lobes with executive function (Lewis, Dove, Robbins, Barker, &Owen, 2003).

Working memory is a fundamental executive function, which is invoked to guide behavior in situations in which habitual actions or implicit memory are inefficient and one has to generate novel lines of action (Shallice & Burgess, 1998). The close association between impaired working memory and executive control functions is exemplified by the cognitive profile of patients with PD. It is well established that PD patients are subject to spatial working memory deficits (Bublak, et al., 2002). Working memory is a dynamic system that governs the concurrent storage and processing of

information (Bublak, et al., 2002). Spatial working memory specifically refers to the storage and manipulation of spatial information. The ability to plan spatial moves in pursuit of a goal may be related to a reduction of working memory capacity. Bublak, et al. (2002) tested 14 PD patients on a test of spatial working memory and found that performance declined significantly in comparison to healthy controls with increasing task demand. The results suggest that the complexity of working memory processing may contribute to the deficits seen in PD patients.

There are different types of working memory, and variability in working memory abilities of PD patients is well documented in the literature (Cooper et al., 1992; Postle, Jonides, Smith, & Corkin, 1997). PD patients have been found to exhibit preserved cognitive abilities on analogous tests of verbal and object working memory presented on a computer (Bradley, et al., 1989; Owen, et al., 1997). In each type of working memory test, the subject was required to search through unique objects/shapes or names. In the case of the object working memory task the subjects were required to look through unique shapes. In the case of the verbal working memory test, the subjects were required to search through names for a blue token. Once the token was found, it could no longer be hidden behind that (shape) or name. The shapes and names to be searched altered their locations after each trial. This provision ensured that the test could not be solved using spatial clues. The PD subjects displayed no deficits on these two working memory tests. In the study by Owen and colleagues (1997), the PD patients displayed deficits on the spatial working memory test that was designed to be similar to the other two working memory tests. PD patients are impaired on spatial working memory tasks. Bublak, et al. (2002) for example, in a sample of 14 PD patients concluded that the complexity of

spatial working memory processing may contribute to the exhaustion of cognitive resources. Importantly, this suggests that the more complex the measure in testing spatial working memory, the more probable that the PD patients would exhibit dysfunction.

Measuring Spatial Working Memory with Tower Tasks

Tower tasks have been noted to provide a measure of specific aspects of executive control (Goldberg and Bougakov, 2005). Although the cognitive expression of PD varies, executive dysfunction occurs even at the time of diagnosis for over half of the patients and is heterogeneous (Williams-Gray et al., 2007). Such deficits include working memory (Bassett, 2005; Brown and Marsden, 1982).

> Working memory is essential not only for the storage of a correct sequence, but also in the search processes required in any analytical problem of the tower task type, by which possible solutions are considered and either accepted or rejected (Owen et al., 1990, p.1032).

These deficits are especially important when task-relevant information has to be maintained, monitored, and manipulated in its use for guiding goal-directed behavior (Petrides, 1994). An example would be the mental manipulation of several pieces of information to organize a sequence of actions necessary in planning and problem solving in a tower task.

The TOL was originally intended to test frontal lobe – injured patients (Shallice, 1982). A tower task is well designed to test spatial working memory abilities

because the planning involved calls for not only the retention of information held in spatial working memory, but also its active manipulation for satisfactory performance.

Each item on the original TOL consists of a starting arrangement and a goal arrangement, each with three upright pegs and three differently colored balls. The three pegs are of differing length, such that one accommodates three balls, the second can hold only two, and the last can hold one. The examinee moves the balls from the starting arrangement in order to match the goal arrangement. The task requires the examinee to move the colored balls from the first (start) configuration so as to match a given pattern established by the goal configuration. The difficulty of the task can be varied in terms of the minimum number of moves necessary to make the match. The most complex items on the TOL, with three stimuli, require five moves minimum. Pertinent rules include moving no more than one ball at a time.

One method to understanding the nature of spatial working memory deficits in PD may be to select a neuropsychological measure such as a Tower task which has demonstrated consistent results with PD patients. A neuropsychological test that has been used extensively to also examine planning/spatial working memory in different populations, including PD, is the Tower of London task (Shallice, 1982).

