PERFORMANCE OVER TIME IN PARKINSON'S DISEASE: THE INFLUENCE OF PROCESSING SPEED AND EXECUTIVE CONTROL

By

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To my husband, Dan and my daughters, Heather and Alyssa, for all they sacrificed so that I could follow my dreams

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
AD	Alzheimer's disease
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
COWA	Controlled Oral Word Association
CRT	Choice reaction time
DLPFC	Dorsolateral prefrontal cortex
DRS-2	Dementia Rating Scale, Second Edition
ERP	Event-related potential
GDS	Geriatric Depression Scale
HC	Healthy control
ISI	Interstimulus interval
OFC	Orbitofrontal cortex
PD	Parkinson's disease
PD-D	Parkinson's disease dementia
RT	Reaction time
SDMT	Symbol Digit Modalities Test
SRT	Simple reaction time
UPDRS	Unified Parkinson's Disease Rating Scale
WCST	Wisconsin Card Sorting Test

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Purpose: The purpose of this study was to examine the role of processing speed and executive demands on within-task performance over time in individuals with idiopathic non-demented Parkinson's disease (PD) and age and education matched non-PD non-demented older adults. The study also investigated the effect of laterality of symptom onset on performance over time.

Background: Individuals with PD are reported to have reduced performance on clinical neuropsychological measures of processing speed and executive function. Little is known, however, as to whether this performance is due to a reduction in output over the duration of individual neuropsychological tests. Sustained behavioral output requires increasing modulation by the prefrontal cortex (Fuster, 1985). In PD, this modulation may be particularly difficult due to disease related disruption of frontal-subcortical circuits and increased resource burden on the frontal lobes. This decline in resources will reduce performance over task duration and with increasing task complexity. To examine this larger hypothesis, there were four specific aims in the current study: 1) determine whether individuals with PD would have increasing difficulty in the latter stages of a verbal fluency test associated with frontal activation (COWA) relative to one

that is dependent upon frontal, temporal and parietal activation (Category Fluency); 2) examine performance over the duration of an increasingly challenging inhibitory task (Stroop) relative to the more automaticized word reading and color naming; and 3) examine aspects of performance over time on computerized tasks shown to be sensitive to frontal lobe deficits (Simple and Choice Reaction Time). These performance patterns are considered in comparison to that of healthy older adults. The effect of oral-motor processing speed was measured using the Symbol Digit Modalities Test (SDMT), a task designed to measure mental speed while limiting the influence of graphomotor speed. Further, the current study examined the role of disease severity, side of symptom onset, and other potential contributors to reduced output over time (e.g., apathy, depression).

Methods: Participants included non-demented patients with idiopathic PD (n=40) and non-PD peers (n=40) that matched on age, education and medical comorbidity (all $p>.05$). Neuropsychological tasks were divided into 15-second intervals and analyzed in mixed repeated measures analyses of variance. Follow up analyses examined the role of basic oral-motor processing speed in performance patterns using the Symbol Digit Modalities Test. Reaction times were examined first by breaking 56 trials into 4 blocks and using the average of each interval as the dependent variables. Reaction time was further examined across different interstimulus intervals. All analyses were repeated using only the Parkinson's group divided by side of symptom onset.

Results: A group by interval repeated measures analysis of variance was used to examine performance over time on neuropsychological and reaction time tasks. Aim 1: both the PD group and controls declined in verbal output over time on the letter fluency

task, [F(3,234) = 203.926, p < .001]; however, as predicted the PD group demonstrated a more rapid decline in the last interval [F(1,78) = 4.322, p = 0.041]. This interaction effect remained even after the magnitude of the effect was p by controlling for processing speed using the oral SDMT [F(1,77) = 5.460, p = .022]. On the category fluency task, the PD group produced fewer words overall than controls F(1,77) = 5.090, p = .027 and both groups declined in verbal output over time F(3,231) = 71.504, p < .001. There were no interactions between group and any interval (all p-values > .05). Both between group and within interval differences on category fluency were completely controlled by processing speed (all p-values > .05). Aim 2: The PD group generated fewer correct responses than controls on Stroop Word Reading F(1,75) = 12.640, p = .001, and Stroop Color Naming F(1,75) = 4.378, p = .040 but not on Stroop Interference, a task requiring inhibition of a competing automatic response. There was a main effect of interval on all three tasks [Word: F(2,150) = 37.528, p < .001; Color: F(2,150) = 65.367, p < .001; Interference: F(5,375) = 8.690, p < .001]; planned comparisons revealed significant differences between all levels on Word Reading and Color Naming but only during the first two intervals on Interference. Controlling for processing speed and apathy explained most of these effects. Aim 3: Performance on simple and choice millisecond reaction time did not change over task duration for either group [Simple: F(1,76) = 3.412, p = .069; Choice: F(1,77) = .874, p = .353]. On the choice task there was a significant main effect of quartile regardless of group F(2.428, 186.928) = 12.661, p < .001 with the first quartile reaction time faster than subsequent quartiles. There were no significant effects on the SRT over time. There were no between group differences on either RT task when data were evaluated by ISI but there were significant main

effects of ISI on both the SRT and CRT task driven by slow RTs at the 3 and 4-second (shortest) interstimulus intervals. Aim 4: Follow-up analyses showed that individuals with right-sided onset were consistently slower across all conditions; however, due to insufficient power, this did not reach statistical significance.

Conclusions: Overall, there was mixed support for slowing over time that was only partially explained by processing speed. Furthermore, the predicted pattern of decline in the latter intervals this pattern was only evident on tasks requiring internally generated responses (i.e., verbal fluency). There was some evidence that the decline in output may occur even in the earlier stages of task performance. These findings suggest the potential benefit of examining performance patterns over time during neuropsychological evaluations as they may be a measure sensitive to early cognitive decline.

CHAPTER 1
BACKGROUND AND LITERATURE REVIEW

Parkinson's Disease and Concerns for Cognitive Deficits

Incidence and Prevalence of PD

Parkinson's disease (PD) is a progressive, neurodegenerative disorder that is estimated to affect over a million individuals in the United States, with approximately 50,000 more diagnosed each year (NINDS, 2006). Parkinson's is considered to be a disease of aging with the average age of onset between 40 and 70, peaking during the sixties (Apetauerova, 2005); however, only about 4-5% are diagnosed before the age of 50 (Van Den Eeden, et al., 2003; Wickremaratchi, et al., 2009). With the increasing number of individuals in the U.S. over the age of 60, we can expect the prevalence and incidence of PD to increase as well. In fact, recent studies project that the prevalence of Parkinson's disease worldwide will double from approximately 4.1 to 4.6 million in to an estimated 8.7 to 9.3 million in 2030 (Dorsey, et al., 2007). Individuals with PD also have a greater likelihood of dementia relative to that of non-diseased age matched peers (Emre, 2003). It is therefore vital that both the clinicians and researchers improve their understanding of the cognitive symptoms and cognitive progression of PD.

Symptoms of PD – More Than Just Motor:

Although most people often classify PD as a motor disorder (resting tremor, bradykinesia, rigidity, and postural instability (Jankovic, 1992), there are other symptoms that may be even more debilitating. Progressive cognitive impairment is unfortunately common. The majority of PD patients who survive more than 10 years after the onset of PD will eventually develop dementia (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). In fact, the prevalence of dementia in PD is 25 to 40%;

this is a risk 1.7-5.9 greater than that of ‘healthy’ adults (Aarsland, et al., 2003; Emre, 2003; Marder, Tang, Cote, Stern, & Mayeux, 1995). These estimates of dementia, however, may actually under-represent the prevalence of cognitive impairment at earlier stages of the disease (Troster & Woods, 2007).

At the time of diagnosis, neuropsychological changes such as cognitive slowing and mild executive deficits are often reported. With careful neuropsychological evaluation subtle changes in cognition can be detected during the early stages of PD—as early as at the time of initial diagnosis (Troster & Woods, 2007). Although many patients diagnosed with PD may develop dementia over the course of the disease, PD itself is not a dementia syndrome. It is more likely that PD dementia lies at the end of a continuum of cognitive decline with individual variability in the rate of progression. This is why it is so important to study cognitive performance in the early stages of the disease process to recognize prodromal symptoms and functions that may underlie later, more advanced cognitive dysfunction.

The neuropsychological deficits observed in PD are similar to those demonstrated in other subcortical syndromes. Individuals with subcortical disruption such as small vessel vascular disease, Huntington’s and multiple sclerosis, demonstrate forgetfulness, slowed information processing, and difficulty manipulating acquired information (Salmon, Heindel, & Hamilton, 2001). Relatively preserved functions are visuoperceptual and semantically-based language skills (Bonelli & Cummings, 2008). Learning and memory profiles of individuals with PD or other subcortical diseases are marked by compromised learning due to poor processing speed rather than pure encoding deficits due to entorhinal/hippocampal degeneration, per se. Indeed,

processing speed deficits appear to be the hallmark trait of PD. A number of studies have examined cognitive changes associated with PD ranging from fundamental processes such as processing speed and attention, to the more complex functions such as memory and executive abilities. The following review of recent research illustrates the many cognitive differences found between healthy older adults and those with PD.

Information processing speed

Information processing speed (i.e., bradyphrenia) is the most well known cognitive deficit in PD (Hanes, Pantelis, Andrewes, & Chiu, 1996; Rogers, 1986; Sawamoto, et al., 2007). Individuals with PD have been shown to be slower on tasks such as word reading and color naming on Stroop task (McKinlay, Dalrymple-Alford, Grace, & Roger, 2009), Trails A and Digit-Symbol coding tasks (Dujardin, et al., 2007; Goldman, Baty, Buckles, Sahrmann, & Morris, 1998).

Observations of cognitive slowing in PD over and above that of normal age related change is particularly convincing when assessed using tasks that are not dependent upon reaction time variables, which can be confounded by the motor component of PD (Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002). Hanes, et al., (1996) showed that it took PD patients disproportionately longer to solve increasingly difficult items on the Tower of London task. This effect remained even after controlling for age, motor performance, intelligence and depression.

Sawamoto et al. (2007; 2002) compared PD patients and healthy age-matched controls on a working memory task where they manipulated the presentation rate to observe the impact of processing speed demands on performance. Using functional MRI, participants were presented with a day of the week which was followed by a random number from 1 to 3. Participants used the number stimulus to advance the

weekday (e.g., given Monday as a starting point followed by ‘2’, the participant would have to mentally note that the day was now Wednesday; the next number ‘1’ would mean advancing by one day with the result being Thursday). After a designated number of trials, the participant had to identify the ending point weekday, which was used as a measure of accuracy. PD patients performed well at slower presentation rates but made errors at the faster rate. This demonstrated that the PD patients could perform the task until processing speed demands were increased.

Revonsuo and colleagues (Revonsuo, Portin, Koivikko, Rinne, & Rinne, 1993) argued that to analyze information processing speed properly, one must consider different levels of processing speed. Automatic processes “are fast, unconscious, informationally isolated and not in contact with other processes or information from other sources in the system;” whereas controlled or more effortful processes such as problem solving and decision making are “slow, effortful and attention-demanding” (p. 90). They used a series of simple-choice reaction time tasks to determine whether slowed information processing was present in both automatic and controlled tasks in cognitively preserved and mildly impaired PD groups compared to controls. They found significant differences in slowing of automatic processes using reaction time to a visual stimulus between all groups, suggesting that slowing in Parkinson’s is evident even at the most rudimentary level.

Event-related potential (ERP) studies have also provided evidence supporting slowed information processing by measuring the latency between a stimulus and P300 activity. One study accomplished this by having participants press a button whenever they saw a word from an infrequent semantic category (plants, 20% frequency) and

withhold response when words from the more frequently represented category appeared (animals, 80% frequency), PD patients consistently had a slower P300 latency compared to age-matched controls, suggesting that the brains of PD patients were slower to respond to stimuli. They did not show differences in N200 or P200 suggesting that basic sensory processing was normal. Although P300 ERPs cannot localize response they are an effective measure of processing speed.

In contrast, some researchers have argued that there is no cognitive slowing that cannot be accounted for by age related decline or motor impairment. For example, Phillips and colleagues (Phillips, et al., 1999) argued that that slowing in PD patients could be fully explained by a combination of age and their motor symptoms. They demonstrated this by using an inspection time paradigm where two lights were flashed with an interstimulus interval ranging from 20 to 250 ms and the participant had to report which light flashed first. Response accuracy for each ISI was used to determine the maximum speed at which 95% of responses are correct. What is particularly nice about this approach is there is no motor input required. They found that while the control subjects were slightly more accurate on shorter ISI trials, there was no significant difference between the two groups. They concluded that PD patients do not demonstrate any cognitive slowing that could not be explained by age-related declines.

Smith, Goldman, Janer, Baty & Morris (1998) carefully controlled a number of potential confounds in both the patient and control samples in their study. They excluded anyone from either group that scored higher than zero on the Clinical Dementia Rating scale. Control subjects with any sign of motor difficulty such as tremor were also excluded. Participants performed a number of speeded same-different

discrimination tasks using a computerized, voice-activated reaction time measure. The tasks were verbal, quantitative and spatial, and difficulty level was either easy or hard. Across all measures, there was no difference between patients and controls performance.

Taken together, there is evidence that underlying processing speed impairment is present in patients with PD. As illustrated above, there is a wide range of methods used to quantify processing speed that have been used to study very heterogeneous samples of PD patients, which undoubtedly contributes to contradictory findings between studies.

As you can see, slowed information processing speed in PD has been demonstrated across a range of measures. Some measure bradyphrenia directly (e.g., ERPs) while other infer cognitive slowing indirectly from behavioral observation in which individuals with PD take longer to complete tasks compared to their non-PD peers. One challenge in these studies is to separate bradyphrenia from a number of confounds. In PD for example, many individuals have a prevalent motor component making it difficult to parse motor from cognitive speed. Second, mood disturbance such as depression and apathy have been reported in patients with idiopathic PD and may contribute to slowing. Third, it is unclear if bradyphrenia in PD is age-related slowing exacerbated by motor dyscontrol or an early indicator of a prodromal dementia. Furthermore, and perhaps most importantly, it is unclear whether bradyphrenia is a constant state of mental slowing or if it fluctuates over time and task.

Attentional processes

Aside from slow processing speed, sustained attention is described as impaired in Parkinson's disease (Bublak, Muller, Gron, Reuter, & von Cramon, 2002; Matsui, et al., 2006; Postle, Locascio, Corkin, & Growdon, 1997). Sustained attention or vigilance

refers to one's ability to maintain focus on a single task over time (Lezak, Howieson, & Loring, 2004). Traditional neuropsychological measures have been used to quantify basic sustained attention in PD. For example, studies have shown that PD patients are able to complete forward digit span tasks as well as age-matched controls (Muslimovic, Post, Speelman, & Schmand, 2005; Revonsuo, et al., 1993).

Deficits in sustained attention have been associated with the presence of dementia. For example, Mayeux, Stern, Sano, Cote & Williams (1987) used the Continuous Performance Test (CPT) to measure sustained attention in a group of PD patients, patients with probable Alzheimer's disease (AD), and age-matched controls. They found that PD patients were slower and less accurate on the task than controls and individuals with AD. When they created a subgroup of error-prone patients with PD they found that these individuals performed similarly to an AD group on a number of global, memory, and reaction time measures, while the remaining PD group was no different than controls. They concluded that bradyphrenia as a disorder of attention and vigilance was likely indicative of prodromal PD dementia but not PD in general. In other words, it was errors in addition to slowing that predicted cognitive impairment.