> Although the Tower tasks have a strong strategic component and in the case of planning tasks—require unique, single-contingency

> solutions, the necessity to monitor and manipulate information within spatial working memory underlies their special sensitivity for revealing deficits in … PD patients (Gabrieli, Singh, Stebbins, & Goetz, 1996, p. 324).

During the tower task, the examinee must hold several intermediate steps in spatial working memory while finding the solution. In order to efficiently solve the tower task, several steps are necessary. First the examinee must generate the sub-units which together comprise the plan (i.e., the individual spatial moves). Second, they must organize these sub-units mentally into a sequential order that permits them to re-arrange the current tower to the goal-state. Finally, they have to maintain the strategic sequence in spatial working memory while they are enacting the solution of the tower structure. Therefore, impairments observed in PD patients on tower tasks such as the Tower of London may, in large part, be due to spatial working memory deficits. For example, Owen, et al. (1992) reported impairment in PD patients on the Tower of London planning task. This could be interpreted as reflecting PD patients' difficulties in preparing a sequence of moves by organizing them within working memory prior to the execution, or planning (Bublak, Muller, Reuter, Gron, & von Cramon, 2002).

TOL Performance in PD

Morris et al. (1988) tested 12 PD patients and 18 healthy age-matched controls on a computer-administered version of the TOL. The PD subjects selected for the

study had minimal motor symptoms because the authors were interested in the planning/spatial working memory abilities of PD patients recently diagnosed. In this version of the test there were two sets of pegs and balls on the computer screen. The set located in the upper half of the screen was unchangeable and represented the goal state and the set at the bottom half of the screen was the set that the examinee was to manipulate. The authors were interested in measuring the time spent thinking or planning and therefore eliminated the motor component from the time to first move. They included a trial that led the participants through a solution sequence (to build a tower) one move at a time. By timing these moves, they were able to calculate the average time it took for the participants to make rote movements without the necessity of thinking before making that move. This was taken as the motor time and was removed from the times the participants took to make their moves on the actual task. In this way, the authors postulated they could exclude any motor effects from the planning time taken to make each move. Morris, et al. (1988) found that although PD patients were as accurate as controls in the number of towers constructed, they were significantly slower initiating their responses as evidenced by the thinking times after rote movement times were excluded. The authors reported this as a deficit in planning. Below it will be shown how intricately intertwined planning and spatial working memory are on the TOL.

Owen et al. (1992) also tested PD patients and healthy, age-matched controls on the TOL. They included three groups of PD patients: the first was composed of recently diagnosed patients with only mild clinical symptoms, the second had longer disease duration, were on dopaminergic medication and displayed only mild clinical impairment, and a third group, also medicated, had more severe clinical motor symptoms and even longer disease duration. Each PD group was appropriately matched to a control group of equal size. The TOL task was presented on a micro-computer as in the Morris et al. study (1988). The PD patients of the first group were unimpaired with respect to time spent thinking as well as the number of towers successfully completed. The second group was only impaired with respect to the time spent thinking/ planning prior to the first move. They correctly solved an equivalent number of towers as the control group. However, the PD group with severe clinical symptoms displayed impairment on both the time spent planning as well as the number of successfully built towers (accuracy of tower completion).

In summary, non-demented subjects with the longest disease duration in this study and the most clinical disability had a propensity to more severe impairment on the TOL. The authors found those PD patients of longer disease duration (groups two and three) took significantly more time to plan the first move compared to control participants even after rote movement times were considered. As the authors reported, the results of this investigation have considerable significance for the

staging of cognitive decline in PD. This study demonstrated that groups of patients at different stages of PD can be differentiated in terms of their performance on the TOL, which measures spatial working memory.

The PD patients having shorter disease duration in the aforementioned studies (the Morris, et al., 1988 patients and the first two PD groups of the Owen, et al., 1992 study) were not impaired in terms of their accuracy of tower completion. The first group in the Owen et al. (1992) study displayed no impairment at all on either time to first move or accuracy of tower completion. However, patients of mild clinical disability yet greater disease duration (group two of the Owen 1992 study and the patients from the Morris study) were significantly slower than controls in their time thinking or planning prior to the first move. The deficits in planning observed in these patients may be attributed to impaired spatial working memory processes which are vital in the initial search for possible solutions (Bublak, et al., 2002). Owen et al. (1990) wrote specifically about the role of spatial working memory in thinking times before a problem in the TOL is initiated, noting "...the use of inappropriate organizational strategies to assess the problem, and then generate and refine a possible solution may place a disproportionate load on spatial working memory during the planning phase prior to the first move" (p. 758).

Even before this, Cohen (1989) described planning and executive novel action sequences:

> Before embarking on an action sequence which is novel or complex, we usually spend some time thinking what we are about to do, how best to achieve the goal, in what order to perform the individual actions, and how much time and effort will need to be allocated to the task. (p.17)

He further illuminates the relationship between the executive functions, planning and working memory:

> Memory is involved in formulating such plans, holding the elements and sequence in mind while the plan is being assembled, evaluated, revised, and implemented. When it comes to implementation of the plan, the component actions are assembled in some sort of output buffer and the memory system monitors the output of actions from the buffer to ensure that the plan is implemented correctly. (p. 18)

In healthy adults, spatial working memory has been linked to the TOL planning task and in PD patients it was found that performance on the TOL was associated with components of spatial working memory (Altgassen, Phillips, Kopp, & Kleigel, 2007). Therefore, planning and spatial working memory are inherently and irrevocably tied to one another in a tower task.

Thus, in this tower task, planning ability may be adversely affected by spatial working memory deficits. However, this working memory deficit was not

significant enough to disrupt the early PD patients' ability to accurately construct towers in the two aforementioned studies. The question arising is, is it the case that early PD patients are unimpaired with respect to accuracy of tower construction or is it a spatial working memory deficit not yet severe enough to reach significance and therefore goes undetected on the TOL? Comparing early vs. late PD patients with differing disease duration on the Tower of California (Delis, Kaplan, & Kramer, 2001), which was designed to be more sensitive to spatial working memory, would be a helpful way to explore this question.

Improving the Tower task

In the above-referenced studies, the PD patients of the shortest disease duration displayed more intact cognitive function. This could indicate a sparing of spatial working memory abilities in the recently diagnosed PD patients. However, an alternative explanation may involve the sensitivity of the task employed. Spatial working memory abilities may be affected in early Parkinson's disease but the deficits remain undetected because the tasks used to test these abilities are insufficiently challenging for patients of shortest disease duration and mildest cognitive involvement. Researchers have posited that newly diagnosed patients with PD may escape impaired performance on the TOL because the task is not challenging enough (Owen et al., 1995; Culbertson, et al., 2004).

With this in mind, Owen et al. (1995) tested PD patients on a more challenging version of the computer-based TOL task. After practice problems were

completed, participants were presented with both arrangements of balls on pegs but also with the numbers 1 – 5 along the bottom of the computer screen. Subjects were instructed to think through the entire problem to completion before responding. To insure this method, instead of moving the balls, subjects were asked to plan an ideal solution (minimal moves) and to select the corresponding number. They did not actually manipulate a configuration of balls on pegs. Because the ideal solution was not defined *a priori* (participants were not told the ideal number of moves to solution), the number of possibilities that had to be considered before the most appropriate solution could be identified was significantly increased, hereby placing a greater demand on spatial working memory. Owen, et al. (1995) hypothesized that all PD patients would display impairment based on the increased complexity of the task. This method resulted in considerably longer planning times in all of the modified TOL trials in the three of the PD groups than did the original version. The effects of this new method may be seen most clearly by comparing the performance of control subjects in this study with those studied previously with an earlier version of this task by Owen, et al. (1992) All four control groups in this study (1995) exhibited clear, difficulty-dependent, monotonic increases in thinking time, which were not consistently observed in the previous study (Owen, et al., 1992).