Language

Language functions have been found to be largely intact in PD (Taylor, Saint-Cyr, & Lang, 1986) except when tasks are based on speeded responses. For example, some (Muslimovic, et al., 2005; Zgaljardic, et al., 2006) have shown that nondemented individuals with PD produce less output on timed letter and category based verbal fluency tasks relative to non-PD peers, while others (Bondi, Kaszniak, Bayles, & Vance, 1993; Goldman, et al., 1998) have found no such differences. The dependent variable in all of these studies was a total fluency score. It is possible that the discrepancy between

these studies may partially relate to the test type (letter versus animal) and how the output was measured. Perhaps examining the pattern of output over the course of the fluency tasks would have helped elucidate more subtle difference between PD and control groups.

Although it is not a timed task, confrontational naming difficulty has also been reported in Parkinson's (Goldman, et al., 1998; Muslimovic, et al., 2005), yet it is widely considered relatively intact by others. Comprehension of written material and knowledge of writing are relatively preserved (Troster & Woods, 2007), however, some have reported difficulty with complex syntax (Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992; Skeel, et al., 2001). Oftentimes patient samples include a range of cognitive impairment including PD-D that may account for these discrepant findings between studies.

Visuospatial perception

Visual perception and spatial abilities are generally intact in individuals diagnosed with PD, especially relative to the prominent deficits observed in speed and attention domains. This is, however, a topic under debate within the literature (Muslimovic, et al., 2005). Performance on line orientation judgment tasks that measure one's ability to estimate relationships between line positions and match them to a key is generally poorer in individuals with PD when compared to age-matched controls (Finton, Lucas, Graff-Radford, & Uitti, 1998; Levin, et al., 1991; Montse, Pere, Carme, Francesc, & Eduardo, 2001; Muslimovic, et al., 2005). Others have argued that individuals with PD perform worse than controls on facial recognition tasks (Kida, Tachibana, Takeda, Yoshikawa, & Okita, 2007; Levin, Llabre, & Weiner, 1989; Pereira, et al., 2009). Furthermore, PD patients have greater difficulty correctly identifying facial emotions

(Clark, Neargarder, & Cronin-Golomb, 2008; Sprengelmeyer, et al., 2003). A similar pattern of performance has been shown on more complex visual form discrimination in which one must identify an exact match from an array that includes stimuli with subtle discrepancies from the target (Pereira, et al., 2009).

In contrast, a number of researchers found no differences between healthy controls and PD patients on facial recognition tasks (Adolphs, Schul, & Tranel, 1998; Pell & Leonard, 2005). Others have argued that between group differences on line orientation and facial recognition are rendered nonsignificant after controlling for frontal dysfunction (Bondi, et al., 1993). Many studies have found mixed results within their own samples. For example, Muslimovic et al. (2005) found significant differences between controls and PD patients on line orientation and spatial tangram-like task, but not on clock drawing. In the Bondi, et al. (1993) study, PD patients were worse than controls on Picture Arrangement and facial recognition but not on Block Design or visual form discrimination.

One explanation for differences on these tasks may lie in neuroanatomical function of the visual system. Once information travels from the retina to the primary visual cortex, it feeds forward into association cortex along two pathways. One pathway carries information ventrally into the temporal lobe where features such as color and form are processed to facilitate object recognition. A second pathway carries information dorsally to the parietal lobe where features such as motion and spatial relationships are processed to facilitate spatial location in relation to an individual. The dorsal stream also has intense fiber tracks leading to the frontal lobes and it may be that visuospatial deficits occur when reciprocal input from the frontal lobes is required.

Verbal learning and memory

A number of different approaches have been used to characterize memory function in patients with PD. As with many studies examining cognitive function in PD, there is a wide range of methodological differences that may, in part, explain the mixed results found in memory performance.

One of the most commonly used measures of memory in both clinical and research settings are list-learning memory tasks. PD patients typically demonstrate a pattern of retrieval difficulty for recently learned information during free recall but improve when provided with semantic cues or yes-no conditions in typical recognition trials (Ivory, Knight, Longmore, & Caradoc-Davies, 1999; Lichter, 2001; Troster & Woods, 2007). For example, newly diagnosed PD patients performed significantly worse on the Rey Auditory Verbal Learning Task immediate and delayed recall trials but their recognition performance was comparable to the healthy control group (Muslimovic, et al., 2005). Similar findings have been shown using the California Verbal Learning Test and the Hopkins Verbal Learning Test. However, some have argued that because PD patients endorse a disproportionate number of false positive errors, even memory recognition is impaired (Higginson, Wheelock, Carroll, & Sigvardt, 2005).

One explanation for poor immediate list-learning memory performance has been attributed to poor learning strategies with failure to use semantic clustering to facilitate learning and/or an over reliance on serial clustering. It is notable that successful mastery of a supra-span word list requires a number of frontally mediated processes such as attention to the words as they are presented, freedom from distractibility, working memory to hold presented words while listening to additional words, and above all, an effective strategy for organizing the information into chunks of associated

material to facilitate encoding and recall. All of these cognitive components also require sufficient processing speed to function efficiently.

Another frequently used measure of verbal memory reported in the literature is story memory, particularly the Logical Memory subtest from the Wechsler Memory Scales. Memory for stories has an added contextual component that, in theory, often facilitates better recall particularly for remembering major story elements. Several studies have demonstrated however, that PD patients perform more poorly than healthy controls on delayed recall of stories (Goldman, et al., 1998; McNamara, Durso, & Harris, 2006). Although there is a recognition component to Logical Memory, the results are rarely reported in empirical studies so it is difficult to confirm if the retrieval deficit pattern observed on list-learning is present in story memory.

Higher level executive function

Although processing speed and attention are certainly components that influence executive functions, this review section is focused on higher level processes such as working memory, planning, organizing, reasoning and cognitive control. PD patients have consistently shown impairment on tasks of working memory. The backward digit span task, for example, requires holding a string of digits in their presentation order and then mentally manipulating them to produce a response in the reverse order. PD patients have been shown to be impaired on this task (Bublak, et al., 2002; Goldman, et al., 1998; Muslimovic, et al., 2005; Zgaljardic, et al., 2006). In fact, a recent meta-analysis reported that data from 14 empirical studies revealed moderate to large effect sizes for digit-span backwards when PD patients were compared to normal controls (Siegert, Weatherall, Taylor, & Abernethy, 2008).

Many of the reported “deficits” in executive functioning are confounded by the effects of dysfunctional processing speed and attention. For example, Dujardin and colleagues (2007) used the PASAT to examine working memory in PD. They found that the PD group performed more poorly at the fastest presentation rate (1.6s) while only the more advanced PD group performed worse than controls on the slower presentation rate (2.8s). They found that performance on the PASAT was highly correlated with an oral symbol substitution task and a Stroop composite of word reading and color naming suggesting that much of the effect was driven by processing speed.

Functional neuroimaging studies have also made the link between working memory and frontal-subcortical circuits. In the Sawamoto (2007) working memory task described in the previous section (i.e., keeping track of days of the week according to digit presentation), functional MRI revealed activated regions of the anterior striatum, dorsolateral and superior medial regions of the prefrontal cortex, and cerebellum in both controls and patients. As the presentation rate increased, activity in the anterior striatum increased in controls but not PD patients. Interestingly, the activation in the PD group was much more diffuse and also included increases in the inferior temporal lobe.

Tower paradigms involve planning a series of moves to reach a specific solution while following a number of rules. Tower tasks must be completed within a certain number of moves and limited time frame. One variation, the Tower of Hanoi, was used to examine the performance of patients with PD, Huntington’s disease and schizophrenia compared to healthy controls (Hanes, et al., 1996). Results from this study revealed that individuals with PD took progressively longer as the items became more difficult, and the slope of the increased reaction time was much steeper than seen

in the other groups. This suggests a disproportionate increase in processing time needed to solve problems of increasing complexity.

The Wisconsin Card Sorting Test (WCST) is a task designed to study problem solving, set shifting and abstraction (Lezak, et al., 2004). Muslimovic and colleagues (2005) examined performance on the WCST in a sample of newly diagnosed PD patients and found that they completed fewer categories, and made more errors and perseverations than the comparison group.

Other important considerations: Apathy and depression

Apathy is syndrome that includes loss of motivation, indifference to one's surroundings, and emotional flattening not due to depression, cognitive impairment or consciousness (Marin, 1991; Pluck & Brown, 2002). In contrast, depression is characterized by low mood and loss of interest as well as feelings of guilt, worthlessness and suicidal ideation (Aarsland, Marsh, & Schrag, 2009; American PsychiatricAssociation, 2000; Zgaljardic, et al., 2007). Depression and apathy have been identified as distinct clinical syndromes that occur in PD (Aarsland, et al., 1999; Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006; Levy, et al., 1998), while others have claimed that apathy largely overlaps with depression (Oguru, Tachibana, Toda, Okuda, & Oka; Starkstein & Leentjens, 2008).

A number of studies have examined the influence of depression and apathy on cognition in PD (Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Varanese, Perfetti, Ghilardi, & Di Rocco). One group of researchers found that depression and apathy were only weakly correlated in their sample and that increased apathy but not depression was highly predictive of poor executive functioning (Butterfield, et al., 2010). In fact, apathy may be predictive of future cognitive decline

and dementia (Dujardin, Sockeel, Delliaux, Destee, & Defebvre, 2009). This may explain why depressed PD patients with higher levels of baseline cognitive function are more likely to respond to antidepressant medications (Dobkin, et al., 2010). Apathy may be related to motor symptom severity suggesting that both may progress in parallel as a function of disrupted subcortical circuitry (Pedersen, Larsen, Alves, & Aarsland, 2009).

Summary of cognition in PD

It is clear from the literature that individuals with PD frequently demonstrate cognitive difficulty in a number of domains. As this review illustrates however, these findings are inconsistent between and within studies and can vary according to a number of patient and control sample variables demonstrating the need to address such confounds. While it is fairly well accepted that many of these impairments are secondary to reduced working memory efficiency and cognitive slowing (Anderson, et al., 2000; Craik, Govoni, Naveh-Benjamin, & Anderson, 1996; Lee, Grossman, Morris, Stern, & Hurtig, 2003; Stebbins, et al., 2002; Stebbins, Gabrieli, Masciari, Monti, & Goetz, 1999), some researchers suggest otherwise. For example, some investigators reported a more generalized pattern of impairment involving memory, abstract reasoning and visuoperception (Levin, et al., 1989) or dominantly abstract reasoning and memory that may be distinct from cognitive slowing and working memory (Muslimovic, et al., 2005). Although some of these impairments suggest cortically-based deficits, it is likely these are secondary to attentional dysfunction due to disruption of the frontal-subcortical circuitry.

It is also important to remain mindful that information processing speed is an important component process in all cognitive abilities and, like attention, is likely to have a pervasive influence across tasks. In the cognitive aging literature, the declining ability

to quickly process information has been implicated as the underlying factor in other areas of cognitive performance (Salthouse, 1996). This is a relevant consideration in PD given the prominent behavioral presentation of both motor and cognitive slowing in many patients. Differences in cognitive domains such as memory, problem solving, and perceptual ability are all driven by speed; when it takes longer to integrate information from one's environment, manipulate it and then respond, chances are higher that important details will be missed or lost. Furthermore, it is unclear if processing speed is a constant state or rather fluctuating in response to task demands.

Pathology of PD

The pathology of the cognitive deficits is theorized to involve frontal-subcortical (basal ganglia) impairment. The pathology of PD motor symptoms has been traced to a small nucleus of cells called the substantia nigra, a midbrain structure named for its dark pigmentation that serves as a critical component of the basal ganglia. The basal ganglia are a group of interconnected subcortical nuclei that also includes the caudate, putamen, globus pallidus and the subthalamic nucleus. Research suggests that once 70-80% of these dopaminergic cells degenerate clinical symptoms begin to appear (Rao, et al., 2003). Dopamine depletion in the basal ganglia results in disruption of important circuits that facilitate movement, motivation, information processing, self-monitoring, and higher intellectual function.

Frontal-Subcortical Circuits

Intricate circuitry connects the basal ganglia nuclei to the frontal lobes. Alexander, DeLong & Strick (1986) identified a number of parallel yet separate basal ganglia circuits that facilitate both motor and cognitive functioning. Conceptually, these circuits work like a funnel—receiving multiple inputs from the frontal lobes that are integrated as

they move through the circuit becoming more refined before being fed back to the originating frontal lobe region. These circuits begin with input from the motor and association cortices of the frontal lobes that project to discrete, generally non-overlapping regions of striatal nuclei (i.e., the caudate and putamen). From the striatum, inputs are projected sequentially to specific, topographically organized areas of the globus pallidus, substantia nigra and thalamic nuclei before being signaled back to the originating, circuit-specific areas of the prefrontal cortex (Figure 1-1). Through the use of neurotropic viruses, a number of additional circuits and subcircuits have since been identified which refined the specificity of these models (Middleton & Strick, 2001).

These basal ganglia circuits can be subdivided into two categories, motor and "complex" cognitive circuits. This distinction is most prominent at the level of the striatum. First, motor inputs from the primary motor and somatasensory cortices are transmitted primarily to the putamen. Just as these primary cortical regions are topographically organized so is the putamen. This primary motor circuit also receives input from the premotor and supplemental motor cortices and its function is control of body movement. In contrast, the second group of circuits originates primarily in the anterior frontal lobes and projects into the caudate nucleus. Three circuits have been identified that moderate "complex" (compared to motor control) behaviors such as motivation, social awareness, and higher cortical function.

Anterior Cingulate Circuit

The first of these complex circuits is the anterior cingulate circuit (Figure 1-2A), which originates in the anterior cingulate cortex (ACC) and transmits input into the ventral striatum (i.e., the nucleus accumbens). A number of limbic areas also project to the ventral striatum including the amygdala, hippocampus and entorhinal and perirhinal

cortices as well as the anterior temporal lobe and posterior portions of the medial orbitofrontal cortex. It is notable that the ventral striatum receives dopaminergic input from the ventral tegmental area, which lies dorsal and medial to the substantia nigra. The ventral striatum in turn projects to the ventral pallidum, the rostrolateral internal globus pallidus, and the rostrodorsal substantia nigra before it travels to the medial dorsal nucleus of the thalamus and is then projected back to the ACC. Functionally, the ventral striatum has been studied extensively in reward-dependent learning, particularly in relation to drug addiction. This circuit has also been studied for its association with emotion regulation. Disruption in this circuit in PD may explain mood disturbances such as anxiety, depression and apathy. Dysregulation of the nucleus accumbens and limbic regions may explain some of the increased pleasure seeking (e.g, hypersexuality, increased desire for sweets) that have been observed in PD. Furthermore, connectivity to the medial temporal structures associated with memory function may also be disrupted and contribute to the retrieval memory deficit associated with PD.

Lateral Orbitorfronal Circuit

The second of these complex circuits is the lateral orbitofrontal circuit (Figure 1-2B) that originates in the lateral orbitofrontal cortex (OFC) and projects to the ventromedial head, body and tail of the caudate nucleus. Other cortical areas that comingle in these regions of the caudate include projections from auditory and visual association cortex in the temporal lobe as well as input from the ACC. The ventromedial caudate in turn projects to the dorsomedial internal globus pallidus and the rostomedial substantia nigra before it travels to the medial ventral anterior nucleus of the thalamus and is then projected back to the lateral OFC. Functionally, the orbitofrontal circuit is involved in personality, social awareness, emotional regulation, and behavioral

inhibition. Damage to the lateral OFC can result in socially inappropriate behavior (e.g., undue familiarity, disinhibition), environmental dependency (e.g., utilization behaviors, imitation), obsessive compulsive behaviors, and mood disturbance (e.g., emotionally lability, mania). Damage to the lateral OFC has also been associated with perseverative behavior and difficulty switching set. Disruption of the orbitofrontal circuit may explain some of the mood and personality changes observed in individuals with PD, as well as difficulty with complex tasks requiring cognitive control.