Owen and colleagues (1995) also tested subjects on a novel spatial working memory task. The goal was to generate as many different four-square sequences

as possible using the four squares arranged symmetrically about the screen. Subjects were instructed to produce as many sequences as possible without repeating one previously revealed, by touching each of the four response boxes in turn. A given sequence could start and end with any of the four squares except every sequence had to include each of the boxes. Thus there were 24 possible combinations. Again, in this case, the executive areas focused upon included rule learning, mental manipulation of spatial working memory list items and their retention while solving the puzzle. One of the observations often published in the literature is that PD patients are specifically impaired on tasks that involve self-directed behavioral planning (Morris et al., 1988; Taylor et al., 1986). If this is true then PD patients should have found the novel spatial working memory task more challenging than the tower task because the TOL goal state is always present to the patient. In fact, the shortest disease duration PD patients that were unmedicated with only mild clinical symptoms did display significant impairment while the two medicated groups (numbers 2 and 3) did not, in terms of the total number of novel sequences produced. It is possible that the dopaminergic therapy aided the two medicated groups in this test. The important point with respect to the present proposal to note is that the unmedicated, early PD patients displayed impairment.

The Owen, et al. (1995) study demonstrated that even early PD patients can exhibit impaired spatial working memory. Apparently the second group, which

was also mildly disabled, but was being medicated, displayed impairment with respect to the time required to successfully plan the solutions. Perhaps this second group would have been even more impaired on this task had they not been medicated. Again, some research claims dopaminergic therapy in PD can selectively improve performance on tests that are sensitive to frontal lobe dysfunction (Lange, Robbins, Marsden, James, Owen, & Paul, 1992; Owen, et al, 1993).

Culbertson, et. al. (2004) also tried to challenge PD patients by increasing the difficulty of the tower task. Specifically, they raised the ceiling of the task by including trials with six and seven moves minimum to solution. Although the study was designed with two groups of PD patients, one with and one without dementia, the non-demented PD patients were similar to the first and second groups tested by Owen (1992) because they experienced mild to moderate clinical disability. The results suggested that these PD patients demonstrated executive deficits relative to normal controls. The authors claimed their measure provided a means of identifying executive dysfunction in patients who were demonstrating mild to moderate symptoms of PD.

These two studies (Owen, et. al. 1995; Culbertson, et. al. 2004) suggest that PD populations with short disease duration and mild symptoms can be impaired with respect to spatial working memory, and a more challenging task may distinguish them from controls. While both studies used slightly more challenging versions of

the tower task, both have their limitations. Owen et al. (1995) changed the methodology of the task in order to present patients with a more challenging version but continued to use 'five-move problems' as the most difficult trials in the task. Culbertson, et al. (2004) created a more complex tower task that included six and seven move minimum problems. However, their design of descending peg heights and the fact that the three moveable pieces were all similar sized and shaped balls renders the overall design very similar to the original TOL. The task used by Culbertson et al. (2004) did have a greater ceiling, but the distinction was only a difference of two moves maximum. In this respect it was hardly more difficult than the original TOL. Both studies, however, pointed to the efficacy of a more challenging task in order to distinguish early PD patients from controls. The question remaining is whether or not a similar, more challenging tower task can help to identify a clear, significant difference between early and late PD patients. Experimental studies have shown that the executive skill of manipulation of working memory information declines in efficiency if the demand on item maintenance increases because of a higher number of list items to be processed (Carlson, Wenger, & Sullivan, 1993).

Bublak, et al (2002) attempted to find if PD patients were impaired on spatial working memory tasks if the complexity was increased albeit the number of list items remained the same. Much like Owen, et al. (1993, 1995) above, Bublak, et al. (2004) found an impairment for early PD patients with increased complexity.

In both cases increased complexity was the limiting factor for performance on tasks that measure spatial working memory.

Tower of California

The original Tower of London, with only three moveable pieces and trials up to five moves minimum to solution may not achieve the appropriate complexity to challenge newly diagnosed PD patients with preserved cognitive abilities. A greater challenge to PD patients may be accomplished with the Tower of California (TOC; Delis, Kaplan, & Kramer, 2001) because of the greater number of moveable pieces and complexity. The TOC starts with very simple trials of only one move to solution and continues up to trials that require twenty-six moves to solution. The design challenges spatial working memory abilities in those who are exceptionally bright as well as those who demonstrate significant functional impairment. In the TOC, the first few items can be solved with concrete problem-solving strategies involving from one to three moves. These simpler items lower the floor effects of the test while providing the opportunity for subjects to acquire the instructional set of the task. The first few trials make use of only two disks while the latter trials make use of three, four and up to five disks. Starting with item #5 the subject is required to make use of more advanced spatial planning strategies if he or she is going to succeed in constructing the towers with the fewest number of moves possible (Delis, et al, 2001). Having more disks as well as trials with more minimum moves to solution allows for a more sensitive

instrument in determining cognitive abilities in a wide range of examinees. By placing a greater demand on spatial working memory, this task may have a better chance of identifying even slight deficits in PD patients.

The design of the TOC has the potential to provide more insight into the possible impairment associated with PD. Just as the more challenging spatial working memory tasks above, it is hypothesized this measure will be more sensitive to differences between groups.

Summary

Research over the past few decades has demonstrated cognitive impairment is commonly associated with PD. Specifically, PD patients display impairments on tasks of executive function, including spatial working memory. Past studies have shown that PD patients early in the course of the disease with mild clinical disability remain unimpaired with respect to planning or spatial working memory on tower tasks. It is possible that this sub-population displays unimpaired performance on tower tasks because the tasks are not challenging enough. Further studies with short duration, mildly disabled PD patients on more challenging spatial working memory tasks have revealed impairment in this sub-population. According to some research, PD patients are susceptible to cognitive impairment in the area of spatial working memory even at the early stages of the disease and progressively worsen as the disease runs its course. A recently developed and more challenging tower task, the Tower of California, has not been utilized with

PD patients to date. The TOC is expected to detect executive impairment in the form of planning or spatial working memory even in early in the course of PD.

CHAPTER THREE

Hypotheses

Overall Goal: To compare the spatial working memory abilities of patients with early PD to those with late PD as well as normal controls on the TOC.

Specific Aim One: To determine how many successful TOC towers the early stage PD group will build in comparison to normal controls and to subjects in the late stage PD group.

Hypothesis 1:

The early stage PD group will build fewer correct towers on the TOC than controls.

Hypothesis 2:

The early stage PD group will build more successful TOC towers than the late stage PD group.

Specific aim two: To assess time to first move across the early stage and late stage PD groups and controls.

Hypothesis 3:

The early stage PD group will take longer than controls to make the first move to correct solution on the TOC, controlling for motor movement.

Hypothesis 4:

The early stage PD group will take less time than the late stage PD group to make the first move to correct solution on the TOC, controlling for motor movement.

CHAPTER FOUR

Method

This study will use archival data collected over several years. Forty patients with Parkinson's disease were recruited from an outpatient clinic at a major medical facility in order to form two groups of twenty. The diagnosis was made by a board-certified neurologist. The patients had similar educational backgrounds. This is especially important since it has been found that PD patients with high educational attainment have a better ability to ward off cognitive dysfunction compared to patients with low education (Muslimovic, Post, Speelman, and Schmand, 2005). The severity of clinical symptoms was also assessed by the same neurologist according to the standard Hoehn and Yahr (H&Y) rating method (Hoehn & Yahr, 1967), which uses a 1 - 5 point rating scale. A score of 1 or 2 indicates mild physical symptoms, and a score of three is considered intermediate as the patient becomes increasingly bradykinetic. A score of four represents severe symptoms and a 5 is the last category, indicating that the patient is at a cachectic stage and the patient is bed-ridden.

Participants

The group with early PD includes twenty patients, aged 60 – 70, and has an average H&Y score of 1 to 2, indicating mild physical symptoms. They have all been diagnosed within the last five years and were not taking medication for PD.

The late PD group consists of twenty patients, aged 60 – 70, and has an H&Y score of 4, indicating severe physical symptoms. They had been diagnosed more than ten years prior to this study and were not taking medication for PD.

A group of twenty control subjects were selected to match the patient groups as closely as possible with respect to age (60 - 70), gender, and education.

Inclusion Criteria

All patients were right-handed, Caucasian males. Care was taken to exclude patients with dementia or depression. Exclusion criteria include evidence of dementia based on the MMSE. Specifically, only patients who score above 24/30 on the MMSE are included. Subjects with evidence of depression (Geriatric Depression Scale score >10; GDS, Yesavage et al., 1982) were excluded. Exclusion criteria for controls included any history of additional neurological or major psychiatric illness or substance abuse.

Neuropsychological Battery

Tower of California

The participants will be administered the TOC in a private testing room by a qualified technician. The TOC is similar to other tower tasks such as the TOL. The TOC will be used because it is the newest and most challenging of the tower tasks available, with five moveable pieces and trials up to 26 moves minimum to solution.