Dorsolateral Prefrontal Circuit

The third circuit that modulates complex behavior is the dorsolateral prefrontal circuit, which originates in the dorsolateral prefrontal cortex (DLPFC; Figure 1-2C) and projects to the dorsomedial head of the caudate and along the dorsomedial surface of the caudate body and tail, much like the projections from the lateral OFC project along the ventromedial surface caudate. The dorsolateral expanse of the caudate also receives input from posterior parietal and arcuate premotor cortices. Projections from the dorsolateral caudate terminate onto the lateral dorsomedial section of the internal globus pallidus and the rostrolateral substantia nigra. From there, input is received by the ventral anterior and medial dorsal nuclei of the thalamus before it is projected back to the DLPFC in its synthesized form. Functionally, the dorsolateral prefrontal circuit has been identified as a primary component of many of the broad range of abilities called “executive functions”. This circuit has been implicated in planning and organizing a behavioral response to solve complex problems, shifting and maintaining behavioral set appropriately, activation of remote memory, self-directed independence from environmental contingencies, and generating and executing motor programs (Mega & Cummings, 2001). Executive functions have been consistently identified as a major

area of dysfunction in PD (Cummings, 1993; Lichter, 2001; Mega & Cummings, 2001; Zgaljardic, Borod, Foldi, & Mattis, 2003; Zgaljardic, et al., 2006) and have been linked to disruption of these complex circuits between the prefrontal cortex and subcortical nuclei.

Using Reaction Time Paradigms to Study Disrupted Circuits

Interruption of these circuits has been studied in other patient populations as well. Stuss and colleagues have studied the effects of focal brain damage and identified similar cognitive deficit patterns associated with specific regions of the prefrontal cortex associated with the cognitive circuits discussed above (Stuss, 2006; Stuss & Alexander, 2007; Stuss, Binns, Murphy, & Alexander, 2002; Stuss & Levine, 2002). Using a series of experimental reaction time (RT) tasks they were able to demonstrate systematically that damage at precise locations of the cortex could produce dissociable patterns of behavior (Stuss, et al., 2005). First, a “simple” reaction time task was used in which the patient pressed a target button in response to the letter ‘A’ appearing on the screen. This was repeated over 50 trials in a block, with three blocks completed over the course of the testing period. This task was intended to isolate the component process of attentional activation they term “energization” comparable to the behavioral initiation modulated by the anterior cingulate circuit. Next, a “choice” condition was used that again required the patient to press a target button when the letter ‘A’ appeared and press a second, nontarget button when any of three distractors appeared. It was expected that this added complexity will result in increased RTs for both patients and controls. Previous studies by this group have demonstrated the importance of the DLPFC in sustained and selective attention, inhibition and set maintenance.

One of the strengths of the research by Stuss and colleagues is their effort to identify and isolate component processes involved in higher cortical functions. Their

studies are systematic, well designed and lend themselves well to replication. They have also been able to show how many of these component processes lateralize differently to the right and left hemispheres. For example, superior medial damage, in the right hemisphere in particular, impacts one's readiness to respond. They have also reported that patients with damage to left DLPFC have difficulty establishing a criterion for responding (i.e., establishing "set"), while damage to the right DLPFC results in sustained attention deficits (Stuss, 2006; Stuss, et al., 2002). Unfortunately, all of their studies have used brain injured patients of mixed etiology (e.g., traumatic brain injury, tumor, stroke). Although they have argued that that lesion localization trumps etiology, it remains unclear how diffuse overlaps of damage interact with endpoint function. For instance, it appears from their lesion mappings that areas ascribed to the DLPFC often overlap with the lateral OFC. Furthermore, this body of work rarely looks at RT tasks in conjunction with more traditional neuropsychological tests in the same patients. Taken together however, these studies demonstrate how damage to frontal-subcortical circuitry can occur at the cortical level and produce behavioral patterns similar to those observed with damage to subcortical nuclei.

Within-Task Performance Over Time

An alternative way of understanding cognitive impairment in PD is to look at cognitive slowing over the duration of a task. There is a substantial body of research that demonstrates that PD patients are slower than age matched controls on a variety of tasks, yet very few attempts have been made to describe *how* they are slower. While it is informative to know whether or not groups differ in terms of their overall scores, the actual pattern of performance over time may be more beneficial to understanding subtle differences in how the disease impacts cognitive functioning. Clinical observations

suggest that individuals with Parkinson's disease may actually have difficulty sustaining their performance over the duration of a task—even when the task itself is brief.

One explanation for this lack of behavioral persistence was proposed in a series of articles by Fuster, who proposed that sustained behavioral output requires increasing modulation by the prefrontal cortex (Fuster, 1985, 1997, 2000, 2002). Consistent with the literature on the complex subcortical circuits outlined above, Fuster emphasizes the role of the DLPFC in higher cortical functions critical to supporting behavioral sequences over time. While this concept of temporal organization of behavior is not new, Fuster sought to clarify the role of the prefrontal cortex in sustaining behavior over time. He identified three specific neuropsychological functions necessary to complete any behavioral sequence: ***working memory, "preparatory" or cognitive set, and inhibition*** of competing behavioral responses. These three cognitive functions are critical for organizing action particularly when a task is novel or outside an overlearned, automaticized routine.

One of the best ways to conceptualize this is to consider the delayed matching to sample tasks used in prefrontal cortex research using primates. The animal has to hold in memory where the reward is located from one trial to the next (i.e., active short-term working memory), the steps necessary to retrieve it successfully (i.e., active short-term cognitive set), while inhibiting alternative responses in view. Fuster demonstrated that sustained behavioral output requires increasing support by the prefrontal cortex—the longer the task or the delay, the harder it becomes for the organism to reach the goal. Furthermore, when faced with multiple behavioral options it becomes easier for the individual to be derailed from the appropriate course of action. In other words, the

longer and/or the more complex the task, the more recruitment of prefrontal resources necessary to reach the goal. It can be inferred that in the face of prefrontal dysfunction like that found in PD, task time and complexity are more likely to result in behavioral breakdown. In fact, the cognitive slowing observed in patients with PD may actually be a function of impersistent output on neuropsychological tests, particularly those that require executive control. A handful of recent studies have examined the role of intra-individual variability on cognitive performance in PD in humans and in animals that may help us characterize how cognitive slowing occurs and what other factors influence this behavior.

The Animal Literature on Task Impersistence

In a series of studies, Schneider and colleagues used nonhuman primate models of Parkinson's disease to study cognition (Roeltgen & Schneider, 1994; Schneider & Pope-Coleman, 1995; Schneider, Sun, & Roeltgen, 1994; Schneider, Unguez, Yuwiler, Berg, & Markham, 1988). These animal models are created by exposing various species of monkey to the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which results in a severe loss of pigmented cells in the substantia nigra pars compacta. In order to produce a model representative of early stage PD, they refined a method that produced an animal with cognitive deficits with no or minimal tremor using a chronic, low dose of MPTP over a period of several weeks.

Prior to MPTP exposure, animals were trained to hold down a lever until one of three colored lights was activated then the animal would press a button associated with the illuminated stimulus. When the task was performed correctly, the animal was rewarded with fruit juice. Training continued until they could perform the task at 90% accuracy or greater over several days or weeks. Next, the animals received injections of

MPTP and were tested daily on the conditioned task to monitor changes in performance. After several injections, the animals' performance on the task deteriorated, even before any motor symptoms were appreciated. This was characterized by an increase in task errors and a pattern of "task impersistence"; the animal would initiate the task when first entering the testing chamber but would not continue through the end of a trial. The animal would either stop holding the lever before the light was activated or it would fail to press a button in order to complete the task. The animal could be redirected successfully but would again fail to stay on task (Schneider, et al., 1988).

A later study designed to specifically look at task persistence in MPTP monkeys used a different task requiring the animal to try and access a raisin placed in a clear acrylic box (Roeltgen & Schneider, 1994). Prior to drug exposure the monkey learned to watch the trainer place the reward in the box and they monkey would reach in through the opening on one end and retrieve the raisin (reinforced trials). On one-third of the trials, a clear block was placed in the opening so that it was impossible for the animal to access the raisin (unreinforced trials). The number of reaches and time spent on the task was recorded. In the first experiment after drug treatment, the MPTP monkeys made the same number of reaches on the reinforced trials as the untreated animals but took much longer to complete the task. On the unreinforced trials, the MPTP group made fewer reaches and spent less time on the task, seeming to lose interest or give up more quickly than the untreated group.

A second experiment with the same group of animals was used to determine if the task impersistence observed in the first experiment could be elicited on a more difficult

delayed response task that required more working memory. Briefly, the animal sits on one side of a raised screen and watches as the trainer places a food reward (usually a raisin) in one of two wells and then the screen is pulled down to block the animal's view. While the view is obstructed the trainer covers the wells. When the screen is raised, the animal is allowed to select one of the wells to open and potentially find the reward. They also altered the "impossible" task so that the box was always open but the raisin was placed in different locations inside the box making it more difficult so that it would require more complex problem-solving ability to access the reward. These two tasks were designed to test the relationship between cognitive performance and task persistence. Results of the study found that 1) MPTP monkeys made more no-response (omission) errors and performance (commission) errors on the delayed-response task, and 2) made fewer responses on the difficult trials of the modified "impossible" task. The authors indicate that task persistence is present in tandem with cognitive deficits that are consistent with damage to the dorsolateral prefrontal cortex or areas of the striatum that receive input from the DLPFC.

In a separate study (Decamp, Tinker, & Schneider, 2004) where the delay period was manipulated on the response task, they found that as the delay increases so do the MPTP animal's errors and at the longest intervals, they performed at chance. They also made more no-response (omission) errors and performance (commission) errors, which rarely occurred at all prior to drug exposure. In part two of that study, a cue was provided to ensure that the animal watched the baiting of the food well before the screen was drawn. This addition of a cue improved the animal's performance on all but the longest interval

Taken together, these studies illustrate that when the substantia nigra is ablated to mimic Parkinson's disease in non-human primates, they 1) performed more slowly than controls, 2) were unable to persist on tasks over time, 3) were easily distracted, 4) made more errors than controls, and 5) gave up easily as tasks became more challenging.

Cognitive Impersistence in Humans

Few studies have addressed the concept of "cognitive impersistence" in humans, however in a case study, Heilman and Adams (2003) described a woman who underwent a collosal sectioning as treatment for intractable seizures. As a teenager, the patient had developed a frontal astrocytoma that was successfully resected but complications (i.e., cardiac arrest) led to subsequent damage to her left frontal, parietal and occipital regions. She made a complete recovery, returned to school, and drove a car without incident until she developed seizures 10 years later. At age 31 she had a collosal sectioning and developed severe left hemispatial neglect. Interestingly, this woman presented a year later as "abulic, bradyphrenic, and bradykinetic" and demonstrated "cognitive impersistence" (p.277). The authors reported that on the three learning trials on the HVLT, the patient was able to recall 7, 5, and 3 words on Trials 1 to 3 respectively. On a letter word list generation task (i.e., FAS) she was able to generate 9, 6, and 1 word, respectively. They speculated that because motor impersistence is often associated with attentional neglect and right hemisphere damage, that perhaps this was true of cognitive impersistence as well.

While "cognitive impersistence" is a term that has rarely been used in the literature, the behavior has been reported under different nomenclature. For example, Lamar, Price, Davis, Kaplan and Libon (2002) examined the concept of maintaining mental set—the ability to understand a task and apply the rules of that task through

completion. They proposed that failure to maintain mental set could be defined as differential performance across the duration of the task; specifically, after establishing set output would decrease and errors would increase. This description parallels the concepts of task persistence illustrated by Schneider and colleagues, as well as the model proposed by Fuster and colleagues described above.

In their study, Lamar et al. (2002) compared nondemented controls to patients with Alzheimer's disease, ischemic vascular dementia and dementia secondary to Parkinson's disease on a letter word-generation task (i.e., FAS). They predicted that failure to maintain mental set would be more prominent among subcortical disease patients (IVD and PD) compared to AD and controls. Although it had been shown previously that the subcortical patients consistently produced fewer words on similar tasks, differential performance over time had not been examined. To accomplish this, words generated were recorded in 15-second blocks. Each block was then computed as a proportion of total trial output in order to control for differences in between-group output. They found that, although patients with PD and IVD produced proportionately more words in the first 15 seconds than patients with AD and controls, both of the groups with subcortical pathology had a precipitous decline in output over the duration of the task. They asserted that, while their results replicate previously findings that patients with subcortical disease produce fewer words overall than AD and controls, they further demonstrated an underlying differential capacity to maintain mental set over the duration of the task.

An earlier study by Flowers and Robertson (1985) also examined the role of mental set maintenance in PD patients and controls using an Odd-Man-Out

discrimination task of varying complexity. Briefly, this task involves presentation of a card with three stimuli and the examinee is required to choose the one that doesn't belong based their own selection of a rule (e.g., shape or size). After completing the first set of 16 cards, they repeat the task but are directed to use a different rule. So, if they matched by *shape* on the first set they should match by *size* on the second set. This was repeated for a series of eight trials. Parkinson's patients performed closely to young and older adult controls on the first rule but had difficulty switching to a second rule. Even when the second rule was provided for them, the PD patients had a greater tendency to spontaneously shift back to the previous rule. Perhaps more importantly, the PD patients performed markedly worse (increased error frequency) across subsequent trials compared to their own Trial 1 and to the two control samples. Furthermore, the other groups performed increasingly better (decreased error frequency) across subsequent trials. The authors equate these findings to loss of mental set; however, it also indirectly reflects the same finding of diminishing performance over time and increased error production described in Lamar et al. (2002).

In one of the few other studies looking at performance over time on reaction time (RT) tasks, Stuss and colleagues used a choice paradigm to examine differences between different patients with damage to the frontal cortex. Patients with damage to the right DLPFC showed a gradual slowing over repeated trials with the third and fourth quarters being significantly slower than the second quarter trials (Stuss, et al., 2005). In another such study, researchers used a computerized digit symbol substitution task in which PD participants had to quickly press a specific number key that corresponded to a specific symbol based on a legend at the top of the screen. They found no difference

between speed on the first 20 items compared to the last 20 items (Rogers, Lees, Smith, Trimble, & Stern, 1987) however, this was a within subjects analysis only. It is unknown whether healthy older adults would demonstrate the same pattern.

Statement of the Problem and Rationale

Individuals with PD are reported to have reduced performance on clinical neuropsychological measures of processing speed and executive function. Little is known, however, as to whether this performance is due to a reduction in output over the duration of neuropsychological tests. In fact, cognitive slowing, also known by its medical term, bradyphrenia, is considered one of the hallmark cognitive deficits observed in Parkinson's disease; however, attempts to characterize this behavior have produced mixed and often contradictory results. This is likely due, in part, to methodological problems arising from mixed patient samples, uncontrolled confounding variables such as motor speed, and the variety of timed measures used to broadly quantify “slowed mental processing.” Furthermore, low scores can result from different patterns of performance and the qualitative effects of bradyphrenia have not been closely examined across measures. One study (Lamar, et al., 2002) found that patients with PD dementia (PD-D) performed well during the first 15 seconds of a letter fluency task but their output slowed dramatically over the course of their performance. Other studies have found similar differences between early and late trial performance (Flowers & Robertson, 1985). This suggests that processing speed may not be constant but may actually decline over the time course of a particular task.