The objective of the task is to place three to five disks varying in size (diameter) with holes in the center onto three pegs of equal height fixed to a small board and equally spaced, to build a specific tower in the fewest moves possible. In building the towers, the examinee is asked to observe two rules: (a) move only one disk at a time with one hand and (b) never place a larger disk atop a smaller one.

Each trial begins with the examiner presenting the disks on the pegs in a predetermined starting position and displaying a picture from the stimulus book that shows the final arrangement of the disks. The examinee is asked to move the disks, keeping the rules in mind, in order to build the goal tower in the fewest number of moves.

Depending on the complexity of the trial, i.e., the number of minimum moves to solution and the number of disks used, the examinee is allotted a time limit. Examinees will be informed when the time limit is exceeded. In order to reduce frustration, however, the examinees will be allowed to continue past the time limit until they either solve the tower or give up, although in either case the trial will be recorded as incorrect.

As the subject moves the disks to match the target tower, the examiner will record the number of successfully built towers (given the move and time limits; the final achievement score), and the time to first move. This study will utilize the final achievement scores of the examinees. Total achievement scores are calculated from the total number of moves within the total time to completion. If the examinees construct the correct tower in the minimum number of moves possible, they are awarded the maximum number of points for that item. If they solve the tower but use more moves than the minimum, they are given fewer points. They are given no points if they are unable to solve the tower within the time limit. On trials one and two, two points are possible. For trials three and four,

three points are possible while four points are possible for trials five through nine. For example, with trial seven, four points are awarded if the tower is solved in the minimum number of moves (thirteen), but only one point is granted if they solve the tower within the time limit in more than fifteen moves. The scores can then be standardized according to the age group of the examinee.

Nine trials will be administered with the following conditions. Trials one through three utilize only two disks and have a time limit of thirty seconds each. Trial four makes use of three disks with a time limit of sixty seconds. Trial five requires three disks and has a time limit of two minutes. Trials six and seven each have four disks. Trial six has a time limit of two minutes and three minutes are allowed for trial seven. Trials eight and nine use all five disks and have a time limit of four minutes.

For the purpose of this study, the time to first move will be recorded only from perfect trials (solved in minimum moves). This will guarantee that the first move is identical for all and the only difference will be the subjects' thinking times. Furthermore, since the PD groups are expected to take longer to make any movement due to bradykinesia, a yoked control will be employed. This means that, prior to completing the TOC, the subjects will be prompted through a series of single moves that correspond exactly to the moves on the tower items. In this manner, the amount of time the subject needs to perform the actual movement can be measured. An average time will be calculated from the times to make the first

move for all items. This average will be subtracted from the actual time to first move, leaving only the thinking or planning time to be recorded.

The TOC is a means of assessing key executive functions, including spatial planning and the ability to establish and maintain the instructional set. It also assesses the examinee's ability to hold the mental manipulation of the solution while performing the task. Specifically, this task requires spatial working memory.

Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975).

The MMSE is a widely used screening measure for cognitive impairment. This test consists of 30items and usually takes 5 to 10 minutes to administer. Test questions assess various domains of cognition such as orientation to time and place, attention/ concentration, immediate and delayed verbal recall, naming ability, ability to follow simple commands, and constructional skills. The test score is determined by totaling the number of correct responses.

Geriatric Depression Scale (GDS; Yesavage et al., 1982)

The GDS, a self-administered, 30-item questionnaire is particularly suited for the assessment of depression in PD patients since it contains relatively few somatic items which may relate directly to the patient's physical disability.

Procedures

All patients were evaluated at the major medical facility. Neuropsychological tests were administered by trained technicians using standardized procedures.

CHAPTER FIVE

Statistical Analyses

Four one way ANOVAs will be conducted. The group (earlyPD, latePD, controls) will be the independent variable (three levels) and overall performance scores (ST) and time to first moves will be the dependent variables. Post Hoc comparisons will be performed if the ANOVAs reveal significant differences.

CHAPTER SIX
Implications

Expected Results

The first aim of this study is to determine how many successful towers (ST) the early PD group will build in comparison to both normal controls and to the late PD group on the TOC. The first two hypotheses are based on the performance, by group, of accuracy of towers built.