One explanation for this pattern is lack of cognitive persistence, an inability to maintain a sustained cognitive performance over time. Such sustained behavioral output requires increasing modulation by the prefrontal cortex (Fuster, 1985, 1987). The

longer a task continues, the greater the demands on the prefrontal cortex. In PD, this modulation may be particularly difficult due to disease related disruption of frontal-subcortical circuits and increased resource burden on the frontal lobes. This decline in resources will reduce performance over task duration and with increasing task complexity. Although it is widely held that individuals with PD score lower on tests of processing speed and working memory compared to controls, the actual reason for this difference is unknown. It is hypothesized that this difference is at least partially explained by a reduction in performance over time. Specifically, we consider a model of performance over time that considers the role of the three frontally mediated “top down” processes suggested by Fuster, mental set, working memory and inhibition, in conjunction with the underlying “bottom up” processing speed (Figure 1-3).

The purpose of this study is to examine the processing speed and executive function deficits in PD as a function of performance over task duration compared to healthy older adults. Understanding the underlying behavioral pattern resulting in reduced performance will inform us about neuroanatomical mechanisms. It may also lead to therapeutic interventions that specifically address sustaining behavioral output over time. Cognitive decline has implications for quality of life, caregiver burden, and financial stress due to medical expenses and/or unplanned disability retirement. In addition to changes in cognitive abilities, the disease process can impact personality and mood placing added strain on interpersonal relationships—possibly impacting caregiver support. Furthermore, identification of cognitive performance in the early stages of the disease process may help understand the functions that underlie later,

more advanced cognitive dysfunction. Early identification of cognitive changes also provides more opportunity for intervention.

Study Aims and Hypotheses

As stated above, the purpose of this study is to examine sustained within task performance in the context of processing speed and executive function in a sample of nondemented patients with idiopathic Parkinson's disease (n=40) and demographically-matched healthy controls (n=40). To examine this larger hypothesis, there were four specific aims in the current study: 1) determine whether individuals with PD have increasing difficulty in the latter stages of a verbal fluency test associated with frontal activation (COWA) relative to one that is dependent upon frontal, temporal and parietal activation (Category Fluency); 2) examine performance over the duration of increasingly challenging inhibitory task (Stroop); 3) examine aspects of performance over time on a computerized task shown to be sensitive to frontal lobe deficits (Simple and Choice Reaction Time); and 4) determine whether side of symptom onset laterality among the PD group would predict cognitive impersistence. These performance patterns are considered in comparison to that of healthy older adults. Further, the current study examined the role of disease severity, side of symptom onset, and other potential contributors to executive dysfunction including apathy.

Aim 1: Determine whether individuals with PD have increasing difficulty in the latter stages of a verbal fluency task associated with frontal activation relative to one that is dependent upon frontal, temporal and parietal activation. Both letter-based and category-based fluency tasks are time-limited and require varying levels of cognitive control to facilitate word generation. For example, while category fluency is dependent on semantically organized, hierarchical networks of semantic knowledge and memory

largely mediated by temporal regions of the language dominant hemisphere, letter fluency requires greater cognitive flexibility and mental search strategies to generate words that are associated by a specific letter or phoneme. It was hypothesized that individuals with PD would produce significantly fewer correct responses than the control group on both tasks overall, but their relative diminished performance over time would only be evident on the letter fluency task. Specifically, it was hypothesized that patients with Parkinson's disease would demonstrate a significantly greater decline in the number of words generated over the length of the task compared to a non-PD comparison group on the letter fluency task but not on category fluency.

Aim 2: Examine performance over the duration of increasingly challenging inhibitory task using a Stroop paradigm. Inhibition of competing responses is an integral component of one's ability to sustain behavioral output over time. The neural substrate for this inhibitory function has been identified through lesion studies and localized primarily in the medial and orbital regions of the prefrontal cortex (Fuster, 1997). The Stroop task was utilized to investigate inhibition performance of patients with PD compared to matched controls. It was hypothesized that individuals with PD would show a greater decline in the latter stages of the Color-Word Interference condition but not on Word Reading or Color Naming. It was expected that as tasks require increasing inhibitory control by the frontal lobes, performance would be increasingly difficult to sustain especially for patients with presumed disruption to prefrontal circuits. While Word Reading and Color Naming trials are relatively simple (word reading is likely the most automatic), the Interference trial requires increased executive control to inhibit the automatic tendency to read the word while providing instead the correct, incongruent ink

color. While all three tasks require continuous performance, it was hypothesized that only the added inhibitory demands during the challenging Interference trial would produce the impersistence effect.

Aim 3: Examine aspects of performance over time on a computerized task shown to be sensitive to frontal lobe deficits. We used a computerized reaction time task modeled after that used by Stuss and colleagues (2005) to assess processing speed and inhibition. Computerized reaction time tasks are more sensitive to timing effects and have the added benefit of precise, unvarying test administration minimizing error. Two subtasks were used. The simple task measures how quickly a participant can press a target key in response to a single stimulus. The choice task measures the speed and accuracy of the participant's reaction to targets and non-target stimuli.

It is hypothesized that the PD group will demonstrate a greater decline in performance (i.e., increased RTs) over the course of the 56 trials than controls on the Choice reaction time task but not on the Simple task. While both groups were expected to take longer to respond on the choice task than on the simple task, it was hypothesized that the PD group would show a disproportionate increase in reaction time over the duration of the choice task. It was further expected that PD patients would not benefit from longer ISI period (i.e., controls will get faster, patient's will not—or at least not as much as the controls.)

Aim 4: Examine the role of symptom onset laterality on performance over time in the same sample of PD and controls for both neuropsychological and reaction time measures assessing speeded performance over time. Previous work by Stuss and colleagues with frontal lobe injury patients suggested that patients with damage to right

frontal regions failed to benefit from the longer ISI. Furthermore, studies of motor impersistence have also implicated the right prefrontal cortex and its role in sustained attention. Therefore, we hypothesized that individuals with left-side symptom onset (i.e., right brain) would demonstrate worse performance over time than those with right-side onset.

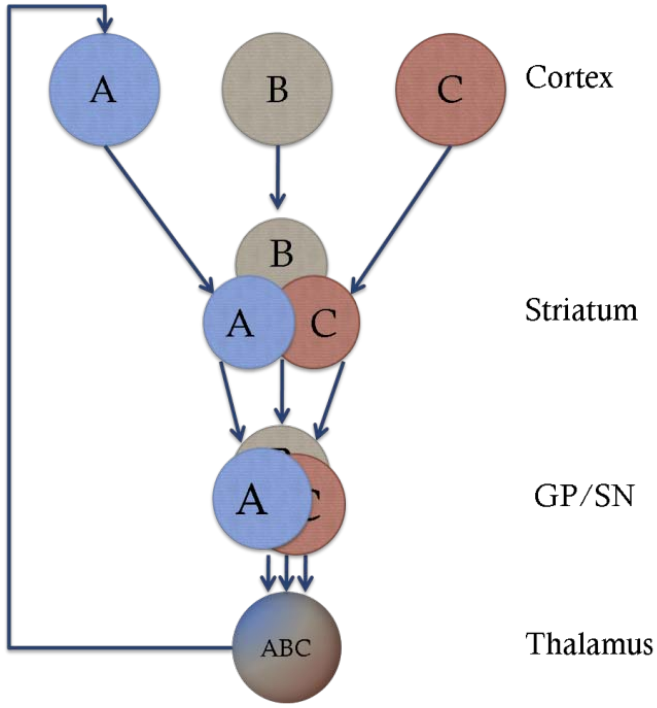

Figure 1-1. General basal ganglia-thalamocortical circuit. Adapted from Alexander, et al. (1986) by J.J. Tanner.

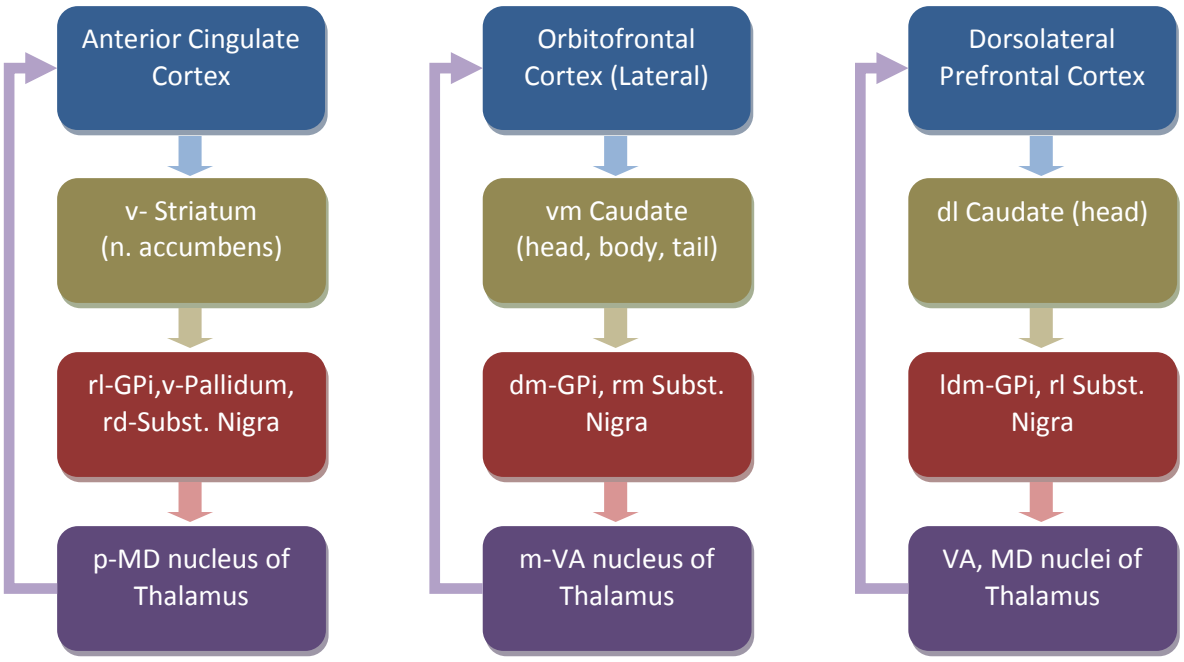

Figure 1-2. The complex cognitive circuits of the basal ganglia. (A) anterior cingulate cortex, (B) lateral orbitofrontal cortex, and (C) dorsolateral prefrontal cortex.

Note: GPi = internal globus pallidus; ldm = lateral dorsomedial; m = medial, md = medial dorsal; n. accumbens = nucleus accumbens; p = posterior; rd = rostrodorsal; rl = rostrolateral; rm = rostromedial; va = ventral anterior; vm = ventromedial

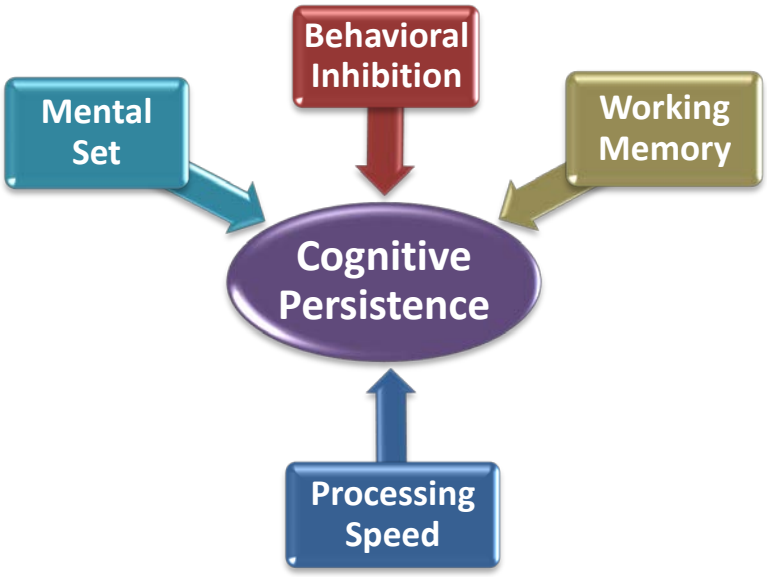

Figure 1-3. Model of "top-down" and "bottom-up" processes supporting sustained performance over time.

CHAPTER 2
METHODS AND PROCEDURES

Participant Recruitment and Screening

Participants diagnosed with idiopathic PD (n=40) were recruited through the University of Florida Movement Disorders Center located at the Shands Medical Plaza complex in Gainesville, Florida. Additional patients were recruited through community service events, public speaking engagements, and referrals from other participants. Healthy controls (n=40) were recruited through existing participant IRB-approved recruitment databases such as the Silver Research Registry and the Participant Registry for Aging Research at the University of Florida. Additional controls were contacted through demographically-specific direct mail address lists and flyers posted in the community.

All participants were age 60 or older with a minimum of 10 years of formal education, predominantly right-handed, and identified English as their first language or learned to speak English before age five. Individuals with PD were diagnosed by a movement disorder fellowship trained neurologist, met criteria outlined by the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Hughes, Ben-Shlomo, Daniel, & Lees, 1992)and had a Hoehn and Yahr scale (Hoehn & Yahr, 1967) ranging from 1-3. All participants were tested while on-medication. All participants had a MMSE ≥ 27 (Folstein, Folstein, & McHugh, 1975) and a total DRS ≥ 130. Exclusion criteria included the following: (1) any underlying medical condition likely to limit lifespan or confound performance (e.g., cancer, dialysis); (2) plans to undergo major surgery during the study period such as deep brain stimulation or other surgery that has been associated with post-operative cognitive dysfunction (e.g., cardiac bypass, joint

replacement); (3) neurological disease other than Parkinson's; (4) major psychiatric disorder; (5) sedating medications (e.g., opiates, benzodiazepines); or (6) any other condition likely to interfere with data collection (e.g., sensory loss, claustrophobia).

Recruitment and data collection for this study occurred as part of a larger ongoing longitudinal study entitled, "White Matter and Cognition in Parkinson's Disease" (UF-IRB #472-2007; Primary Investigator: Catherine Price, PhD) that was reviewed and approved by the University of Florida Institutional Review Board and complied with the ethical principles of the Belmont Report and the provisions of the Common Rule (45 CFR 46, Subpart A) for all research.

Procedure

Study participants were admitted to the General Clinical Research Center at Shands Hospital where they were provided with a private room and had the option of having a spouse or other caregiver accompany them during their stay. During testing, multiple breaks were provided for meals and to reduce fatigue. All study participants received a $50 stipend for their involvement as well as reimbursement for travel expenses.

Neuropsychological Performance Measures

Two established neuropsychological measures requiring speeded performance, the Controlled Oral Word Association Test (Benton & Hamsher, 1989) and the Stroop Color Word Test (Benton & Hamsher, 1989), were selected to examine performance over time for Aims 1 and 2. These tests were chosen due to their known association to frontal lobe damage/dysfunction (Baldo & Shimamura, 1998; Kemmotsu, Villalobos, Gaffrey, Courchesne, & Muller, 2005; Stuss, et al., 1998; Stuss, Floden, Alexander, Levine, & Katz, 2001; Vendrell, et al., 1995; Zysset, Schroeter, Neumann, & Yves von

Cramon, 2006). Performance changes over time were quantified by segmenting each executive function test into 15-second intervals.

Symbol Digit Modalities Test (SDMT)

The SDMT was used as a measure of oral-motor processing speed. The SDMT (A. Smith, 1982) was designed as the oral analog of the Digit Symbol-Coding test. This measure requires the same visual scanning, substitution and memory components as Digit Symbol-Coding while eliminating the effects of graphomotor impairment by providing responses verbally. This makes the SDMT a cleaner measure of cognitive speed in samples with movement disorders such as PD. On this task, the examinee was given a sheet with a series of vertically paired boxes—the top box has a symbol in it and the box below is blank. Participants are instructed to speak the number that goes in the box based on the key at the top of the page. They are instructed to work quickly and sequentially without skipping items. A written administration is optional but was not used in this study. The examinee was given 120 seconds to complete the task and progress is recorded in 15-second intervals. The dependent variable used to control for the "bottom-up" effects of processing speed was the total raw score.

Controlled Oral Word Association Test (COWA)

The COWA is a measure of verbal fluency of words beginning with a specific letter of the alphabet (e.g., F, A, S). Participants were given 60 seconds to generate as many words as possible that begin with letters F, then A, and finally S. There were two rules: a) to refrain from saying proper nouns, and b) to refrain from saying the same word with different endings (e.g., eat, eats, eating). The examiner recorded each participant's responses in 15-second increments. The primary dependent variables used were: 1)

raw correct responses generated in each 15s interval and 2) summed across each letter (F, A, S).

Category Fluency

Category fluency (Baldo & Shimamura, 1998; Lezak, et al., 2004) required participants to produce as many words as possible to the category of “animals” as they can in a 60-second period. The primary dependent variables used were: 1) the raw correct responses generated in each 15s interval for the category, 2) total raw score.

The Stroop Test

The Stroop task (Golden, 1978; Stroop, 1935) includes three basic subtests: Word Reading, Color Naming, and Color Word Interference. The interference trial requires inhibition of the automatic response to read a color word (e.g., “blue”) that is printed in a different color ink (e.g., red) when instructed to name the color not read the word. For all three trials, the examiner recorded the number of completed items in 15-second increments while correcting any mistakes the participant made along the way. Normative data for the Golden (1978) version are based on 45-second administration of each trial; however, in this study, participants are asked to continue reading until they reach the last item. This approach was intended to provide a longer observation of performance in which impersistence may be elicited.

Word Reading

The task is administered by presenting the first of three stimulus cards with six columns of the words “red”, “blue”, and “green” arranged in a random order and printed in black ink. The participant was instructed to read down each column as quickly and accurately as possible. The primary dependent variables used: 1) raw correct

responses generated at each of three 15s intervals, and 2) total correct responses generated in 45 seconds.

Color Naming

On the next subtest the participant is given a second stimulus card that has six columns of 'XXX' printed in red, blue, or green ink in random order. The participant was asked to name the ink colors down each column as quickly and accurately as possible. The primary dependent variables used: 1) raw correct responses generated at each of three 15s intervals, and 2) total correct responses generated in 45 seconds.

Color-Word Interference

The final subtest is the Color-Word interference trial. Again, six columns of the color words were presented but they are no longer black. Instead each word is printed in a different color ink (e.g., the word "red" is printed in green ink). The participant was instructed to name the color of the ink and not read the word. The primary dependent variables used: 1) raw correct responses generated at each of six 15s intervals, and 2) total correct responses generated in 45 seconds.

Reaction Time Paradigms

Based on the Rotman-Baycrest Battery to Investigate Attention (Stuss, et al., 2005), two computer-based reaction time tasks were also used to examine performance over time. The first task was simply a measure of basic reaction time to a single stimulus (Simple) and the second measured reaction time after making a choice between different stimuli (Choice).

Simple Reaction Time (SRT)

One symbol 'A' is presented repeatedly with the instructions to press a target key with the dominant hand as quickly as possible after seeing the stimulus. The

interstimulus interval (ISI) is varied between 3 and 7 seconds and each ISI is repeated randomly 10 times. The ISI is defined as the time between one response and the display onset of the next stimulus. Each stimulus remains on the screen until the participant makes a key press. The SRT task was performed three times throughout the day interspersed with other RT tasks and neuropsychological tests on Day 2. Reaction times are measured from the onset of the stimulus until a key press is made.

Analogous to the within subjects variables used in the neuropsychological analyses, the 56 trials were divided into quartiles (i.e., four equal sets) consisting of 14 consecutive trials each. Means were computed for each of the four quartiles (e.g., quartile 1 was the mean of Trials 1-14). First, the tasks were broken into four quartiles based on trials (Quartile 1 = Trials 1-14, Quartile 2 = Trials 15-28, Quartile 3 = 29-42, Quartile 4 = 43-56) and an average reaction time was calculated for each subject at each quartile. This was repeated for Blocks 2 and 3 and then a grand mean was computed for each quartile across the three blocks. Mean RTs were also calculated for each ISI within each of 4 blocks and then a grand mean was computed for each ISI for each participant. The primary dependent variables were: 1) the grand means for each quartile regardless of ISI, and 2) a grand mean for each ISI.

Choice Reaction Time (CRT)

On this task, four letters (A, B, C, D) are presented randomly, one at a time, each with a 25% probability. Participants are instructed to press the target key when the letter ‘A’ appears and the nontarget key when any of the other three letters appears. ISI rates and frequencies as well as reaction times are measured in the same manner as on the SRT task. The CRT task was performed four times throughout the day interspersed with other RT tasks and neuropsychological tests. RT thresholds for errors in responding are

greater given the added complexity of the CRT task. The primary dependent variables were 1) the grand means for each quartile regardless of ISI and 2) a grand mean for each ISI.

Apparatus for Stimulus Presentation

The stimuli were presented on a Dell Inspiron laptop computer with a Pentium processor and color monitor. The participant was positioned 12 to 15 inches from the screen. The monitor was positioned at an angle of approximately 95 to 100 degrees in relation to the keyboard to minimize glare from overhead lighting. Stimuli were presented as white characters on a black background for maximum contrast. Programming based on Visual Basic 6.0 (Microsoft Corporation). The target key was assigned to '? /' and the non-target key was assigned to 'Z', spaced roughly 7 inches on center.

Covariates of Interest

Geriatric Depression Scale (GDS)

The Geriatric Depression Scale (Yesavage, 1988) consists of 30 yes/no items designed to identify depression in older adults. The GDS assess five criteria areas: sadness, lack of energy, positive mood, agitation and social withdrawal (Sheikh, et al., 1991). The GDS correlates well with other measures of depression. The dependent variable used was the total raw score.

Apathy Scale

A self-report scale adapted from Marin and colleagues (Marin, Biedrzycki, & Firinciogullari, 1991) was used to quantify apathy symptoms. They defined apathy as a lack of motivation that is not better explained by altered consciousness, cognitive impairment or emotional distress. The scale includes 14 items with a range of 0 to 42

points possible. Scores of 14 or higher are considered clinically significant. The dependent variable used was the total raw score.

Unified Parkinson's Disease Rating Scale (UPDRS) – Part III

The UPDRS Part III (Stebbins & Goetz, 1998) is used to quantify the severity of motor symptoms. Part III is based on clinical observations while the patient performs a series of motor movements intended to induce motor symptoms. Inter-rater reliability for Part III is generally quite high (Richards, Marder, Cote, & Mayeux, 1994). In the current sample, interclass correlations indicated strong inter-rater reliability. The dependent variable used was the total raw score.

Statistical Analyses

Demographic, Mood and Disease Variables

Independent samples t-tests examined group differences in group demographic variables (e.g., age, education, gender), mood (depression, apathy), estimated intellectual functioning, and cognitive status. Detailed demographics are shown in Table 2-1. Analyses identified two participants in the PD group that met criteria for clinically significant depression, a condition that frequently occurs in patients with PD. Post-hoc analyses were conducted after excluding these individuals to examine their influence on overall results. Significant between group differences of apathy were found, $t(78) = -2.172$, $p = .033$, and in motor symptoms, $t(78) = 42.455$, $p < .001$; so they were also examined in post-hoc analyses.

Processing Speed

Initial analyses of processing speed were conducted using independent samples t-test. It was expected that significant between group differences would be found on the SDMT consistent with previous research (Dujardin, et al., 2007; Goldman, et al., 1998).

Once confirmed, the SDMT was included as a covariate to control for the effects of processing speed on cognitive impersistence.

Verbal Fluency

Separate mixed between-within analyses of variance were used to analyze data for letter and category fluency. As such, both models looked at differences between the groups, differences between intervals, and the interaction between group and interval. Follow-up analyses repeated the original mixed ANOVA by 1) removing individuals with GDS scores greater than 13; and 2) adding oral motor processing speed as measured by the SDMT as a covariate; and 3) adding apathy as a covariate.

Stroop Task

Separate mixed between-within analyses of variance were used to analyze data for the three Stroop subtests. On the Word Reading and Color Naming trials, many of the participants finished before the 60-second mark; therefore, only three intervals were used in the within-subject analyses. Color Word Interference is more challenging and takes longer to complete all 100 items. As a result, all participants took at least 90 seconds to complete the task thereby providing six within-subject intervals for this task. As described in Verbal Fluency, all Stroop analyses were repeated 1) removing individuals with GDS scores greater than 13; and 2) adding oral motor processing speed as measured by the SDMT as a covariate; and 3) adding apathy as a covariate.

Reaction Time Tasks

Data cleaning followed methods established by Stuss and colleagues (2005). RTs less than 150 ms were excluded on the basis that they were too fast to reflect a true response to the stimulus. RTs greater than 5 seconds were also excluded as omissions. Less than 1% of total responses across participants were excluded. After these extreme

errors were removed, means and standard deviations were calculated for each individual's performance on a given block consisting of 56 trials were computed and outliers (greater than 4 standard deviations outside the mean) were removed.

Disease Onset Laterality

To address the role of disease symptom onset laterality, the same mixed between-within ANOVAs were repeated using only the Parkinson's group divided by side of symptom onset. One individual was excluded from these analyses as his first motor symptoms were classified as axial. See Table 2-2 for revised group demographics.

Table 2-1. Sample characteristics of PD and control groups

	PD group (N = 40)	Control group (N = 40)	
Characteristic	Mean (SD)	Mean(SD)	p-value
Males/Females	33/7	33/7	--
Age	67.60 (5.31)	67.80 (4.83)	0.861
Education	16.27(3.02)	16.50 (2.56)	0.720
WTAR IQ	107.23 (7.30)	108.65 (8.82)	0.433
DRS-2 Total	139.33 (3.56)	140.40 (2.45)	0.124
GDS	4.35 (5.16)	1.60 (2.04)	0.002
Apathy Scale	11.58 (6.42)	9.00 (3.88)	0.034
UPDRS Motor Scale	19.45 (12.01)	2.55 (2.53)	<.001
Disease Duration	7.10 (5.08)	--	--
Hoehn & Yahr Rating	1.44 (0.79)	--	--

Note. WTAR = Wechsler Test of Adult Reading; DRS-2 = Dementia Rating Scale; GDS = Geriatric Depression Scale; STAI = State-Trait Anxiety Inventory; UPDRS = Unified Parkinson Disease Rating Scale

Table 2-2. Sample characteristics of PD patients with right and left-side symptom onset

	Right side onset (N = 26)	Left side onset (N = 13)	
Characteristic	Mean (SD)	Mean(SD)	p-value
Males/Females	21/5	11/2	--
Age	67.65 (5.67)	67.00 (4.56)	0.720
Education	16.04 (3.13)	16.46 (2.82)	0.684
WTAR IQ	106.96 (7.69)	107.38 (6.92)	0.868
DRS-2 Total	139.04 (3.84)	140.00 (3.07)	0.452
GDS	5.31 (5.77)	2.77 (3.32)	0.064
Apathy Scale	11.85 (6.05)	10.54 (7.26)	0.555
UPDRS Motor Scale	18.73 (12.41)	21.69 (11.53)	0.477
Disease Duration	8.19 (5.82)	5.15 (2.41)	0.080
Hoehn & Yahr Rating	1.35 (0.85)	1.62 (0.68)	0.326

Note. WTAR = Wechsler Test of Adult Reading; DRS-2 = Dementia Rating Scale; GDS = Geriatric Depression Scale; STAI = State-Trait Anxiety Inventory; UPDRS = Unified Parkinson Disease Rating Scale

CHAPTER 3
RESULTS

Aim 1 – Verbal Fluency

Letter Fluency (FAS)

The first step was to examine whether overall between group differences could be detected on FAS. Data were reviewed for assumptions of normality. The two participant groups were nondemented patients with idiopathic Parkinson's disease (PD) and matched healthy controls (HC). An independent measures t-test compared the total number of words generated across all intervals on three trials of letter fluency (i.e., FAS) but the differences did not reach statistical significance, $t(78) = 1.76$, $p = .088$.

Next, a mixed between-within analysis of variance (ANOVA) was conducted for letter fluency to examine whether differences were detectable at different within-task intervals. The between-subjects factor was participant group. The within subjects factor was the sum of words generated on the three trials of a letter fluency task (i.e., FAS) at four, 15-second intervals (15 seconds, 30 seconds, 45 seconds, and 60 seconds). Refer to Table 3-1 for word generation by interval data. Levene's test for the homogeneity of variance between the participant groups did not reach significance for any of the within-subjects conditions, so regular F-tests are reported. For the within-subjects factors and their interactions, Mauchly's test was also non-significant, $\chi^2(5) = 5.69$, $p = .338$, indicating that the assumption of sphericity was not violated.

Table 3-2 shows a summary of the analysis of variance. There was a significant main effect of interval $F(3,234) = 203.926$, $p < .001$ but not for group $F(1,78) = 2.784$, $p=.099$ or the interaction of group and interval $F(3,234) = 1.764$, $p = .155$. Planned within-subject contrasts revealed that participants generated fewer words at each

subsequent interval regardless of group. While the interaction main effect between group and interval was not significant, planned within-subject contrasts revealed that significant between group differences emerged during the last interval relative to the previous intervals, $F(1,78) = 4.322$, $p = 0.041$. These findings support the prediction that while both PD and healthy older adults decline in the number of words generated over time on the letter fluency task, individuals with PD produce fewer words than controls during the last interval.

Letter Fluency: Controlling for depression and apathy

Follow-up analyses re-examined results after excluding two participants with depressive symptoms in the clinical range. This ANOVA revealed a pattern of results consistent with the previous analyses. Mauchly's tests of sphericity remained non-significant, $\chi^2(5) = 5.215$, $p = .390$. The main within-subjects effect of time interval was significant $F(3,231) = 199.406$, $p < .001$ and Bonferroni adjusted post-hoc tests on the interval revealed significant differences in word generation between all levels (all p-values < .05). There was no main effect of group $F(1,76) = 1269.176$, $p = .177$, or the group by interval interaction $F(3,228) = 2.116$, $p = .099$. Planned within subjects contrasts demonstrated a significant interaction of group and time, $F(1,76) = 4.591$, $p = .035$ at the last interval, indicating that the individuals with PD generated significantly fewer words than controls during the last 15-second interval relative to output on previous intervals.

Several participants reported clinically significant levels of apathy symptoms (PD: N=16; HC: N=6). Therefore, instead of removing those individuals, apathy was added to the initial mixed repeated measures ANOVA as a covariate. Mauchly's tests of

sphericity remained non-significant, $\chi^2(5) = 5.912$, p = .315. There was no main effect of apathy or the apathy x interval interaction on the dependent variables, F(1,77) = .467, p = .497 and F(3,231) = .431, p = .731. The remaining pattern of results was consistent with the initial model [main effect of interval F(3,231) = 38.234, p <.001, that was significant at all levels (all p-values <.05); no main effect of group, F(1,77) = 2.107, p = .151, or the group x interval interaction, F(3,231) = 1.645, p = .180; however a significant interaction remained during the last interval F(1,77) = 4.462, p = .038].

Letter Fluency: Controlling for speed

Next, a mixed between-within analysis of covariance (ANCOVA) was used to determine whether underlying information processing speed could fully explain the observed performance over time effects described above. This was accomplished by using scores on the Symbol Digit Modalities Test (SDMT) as a covariate in the initial model. Mauchly's tests of sphericity remained non-significant, $\chi^2(5) = 5.19$, p = .393. There was no main effect of group F(1,77) =.710, p = .402 or processing speed F(1,77) = 1.843, p = .179. After controlling for processing speed, only the difference between the first two intervals remained marginally significant F(1,77) = 3.777, p = .056. Importantly, after controlling for underlying processing speed, the group x interval interaction remained significant at the fourth interval, F(1,77) = 5.460, p = .022. Figure 3-1 illustrates the effect of controlling for underlying oral motor processing speed on letter fluency.