The first hypothesis is that the early PD group will build fewer ST than the control group. If hypothesis one is supported it is possible the differences may be due to the early onset of executive impairment, with respect to spatial working memory abilities/planning. The results of this study would suggest that spatial working memory/planning may be one of the cognitive impairments in early PD. Hypothesis one may also be supported, in part, because of the high ceiling of the TOC. In contrast, some previous researchers claim the low ceiling of the TOL may have effectively masked the dysfunctional performance of the early PD patients (Culbertson, et al., 2004; Owen et al., 1995). Importantly, in these studies, the TOL did not detect significant impairment within the early PD patients, but it did reveal a motor-independent slowing on their part – especially with respect to the time to first move. If hypothesis one is supported, the complexity of the TOC may have helped to reveal a difference on the part of the early PD group. In this case, the dysfunctional performance of the early PD group

could be due to the fact that the TOC has more items (moveable pieces) as well as more complex towers (the most complex trial requires 26 moves minimum to solution vs. five in the TOL). The normal control group may be able to successfully build more difficult towers than the early PD group. This result would suggest that PD often causes executive deficits early on in the disease. The importance of hypothesis one being supported is that it bolsters what many researchers believe (Owen, et al., 1995; Filoteo, et al., 2007; & Williams, et al., 2007), that by the time PD is detected and diagnosed, cognitive impairment is often present. On top of this, it implies that the cognitive deficit is not due to rule learning or concept formation but possibly to planning/spatial working memory, since the subjects were able to complete the easier trials. Moreover, it has been shown that patients with PD have difficulties performing several behaviors sequentially or simultaneously (Sawamoto, 2002). This could negatively affect the performance of PD patients on the TOC.

If the first hypothesis is not supported and the early PD patients do not build fewer ST than the control group, then it is possible that the TOC may not be a sensitive enough instrument to detect planning/spatial working memory impairment in PD. The demands of the TOC may not be useful in assessing early dysfunction in PD. Additionally, if the first hypothesis is not supported, these results could be due to the heterogeneity of the sample. Finally, if hypothesis one were not supported, perhaps the early PD group is not impaired or only slightly

impaired and the task results accurately reflect this fact. The early PD group may truly express no impairment on the number of ST built in the TOC because they are not significantly impaired in executive functioning.

The second hypothesis is that the early PD group will build more ST than the late PD group. Many PD patients display frontal/executive dysfunction, and continue to worsen with increasing disease duration (Filoteo, et al., 2007). Because patients with dementia were not included, this study's sample may represent a distinct sub-population of PD patients with specific impairment in executive functioning. If hypothesis two is supported, the results would suggest that late PD patients will be worse with respect to cognition, even if they do not develop dementia.

If hypothesis two is not supported, and the early PD group does not build more ST than the late PD group, then the results from testing the first hypothesis are important. Either both of the PD groups perform as well as the control group or they both are equally impaired (it is unlikely that both groups would out-perform the controls). If the PD groups do as well as the controls on the number of ST, then perhaps the PD patients have been relatively spared with respect to their abilities to construct ST. Conversely, this result may suggest that the TOC is not sensitive to some of the suspected deficits in this sample of PD patients. If they are both impaired, then it may be due to a methodology issue. It may be that the study's method for separating the early and late groups is faulty and/or does

not maximize the ability to find group differences. Perhaps a lack of significant difference in disease duration and motor impairment might be accountable. For example, if the groups were not significantly different in disease duration/ clinical severity, it may be that there simply exists no significant difference within the first ten years of diagnosis. In this case, we would not expect hypothesis two to be supported.

The second aim of this study is to assess time to first move in a ST, controlling for motor movement, between the early and late PD groups and controls. The third and fourth hypotheses are based upon differences between the groups in initial response time.