Category Fluency

Analyses for category fluency followed those used for letter fluency above. The sample size was reduced due to missing data for one participant in the PD group. An

independent measures t-test compared the total number of words generated across all intervals on a single category fluency trial (i.e., animals) showed that the PD group produced significantly fewer words overall than the HC group, $t(78) = -2.1174$, $p = .033$.

A mixed between-within ANOVA was performed for category fluency. The within subjects factor was the number of words generated (i.e., animals) at four consecutive 15-second intervals (15 seconds, 30 seconds, 45 seconds, and 60 seconds). Refer to Table 3-3 for word generation by interval data. Levene's test for the homogeneity of variance between the participant groups did not reach significance for any of the within-subjects conditions, so regular F-tests are reported. For the within-subjects factors, and their interactions, Mauchly's test was also non-significant, $\chi^2(5) = .955$, $p = .621$ indicating that the sphericity assumption was not violated.

Table 3-4 shows a summary of the ANOVA for Animal Fluency. There was a significant main effect of group $F(1,77) = 5.090$, $p = .027$ and interval $F(3,231) = 71.504$, $p < .001$. Planned within-subject contrasts revealed that there was a significant difference in word generation at each subsequent interval regardless of group. The interaction main effect between interval and group was not significant, $F(3,231) = 1.691$, $p = .170$ nor did within-subject contrasts reveal significant between group differences at any of the 15-second intervals. There was, however, a trend between the first two intervals by group $F(1,77) = 3.734$, $p = .057$, suggesting that the PD group's word generation declined much more quickly during the second interval compared to those in the HC group. These findings support the hypothesis that while between-group differences in category fluency may exist the patterns of decline are roughly parallel between PD and HC participants.

Category Fluency: Controlling for depression and apathy

Follow-up analyses re-examined results after excluding the two participants with depressive symptoms in the clinical range and a consistent pattern of results was found [Mauchly's tests of sphericity remained non-significant, $\chi^2(5) = 3.773$, $p = .583$; group main effect $F(1,75) = 5.284$, $p = .024$; interval $F(3,225) = 69.320$, $p < .001$; interaction $F(3,228) = 1.667$, $p = .175$; no significant planned comparisons]. When apathy scores were added as a covariate a main effect of group emerged $F(1,76) = 3.948$, $p = 0.51$. The remainder of the results indicated there were no other significant changes in the overall model [Mauchly's tests of sphericity remained non-significant, $\chi^2(5) = 3.398$, $p = .639$; main effect of interval $F(3,228) = 10.879$, $p < .001$; apathy $F(1,76) = .473$, $p = .494$; no significant planned comparisons].

Category Fluency: Controlling for speed

Consistent with the letter fluency analyses, a mixed between-within ANCOVA was performed to determine whether processing speed would reveal a performance over time pattern observed in letter fluency output. This was again accomplished by using the SDMT as a covariate in the initial model. Mauchly's test of sphericty was non-significant $\chi^2(5) = 3.70$, $p = .593$. There was a significant between subjects main effect of processing speed $F(1,76) = 11.94$, $p = .001$ but not group $F(1,76) = .265$, $p = .608$ on category word generation. Planned within subjects contrasts revealed that processing speed explained the effect of interval at all levels. There were no significant group x interval interactions. Figure 3-2 illustrates the effect of controlling for underlying oral motor processing speed on letter fluency.

Aim 2 – Stroop Task

Data were reviewed for assumptions of normality and found all dependent variables were normally distributed. Mauchly's tests were not significant for any of the three subtests; therefore, results for the following three analyses were interpreted assuming equal sphericity of within-subject factors. Three participants from the original sample were excluded due to colorblindness.

Stroop Word Reading

A mixed between-within ANOVA was used to examine the number of words read across three consecutive15-second intervals. There were significant main effects of group $F(1,75) = 12.640$, $p = .001$, and interval $F(2,150) = 37.528$, $p < .001$; however, the group x interval interaction was not significant $F(2,150) = .277$, $p = .758$. Planned within-subjects contrasts revealed that significant differences occurred at each interval of word reading output (all p-values <.05) regardless of group but there was no interaction at any interval. Table 3-6 provides a summary of the analysis of variance data.

Stroop Word Reading: Controlling for depression and apathy

Data were reanalyzed after excluding the two individuals with PD with elevated depression symptoms. There was no significant change to the initial model [main effect of group $F(1,73) = 10.196$, $p = .002$, and interval $F(2,146) = 35.294$ but not the group x interval interaction $F(2,146) = .148$, $p = .862$, or the any of the planned contrasts reported above].

Next, a mixed ANCOVA was used to control for the potentially confounding effect of apathy on the dependent variable. There was no significant main effect of apathy, $F(1,74) = .028$, $p = .867$. The rest of the model was consistent with results shown the initial analyses [main effect of group $F(1,74) = 12.152$, $p = .001$, and interval $F(2,148) =$

8.790, p < .001 but not the group by interval interaction, F(2,146) = .164, p = .849.] Controlling for apathy did change the outcome of interval planned comparisons, in that the only significant difference remaining occurred between the first two intervals, F(1,74) = 20.490, p <.001.

Stroop Word Reading: Controlling for speed

Follow up ANCOVA was used to control for the between group differences on the SDMT. There was a significant main effect of SDMT F(1,74) = 6.037, p = .016, on the dependent variable. The main effect of group was moderated by processing speed but remained significant, F(1,74) = 4.291, p = .042, while the main effect of interval no longer reached statistical significance F(1,74) = 2.649, p = .074. Planned contrasts revealed that the only effect of interval was between the first two intervals F(1,74) = 6.351, p = .014. There were no significant interactions of group and interval or SDMT and interval. Figure 3-3 illustrates the parallel pattern of output between the groups before and after controlling for processing speed.

Stroop Color Naming

A mixed between-within analysis of variance was used to examine the number of colors named consecutively across three, 15-second intervals. There was a significant main effect of group F(1,75) = 4.378, p = .040 and interval F(2,150) = 65.367, p < .001. Planned within-subjects contrasts revealed that the significant effects of interval occurred at all levels. There was no significant main effect interaction of group and interval F(2,150) = .462, p = .631 or within subjects contrasts (all p-values > .05). Table 3-7 provides a summary of the analysis of variance data.

Stroop Color Naming: Controlling for depression and apathy

Data were reanalyzed after excluding the two participants in the PD group with elevated depression symptoms. The main effect of group was no longer significant, $F(1,73) = 3.518$, $p = .065$. The remaining main effect and planned contrasts of interval and the group x interval interaction remained consistent with the previous analysis [interval $F(2,146) = 60.640$; interval x group, $F(2,146) = .429$, $p = .652$.significant effects of interval at all levels (all p-values <.001)].

After adding apathy scores to the model using a mixed ANCOVA, the main effect of group was no longer significant, $F(1,74) = 3.589$, $p = .062$, nor was the effect of apathy significant on the dependent variable, $F(1,74) = .435$, $p = .512$. The main effect of interval remained significant $F(2,148) = 10.527$, $p < .001$, and planned contrasts revealed significant differences across all intervals. The interaction between group and interval remained non-significant overall, $F(2,148) = .299$, $p = .742$ and at each interval.

Stroop Color Naming: Controlling for speed

Next, a mixed ANCOVA was performed to determine whether controlling for processing speed would reveal a different pattern of performance over time. There was a significant main effect of SDMT on the dependent variable, $F(1,74) = 30.784$. Subsequently, the main effect of group was no longer significant $F(1,74) = .202$, $p = .655$, nor was the main effect of interval $F(2,148) = .444$, $p = .642$. This suggests that oral motor processing speed as measured by the SDMT explained the observed between and within-subject variance in color naming performance. Refer to Figure 3-4 for an illustration of the results before and after controlling for processing speed.

Stroop Color-Word Interference

The third repeated measures ANOVA examined the between and within subjects effects on the Color-Word Interference trial of the Stroop. This subtest generally takes longer to complete and therefore, a greater number of 15-second intervals were available for analysis. The 77 participants in this sample each completed at least six 15-second intervals. There was a significant main effect of interval $F(5,375) = 8.690$, $p < .001$ but not group $(1,75) = 2.199$, $p = .142$. The main effect of interval $F(5,375) = 8.690$, $p < .001$ was driven entirely by the significant difference between output in the first and second intervals, $F(1,75) = 34.441$, $p < .001$. There was a nearly significant trend of the group by interval interaction, $F(5,375) = 2.164$, $p = .057$; planned comparisons indicated that this was driven by significant group x interval interactions at the fifth and sixth intervals, $F(1,75) = 5.829$, $p = .018$ and $F(1,75) = 4.447$, $p = .038$, respectively. Table 3-8 provides a summary of the analysis of variance main effects and planned contrasts results.

Stroop Color Word Interference: Controlling for depression and apathy

After excluding the patients with clinically significant symptoms of depression, the pattern of results was generally consistent with the previous analysis [main effect of interval $F(5,365) = 8.221$, $p < .001$; group $F(1,73) = 1.583$, $p = .212$; and interaction $F(5,365) = 2.060$, $p = .070$)]. Planned contrasts revealed that there were significant differences between the first and all other intervals except the fifth; the group x interval interaction remained significant only at the fifth interval $F(1,73) = 6.569$, $p = .012$ after controlling for depression.

Next, the initial mixed ANOVA was repeated while controlling for the influence of apathy on the dependent variable. There was no main effect of apathy $F(1,74) = .734$, p

= .394; group F(1,74) = 1.592, p = .211, interval F(2,148) = 1.847, p = .103 or group x interval interaction F(2,148) = 2.055, p = .070. Planned within subjects contrasts revealed significant difference remained between the first and second intervals regardless of group F(1,74) = 6.765, p = .011. In addition, the significant interaction between group and interval was significant at the fifth F(1,74) 5.592, p = .021, and sixth F(1,74) = 4.150, p = .045 intervals.

Stroop Color Word Interference: Controlling for speed

Consistent with previous analyses, a mixed between-within analysis of covariance was performed to control for between-group differences in processing speed. There was a significant main effect of processing speed on the dependent variable F(1,74) = 21.539, p < .001. There were no main effects of group F(1,74) = .523, p = .472, interval F(5,370) = .863, p = .506, or the group by interval interaction F(5,370) = 1.739, p = .125. These results suggest that processing speed explained the observed effects of the initial model in the current sample. Figure 3-5 illustrates the pattern of output between the groups before and after controlling for processing speed.

Aim 3 – Reaction Time Tasks

Data were reviewed for assumptions of normality and all variables of interest were logarithmically transformed to correct for significant skewness and kurtosis. Data were lost for two participants from the HC group due to computer malfunction. Initial plans were to control for between group differences in motor speed based on dominant hand finger tapping speed. This step was skipped however, due to non-significant differences between the groups, t(78) = .587, p = .559.

Simple Reaction Time

A mixed between-within analysis of variance was conducted for the Simple Reaction time (SRT) task. The between-subjects factor was participant group (PD and HC). The within subjects factor was the average reaction times of four consecutive quartiles in a block of 56 trials (i.e., Quartile 1 is the average of Trials 1-14; Quartile 2 is the average of Trials 15-28; Quartile 3 is the average of Trials 29-42; and Quartile 4 is the average Trials 43-56). This was repeated over three blocks and then a grand average was calculated for each quartile.

Refer to Table 3-9 for raw SRT reaction times at each quartile. Levene's test for the homogeneity of variance did not reach significance for any of the within-subjects conditions, so regular F-tests are reported. For the within-subjects factors and their interactions, Mauchly's test was significant, $\chi^2(5) = 25.242$, $p < .001$, indicating that the assumption of sphericity was violated, therefore, Greenhouse Geisser corrections are reported.

Table 3-10 provides a summary of the analysis of variance data for the SRT. There was a non-significant trend for the main effect of group, $F(1,76) = 3.412$, $p = .069$. The main effects of interval and the group by interval interaction were not significant, [$F(2.428, 184.520) = 1.680$, $p = .182$ and $F(2.428, 184.520) = .824$, $p = .460$, respectively.] None of the within subjects planned comparisons for interval or interaction reached statistical significance. The data are also illustrated in Figure 3-6(A).

SRT by quartile: Controlling for depression and apathy

Consistent with analyses conducted on Fluency and Stroop tasks, data were reanalyzed after excluding the two individuals with PD who had elevated depression symptoms. Repeated measures ANOVA was repeated on this smaller sample and

produced similar results [no main effect of group F(1,74) = 2.461, p = .121, quartile F(2.529, 187.137) = 2.347, p = .085, or the group x quartile interaction F(2.529, 187.137) = .639, p = .565.] All planned within subject contrasts were also non-significant.

A subsequent ANCOVA looked at the between and within group differences on RT performance after controlling for the effects of apathy on the dependent variable. There was no main effect of apathy F(1,74) = .027, p = .870, group F(1,74) = 3.333, p = .072, or the group x quartile interaction F(2.406, 180.463) = .537, p = .618. There was a significant main effect of quartile F(2.406, 180.463) = 4.688, p = .007, which planned contrasts revealed were driven by the difference at the third level F(1,75) = 13.179, p = .001.

SRT by Interstimulus Interval

Another way to characterize performance over time is to examine the effect of varying interstimulus intervals on reaction time (e.g., maintaining set while anticipating stimuli over long pauses.) For this set of analyses, the within subjects factor was the average reaction time for all trials with the same ISI (ranging from 3 to 7 seconds) across three blocks of 56 trials each. Refer to Table 3-12 for average of raw SRT reaction times at each ISI. Levene's test for the homogeneity of variance between the participant groups did not reach significance for between-subjects conditions, so regular F-tests are reported. For the within-subjects factors and their interactions, Mauchly's test of sphericity was not significant, $\chi^2(9) = 11.995$, p = .214.

There was a non-significant trend for the main effect of group. F(1,76) = 3.389, p = .070. There was a significant main effect of ISI F(4, 304) = 47.758, p < .001 and

planned contrasts revealed that there were significant differences between each level (all p-values < .05). Post hoc test indicated that the shortest ISIs had the slowest RTs. There was no interaction between group and ISI F(4, 304) = .409, p = .786. Results of the analysis of variance are shown in Table 3-13 and illustrated in Figure 3-7(A).

SRT by ISI: Controlling for depression and apathy

Data were reanalyzed after excluding the two individuals with PD who had elevated depression symptoms. Mauchly's test of sphericity was not significant, $\chi^2(9) = 15.613$, p = .075. The mixed between-within ANOVA revealed the same pattern of results as the initial analysis [no main effect of group F(1,74) = 2.442, p = .122 or group x ISI interaction F(4,296) = .671, p = .612; main effect of ISI F(4,296) = 46.014, p < .001 with significant contrasts at all ISIs.]

Controlling for apathy in a follow up ANCOVA had no effect on the pattern of results There was no main effect of apathy F(1,75) = .033, p = .857, group F(1,75) = 3.325, p = .072, or the group x ISI interaction F(4,300) = .217, p = .929. There was a main effect of ISI F(4,300) = 11.613, p < .001, that was significant at all ISIs except the longest (7s).

Choice Reaction Time

A mixed between-within analysis of variance was conducted for the Choice Reaction time (CRT) task. The between-subjects factor was participant group (PD and HC). The within subjects factor was the average reaction time of the four quartiles (each quartile consists of 14 consecutive trials) across three blocks of 56 trials each. Refer to Table 3-9 for average CRT reaction times at each ISI. Levene's test for the homogeneity of variance between the participant groups did not reach significance for any of the within-subjects conditions, so regular F-tests are reported. For the within-

subjects factors and their interactions, Mauchly's test was significant, $\chi^2(5) = 24.738$, p<.000, indicating that the assumption of sphericity was violated; therefore, Greenhouse Geisser corrections are reported.

The main effect of group was not significant F(1,77) = .874, p = .353, and there was no interaction between group and quartile F(2.428, 186.928) = .792, p = .476. There was a significant main effect of quartile F(2.428, 186.928) = 12.661, p < .001 and planned contrasts revealed that there were significant differences between all quartiles (all p-values < .05). Bonferroni corrected post-hoc tests indicate that reaction time in the first quartile is faster than subsequent quartiles. A summary of the ANOVA data are summarized in Table 3-11 and illustrated in Figure 3-6(B).

CRT by quartile: Controlling for depression and apathy

Removing the two individuals with elevated depressive symptoms did not change the overall pattern of results [main effects of group F(1,75) = .587, p = .446; interaction F(2.391, 179.360) = 1.003, p = .380; and interval F(2.391, 179.360) = 11.885, p < .001]. Planned contrasts and post-hoc tests for quartile were also consistent with the initial results.

Adding apathy as a covariate to the model moderated the main effect of interval F(2.428, 184.507) = 2.331, p = .089, which planned contrasts revealed that only the third quartile remained significantly slower than the average of the previous quartiles. There was no main effect of apathy on the dependent variable F(1,76) = .453, p = .503.

CRT by Interstimulus Interval

Consistent with the SRT analyses, the CRT data were also examined for the effect of varying interstimulus intervals on reaction time. Again, the within subjects factor was the average reaction time for all trials with the same ISI (ranging from 3 to 7 seconds)

across four blocks of 56 trials each. Mauchly's test was not significant, $\chi^2(9) = 15.494$, $p = .078$, indicating that the assumption of sphericity was not violated. There was no main effect of group $F(1,77) = .875$, $p = .353$, or the group x ISI interaction $F(4,308) = .128$, $p = .972$. There was a significant main effect of ISI on the CRT, $F(4,308) = 12.303$, $p < .001$ and planned contrasts revealed that were significant differences between ISIs except between the 3 and 4-second ISIs. A summary of these findings is shown In Table 3-14 and illustrated in Figure 3-7(B).

CRT by ISI: Controlling for depression and apathy

After removing two patients with high levels of depressive symptoms, the overall pattern of results remained consistent with the initial results [main effect of group $F(1,75) = .591$, $p = .444$, ISI $F(4,300) = .097$, $p = .983$, and the group x ISI interaction $F(4,300) = .097$, $p = .983$].

Finally, an ANCOVA was used to examine the influence of apathy on the dependent variable. There was no main effect of apathy $F(1,76) = .460$, $p = 499$, group $F(1,76) = 1.129$, $p = .291$, or interaction of ISI and group $F(4,304) = .351$, $p = .843$. The significant main effect of ISI remained $F(4,304) = 7.381$, $p < .001$. Planned comparisons indicated that only the 5 and 6-second ISIs remained significantly different than the shorter ISIs.

Aim 4 – Role of Onset Laterality

In order to examine the role of lateralized symptom onset, the PD group was divided into two groups, those whose first motor symptoms appeared on the right or left side (i.e., left and right brain, respectively). This resulted in a 2 to 1 ratio of patients with right-side onset (Right: N = 26; Left: N = 13) and limited power.

Verbal Fluency

A mixed between and within analysis of variance was performed to examine the role of onset laterality in verbal fluency. As described in previous sections, the within subjects variable for letter fluency is the total words generated at each of four, 15-second intervals. The between subjects variable was PD group based on symptom onset laterality as described above. Mauchly's Test of Sphericity was non-significant $\chi^2(5) = 4.718$, $p = .451$, indicating that uncorrected F values may be reported.

On letter fluency, results indicated that there was no significant difference between the two patient groups $F(1,37) = .198$, $p = .659$. There was a significant main effect of interval $F(3,111) = 97.461$, $p < .001$, that post-hoc tests showed was significant at each interval. There was no significant interaction between group and interval, $F(3,111) = .925$, $p = .431$.

Results of the Category Fluency task were similar to Letter Fluency. Mauchly's Test of Sphericity was non-significant, $\chi^2(5) = 6.421$, $p = .268$. Neither the main effect of group, $F(1,36) = .712$, $p = .439$, nor the interaction between group and interval $F(3,108) = .437$, $p = .727$ was significant. Within subject contrasts of the significant interval main effect on category fluency indicated that both groups declined after the first two intervals but not during the last 15-seconds as it appeared both groups had bottomed out by the end of the third interval.

Stroop Task

On Stroop Word Reading, the main effect of group was not significant $F(1,36) = 1.298$, $p = .262$; however, there was a significant interaction between group and interval $F(2,72) = 5.450$, $p = .006$. Planned contrasts showed that the group with symptom onset

on the right had a sharp decline in the number of words they read between the first and second interval $F(1,36) = 10.863$, $p = .002$. There was also a significant main effect of interval $F(2,72) = 12.173$, $p < .001$ that was driven by the difference between the first and second intervals $F(1,36) = 23.079$, $p < .001$. On Stroop Color Naming, there was again a main effect of interval $F(2,72) = 41.518$, $p < .001$, that was significant between all levels. There was no main effect of group $F(1,36) = 1.900$, $p = .177$ or group by interval interaction $F(2,72) = .346$, $p = .709$.

There were a total of six 15-second intervals on the Color-Word Interference subtest of the Stroop. Even so, there was a pattern of results similar to that on the previous trials [main effect of interval $F(5,180) = 6.497$, $p < .001$; no main effect of group $F(1,36) = 1.932$, $p = .173$; no significant interaction $F(5,180) = .930$, $p = .463$]. Planned contrasts revealed that there were significant differences at the second and fifth intervals.

Table 3-1. Descriptive statistics of word generation across four 15-second intervals on Letter Fluency (FAS).

Interval	PD group Mean (sd)	HC group Mean (sd)	Cohen's *d*	Range (Min-Max)	Skew	Kurtosis
0-15s	16.33 (3.64)	16.82 (3.59)	-0.14	8-25	.057	-.169
16-30s	10.20 (3.92)	10.55 (3.44)	-0.10	3-21	.344	.219
31-45s	7.95 (3.57)	9.15 (3.25)	-0.35	1-16	.147	-.353
46-60s	6.50 (2.97)	8.50 (3.51)	-0.62	0-19	.459	.691

Note: PD Group N=40; HC Group N=40

Table 3-2. Repeated measures analysis of variance with planned contrasts examining performance over time on Letter Fluency (FAS)

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	20.50	1	20.50	2.78	.099	.034
Interval	3957.90	3	1319.30	203.93	.000	.723
Interval*Group	34.24	3	11.413	1.76	.155	.022
Planned Contrasts – Interval						
16-30s vs. 0-15s	3075.20	1	3075.20	239.78	.000	.755
31-45s vs. 0-30s	1940.45	1	1940.45	185.36	.000	.704
46-60s vs. 0-45s	1502.22	1	1502.22	187.25	.000	.706
*Planned Contrasts – Interval*Group*						
16-30s vs. 0-15"	.45	1	.45	.035	.852	.000
31-45s vs. 0-30s	12.01	1	12.01	1.15	.287	.014
46-60s vs. 0-45s	34.67	1	34.67	4.32	.041	.052

*Computed using alpha = .05
Note: PD Group N=40; HC Group N=40

Table 3-3. Word generation across four 15-second intervals on Category Fluency (Animals).

Interval	PD group Mean (sd)	HC group Mean (sd)	Cohen's *d*	Range (Min-Max)	Skew	Kurtosis
0-15s	8.10 (2.09)	7.90 (2.02)	0.10	3-13	-.175	-.055
16-30s	5.13 (2.04)	6.15 (2.03)	-0.50	0-11	.062	.096
31-45s	3.97 (1.60)	4.88 (2.43)	-0.44	0-12	.562	1.204
46-60s	3.62 (1.90)	4.33 (2.04)	-0.36	0-9	.315	-.264

Note: PD Group N=39; HC Group N=40

Table 3-4. Repeated measures analysis of variance with planned contrasts examining performance over time on Category Fluency (Animals)

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	7.29	1	7.29	5.09	.027	.062
Interval	771.87	3	257.29	71.50	.000	.481
Interval*Group	18.25	3	6.08	1.69	.170	.021
Planned Contrasts – Interval						
16-30s vs. 0-15s	440.74	1	440.74	55.59	.000	.419
31-45s vs. 0-30s	453.27	1	453.27	90.75	.000	.541
46-60s vs. 0-45s	332.43	1	332.43	71.22	.000	.480
*Planned Contrasts – Interval*Group*						
16-30s vs. 0-15”	29.60	1	29.60	3.73	.057	.046
31-45s vs. 0-30s	4.76	1	4.76	.953	.332	.012
46-60s vs. 0-45s	.367	1	.367	.079	.780	.001

*Computed using alpha = .05
Note: PD Group N=39; HC Group N=40

Table 3-5. Number of responses on the Stroop across 15-second intervals on the Word Reading, Color Naming and Color-Word Interference subtests.

Interval	PD group Mean (sd)	HC group Mean (sd)	Cohen's *d*	Range (Min-Max)	Skew	Kurtosis
Word Reading						
0-15s	30.44 (4.91)	33.55 (3.85)	-1.16	20-41	-.421	-.076
16-30s	26.79 (4.79)	29.92 (4.82)	-0.65	18-41	.165	-.297
31-45s	27.28 (4.99)	30.97 (4.48)	-0.78	18-40	-.147	-.434
Color Naming						
0-15s	22.67 (3.68)	24.13 (4.15)	-0.37	15-33	.169	-.480
16-30s	18.67 (3.85)	20.76 (4.38)	-0.51	10-33	.395	.600
31-45s	18.23 (4.00)	19.58 (4.12)	-0.33	10-30	.271	-.394
Color-Word Interference						
0-15s	11.77 (3.05)	12.42 (2.46)	-0.23	3-18	-.271	.622
16-30s	9.72 (2.80)	10.39 (2.95)	-0.23	4-17	.168	-.033
31-45s	10.49 (3.92)	11.34 (3.13)	-0.24	2-18	-.134	-.270
46-60s	10.21 (3.22)	11.66 (3.18)	-0.45	2-19	-.066	.471
60-75s	11.31 (3.07)	11.11 (3.07)	0.65	4-18	-.222	-.223
75-90s	10.05 (2.85)	11.68 (2.92)	-0.56	4-18	.026	-.280

Note: PD Group N=39; HC Group N=38

Table 3-6. Repeated measures analysis of variance with planned contrasts examining performance over time on the Stroop Word Reading subtest.

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	211.06	1	211.06	12.640	.001	.144
Interval	565.38	2	282.69	37.53	.000	.333
Interval*Group	4.172	2	2.09	.277	.758	.004
Planned Contrasts – Interval						
16-30s vs. 0-15s	.1017.98	1	1017.98	80.38	.000	.517
31-45s vs. 0-30s	84.59	1	84.595	6.46	.013	.079
*Planned Contrasts – Interval*Group*						
16-30s vs. 0-15”	.002	1	.002	.000	.991	.000
31-45s vs. 0-30s	6.26	1	6.26	.478	.492	.006

*Computed using alpha = .05

Note: PD Group N=38; HC Group N=39

Table 3-7. Repeated measures analysis of variance with planned contrasts examining performance over time on the Stroop Color Naming subtest.

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	51.547	1	51.547	4.378	.000	.974
Interval	883.503	2	446.733	65.367	.000	.466
Interval*Group	6.239	2	3.120	.462	.631	.006
Planned Contrasts – Interval						
16-30s vs. 0-15s	1044.976	1	1044.976	74.440	.000	.498
31-45s vs. 0-30s	541.523	1	541.523	55.565	.000	.426
*Planned Contrasts – Interval*Group*						
16-30s vs. 0-15”	7.677	1	7.677	.547	.462	.007
31-45s vs. 0-30s	3.601	1	3.601	.369	.545	.005

*Computed using alpha = .05
Note: PD Group N=39; HC Group N=38

Table 3-8. Repeated measures analysis of variance with planned contrasts examining performance over time on the Stroop Color-Word Interference subtest.

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	13.725	1	13.725	2.199	.142	.028
Interval	166.374	5	33.275	8.690	.000	.104
Interval*Group	41.439	5	41.439	2.164	.057	.028
Planned Contrasts – Interval						
16-30s vs. 0-15s	320.012	1	320.012	34.441	.000	.315
31-45s vs. 0-30s	1.998	1	1.998	.367	.547	.005
46-60s vs. 0-45s	.631	1	.631	.108	.743	.001
61-75s vs. 0-60s	3.301	1	3.301	.809	.371	.011
76-90s vs. 0-75s	2.306	1	2.306	.595	.443	.008
*Planned Contrasts – Interval*Group*						
16-30s vs. 0-15”	.012	1	.012	.001	.971	.000
31-45s vs. 0-30s	.699	1	.699	.128	.721	.002
45-60s vs. 0-45s	10.114	1	10.114	1.733	.192	.023
60-75s vs. 0-60s	23.778	1	23.778	5.829	.018	.072
76-90s vs. 0-75s	17.230	1	17.230	4.447	.038	.056

*Computed using alpha = .05
Note: PD Group N=39; HC Group N=38

Table 3-9. Average reaction times in milliseconds across four quartiles on the Simple and Choice Reaction Time tasks.

Interval	PD group Mean (sd)	HC group Mean (sd)	Cohen's *d*	Skew	Kurtosis
Simple Reaction time (ms)					
Trials 1-14	433.97 (102.25)	398.57 (107.10)	0.34	1.349	1.975
Trials 15-28	433.19 (127.19)	395.55 (128.52)	0.29	1.647	2.369
Trials 29-42	431.08 (116.34)	390.20 (119.33)	0.35	1.366	1.313
Trials 43-56	439.47 (136.81)	389.03 (118.30)	0.39	1.502	1.725
Choice Reaction time (ms)					
Trials 1-14	623.45 (113.84)	597.34 (113.47)	0.23	1.735	5.604
Trials 15-28	641.72 (152.93)	621.10 (121.51)	0.15	2.311	8.279
Trials 29-42	655.13 (178.80)	625.74 (122.79)	0.19	3.008	12.867
Trials 43-56	660.45 (165.94)	623.57 (129.80)	0.25	2.083	5.798

Note: PD Group N=40; HC Group N=39

Table 3-10. Repeated measures analysis of variance with planned contrasts examining performance over time on the Simple Reaction Time task by quartile.

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	.198	1	.198	3.412	.069	.043
Interval	.020	2.428	.008	1.680	.182	.022
Interval*Group	.010	2.428	.004	.824	.460	.011
Planned Contrasts – Interval						
Trials 15-28 vs.1-14	.017	1	.017	2.041	.157	.026
Trials 29-42 vs. 1-28	.014	1	.014	2.709	.104	.034
Trials 43-56 vs. 1-42	.002	1	.002	.448	.506	.006
*Planned Contrasts – Interval*Group*						
15-28 vs.1-14	.000	1	.000	.054	.816	.001
29-42 vs. 1-28	.003	1	.003	.572	.452	.007
43-56 vs. 1-42	.010	1	.010	1.843	.179	.024

*Computed using alpha = .05

Note: PD Group N=40; HC Group N=38

Table 3-11. Repeated measures analysis of variance with planned contrasts examining performance over time on the Choice Reaction Time task by quartile.