Hypothesis three predicts that the early PD group will take longer than controls to make the first move in a ST, controlling for motor movement. If hypothesis three is supported, then this latency may point to a deficit in an executive ability necessary to formulate and begin a novel solution. Another possibility is that the latency is due to a deficit in attention. This may further strengthen the idea that the TOC is appropriately challenging for this early PD group. Since time spent planning has been shown to depend on the individual's spatial working memory capacity and ability (Bublak, et al., 2002), these results would suggest that these abilities are compromised in the early PD group. This latency could be related to bradyphrenia, and perhaps stands as a clear example. It is much less likely that the group latency is due to bradykinesia since care was

taken to control motor movement. Assuming that the TOC is more complex, with more items, it is believed that this study will find a similar outcome as the TOL with respect to the latent time to first move in an ST (Morris, et al., 1988; Owen, et al., 1993).

It is possible that hypothesis three will not be supported. Given that early PD patients have displayed this latency in other studies using the TOL (Morris, et al., 1988; Owen, et al., 1993), these results would be unexpected. However, a shorter latency may be due to the method of the TOC or an optimal performance on the part of this patient group. It is possible that the early PD group will perform as well as the control group simply because they are not impaired with respect to planning time or time to initiate a ST.

Hypothesis four is that the early PD group will take less time than the late PD group to make the first move to a ST on the TOC, controlling for motor movement. Especially for the late PD group, it is important to control for motor deficits since they are the most physically challenged of the three groups. Their average rating of H&Y 4 attests to this. It is expected that they will be the slowest of the three groups. Hypothesis four may be supported because of the fact that in addition to bradykinesia, the late PD patients are dealing with increasing bradyphrenia. The further along in their course of the disease, the more disabled they may be both physically as well as cognitively. Earlier it was noted that the latency at the outset of a tower task trial can be due to the inability to properly

order consecutive planned moves or to hold these planned moves in mental order while continuing to solve the task (Bublak, et al., 2002). Thus, if hypothesis four is supported, it suggests that the late PD group may be more cognitively impaired than the early PD group either in terms of spatial working memory/planning or in another skill such as attention or the ability to begin a task.

If hypothesis four is not supported, it may be due to the greater complexity of the TOC vs. the TOL. In this case, perhaps the early PD group might have particular trouble in solving the later TOC trials, thereby bringing down their average time to first move. Additionally, this could imply that the span of disease duration was not great enough between the two patient groups to maximize finding a difference.

In summary, if the hypotheses are supported, it is possible that a person with PD may not only be faced with worsening physical symptoms, but simultaneously with the loss of spatial working memory/planning abilities. If the hypotheses are not supported, on the other hand, it may be that patients with early PD simply do not exhibit impaired planning/spatial working memory on the TOC. It also may be that the TOC is not sensitive enough an instrument.

Limitations of the Current Study

The first limitation of this study is that it has limited generalizeability. The PD groups proposed are intentionally homogeneous; therefore, any results may only be relevant to PD patients with similar demographics. In order to counter this, this study design could include PD patients of different race, gender and handedness. Particularly, most PD patients are on some form of medication while the subjects in this study are not. Therefore, although this study may illuminate a discrete group of patients with PD, it may not be representative of the typical clinical population. An additional limitation is that the method for defining group membership (early vs. late) may be flawed. The selected method may not maximize group differences that may exist. Furthermore, the sample size may be too small to allow for true group differences to emerge. Finally, other tests that more specifically measure spatial working memory may add clarity to these findings.

Future Research

Future study designs would be improved by including other tasks in addition to the TOC that readily test other cognitive domains relevant to planning and spatial working memory, such as the token task used by Owen and colleagues (1993a). This is a task designed to test spatial working memory by requiring the subject to complete each trial by searching through several boxes presented on a computer screen for a concealed token. By including this type of task along with the TOC, the study can more specifically determine the impact of a potential spatial working memory deficit upon performance on the TOC.

Future research could focus on other executive domains in the pursuit of more accurate descriptive information on the early PD subpopulation. Especially if the TOC were to be found sensitive to this population, there should be a focus on designing more complex, sensitive tasks to assess mildly impaired early PD patients. A possible future research direction would be to design a longitudinal study and compare PD patients to themselves as they progress in the disease.

Finally, the method for including participants could utilize random selection in order to better represent the typical clinical population of PD. Alternatively, since consecutive cases of PD have been used in other study designs to include all potential PD patients, this method might be utilized to reduce selection bias in the PD sample. Adding a variable of medication type

and/or use also would make a future sample more representative of typical PD patients.

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