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	.032	1	.032	.874	.353	.011
Interval	.095	2.428	.039	12.661	.000	.141
Interval*Group	.006	2.428	.002	.792	.476	.010
Planned Contrasts – Interval						
Trials 15-28 vs.1-14	.066	1	.066	11.969	.001	.135
Trials 29-42 vs. 1-28	.056	1	.056	20.739	.000	.212
Trials 43-56 vs. 1-42	.032	1	.032	8.345	.005	.098
*Planned Contrasts – Interval*Group*						
15-28 vs.1-14	.005	1	.005	.947	.334	.012
29-42 vs. 1-28	.000	1	.000	.000	.995	.000
43-56 vs. 1-42	.004	1	.004	1.133	.290	.015

*Computed using alpha = .05
Note: PD Group N=40; HC Group N=39

Table 3-12. Average reaction times by interstimulus interval (ISI) on the Simple and Choice Reaction Time tasks.

Interval	PD group Mean (sd)	HC group Mean (sd)	Cohen's *d*	Skew	Kurtosis
Simple Reaction time (ms)					
3s ISI	460.20 (125.34)	423.40 (139.11)	0.28	1.547	1.896
4s ISI	444.61 (120.06)	399.09 (118.94)	0.36	1.390	1.904
5s ISI	426.15 (112.69)	386.03 (113.46)	0.35	1.436	2.184
6s ISI	421.88 (123.10)	378.65 (106.65)	0.38	1.398	1.427
7s ISI	417.63 (118.30)	380.04 (117.27)	0.32	1.787	3.761
Choice Reaction time (ms)					
3s ISI	657.97 (142.77)	628.76 (113.47)	0.23	2.074	7.534
4s ISI	654.47 (158.70)	623.85 (127.35)	0.22	2.434	8.614
5s ISI	640.13 (148.66)	611.61 (119.39)	0.21	2.376	8.369
6s ISI	636.71 (154.53)	611.99 (124.87)	0.18	2.428	9.008
7s ISI	637.28 (155.57)	608.34 (116.62)	0.21	2.190	6.916

Note: PD Group N=40; HC Group N=39

Table 3-13. Repeated measures analysis of variance with planned contrasts examining performance over time on the Simple Reaction Time task by interstimulus interval (ISI).

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	.196	1	.196	3.389	.070	.043
Interval	.589	4	.147	47.758	.000	.386
Interval*Group	.005	4	.001	.409	.802	.005
Planned Contrasts – Interval						
4s ISI vs. 3s	.162	1	.162	23.813	.000	.239
5s ISI vs. 3-4s	.283	1	.283	56.072	.000	.425
6s ISI vs. 3-5s	.250	1	.250	58.599	.000	.435
7s ISI vs. 3-6s	.165	1	.165	55.595	.000	.422
*Planned Contrasts – Interval*Group*						
4s ISI vs. 3s	.009	1	.009	1.305	.257	.017
5s ISI vs. 3-4s	.000	1	.000	.047	.829	.001
6s ISI vs. 3-5s	.000	1	.000	.049	.001	.001
7s ISI vs. 3-6s	.000	1	.000	.126	.724	.002

*Computed using alpha = .05

Note: PD Group N=40; HC Group N=38

Table 3-14. Repeated measures analysis of variance with planned contrasts examining performance over time on the Choice Reaction time task by interstimulus interval (ISI).

Source	Type III Sums of Squares	df	Mean Square	F	Sig.*	Partial Eta Squared
Group	.032	1	.032	.875	.353	.011
Interval	.078	4	.020	12.303	.000	.138
Interval*Group	.001	4	.000	.128	.972	.002
Planned Contrasts – Interval						
4s ISI vs. 3s	.008	1	.008	3.052	.085	.038
5s ISI vs. 3-4s	.047	1	.047	18.523	.000	.194
6s ISI vs. 3-5s	.032	1	.032	16.015	.000	.172
7s ISI vs. 3-6s	.023	1	.023	10.015	.002	.115
*Planned Contrasts – Interval*Group*						
4s ISI vs. 3s	.000	1	.000	.048	.828	.001
5s ISI vs. 3-4s	.000	1	.000	.009	.927	.000
6s ISI vs. 3-5s	.001	1	.001	.482	.489	.006
7s ISI vs. 3-6s	.000	1	.000	.004	.949	.000

*Computed using alpha = .05

Note: PD Group N=40; HC Group N=39

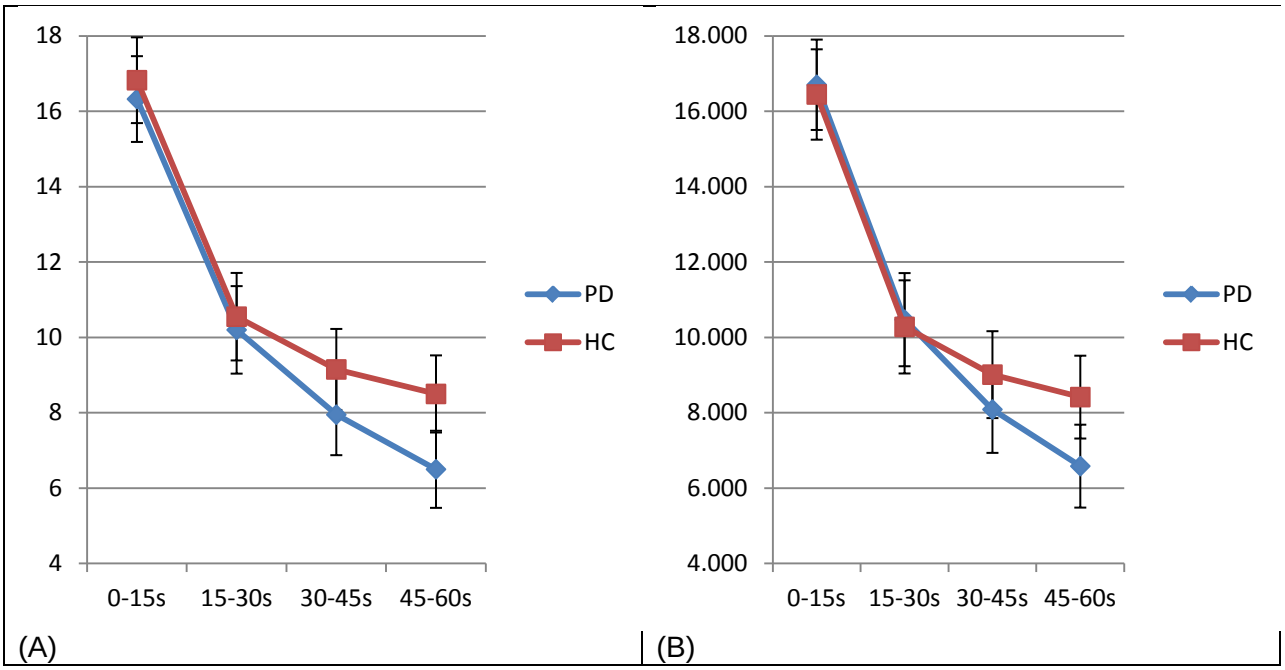

Figure 3-1. Means and 95% confidence intervals of between group differences in word generation over time on Letter Fluency before (A) and after (B) controlling for processing speed with the SDMT.

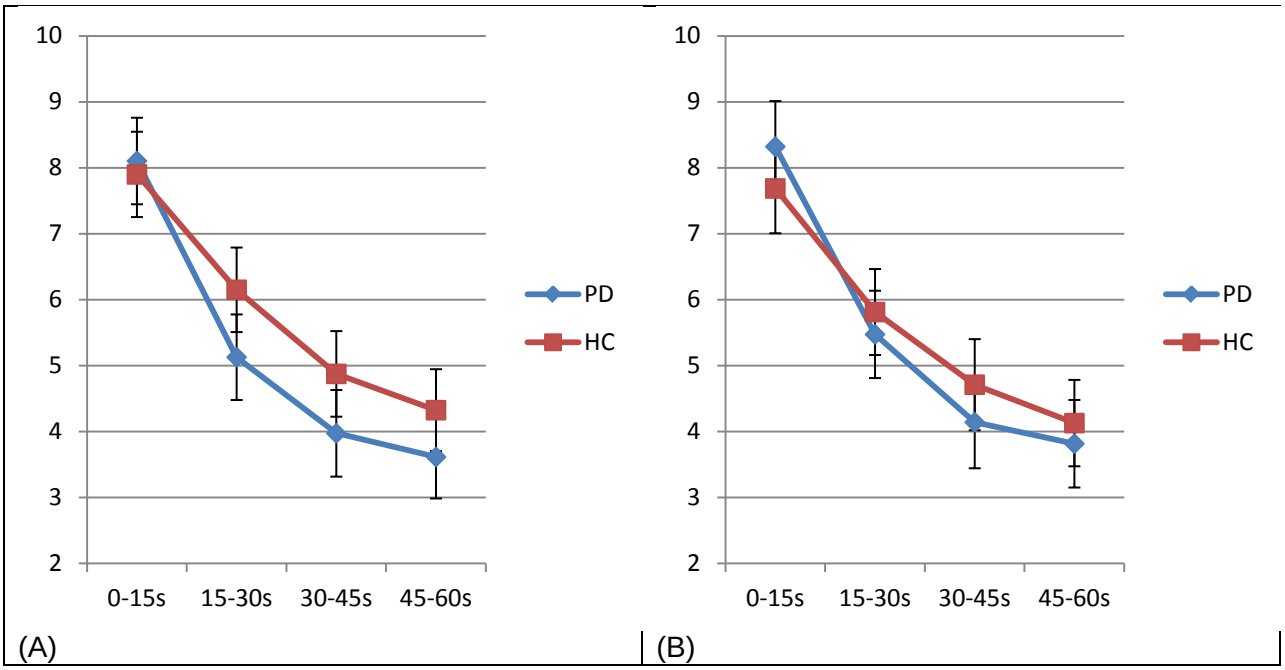

Figure 3-2. Means and 95% confidence intervals of between group differences in word generation over time on Category Fluency (Animals) before (A) and after (B) controlling for processing speed with the SDMT.

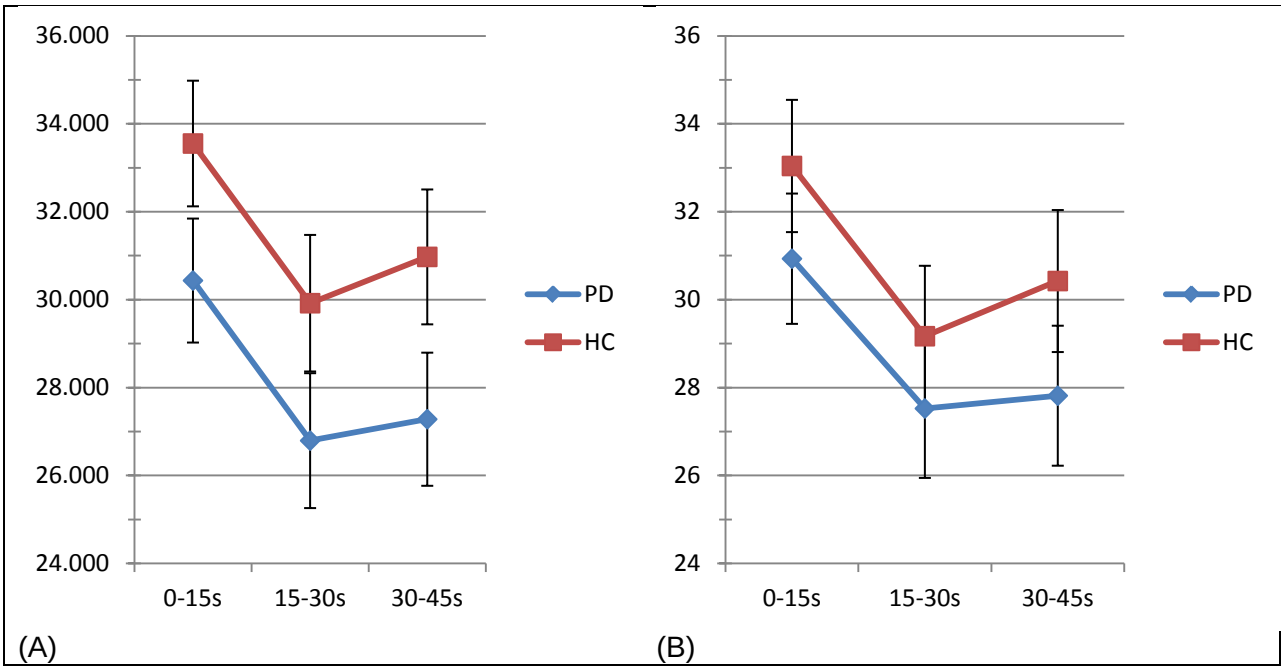

Figure 3-3. Means and 95% confidence intervals of between group differences in response output on Stroop Word Reading before (A) and after (B) controlling for processing speed with the SDMT.

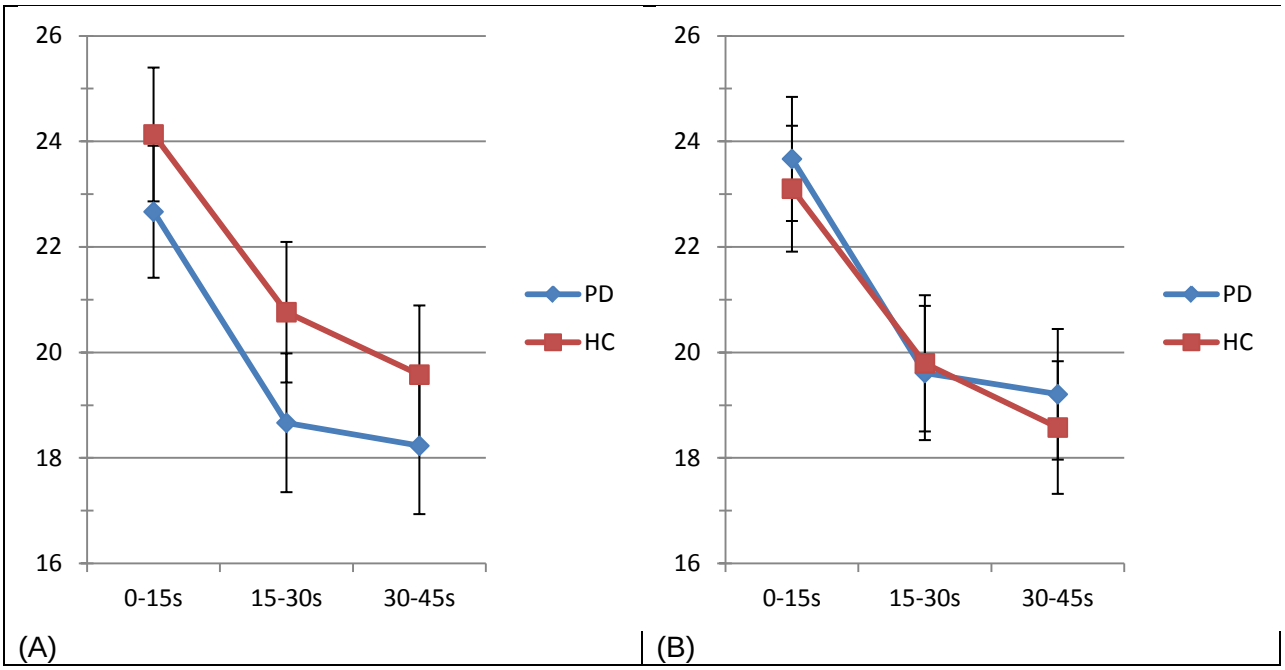

Figure 3-4. Means and 95% confidence intervals of between group differences in response output on Stroop Color Naming before (A) and after (B) controlling for processing speed with the SDMT.

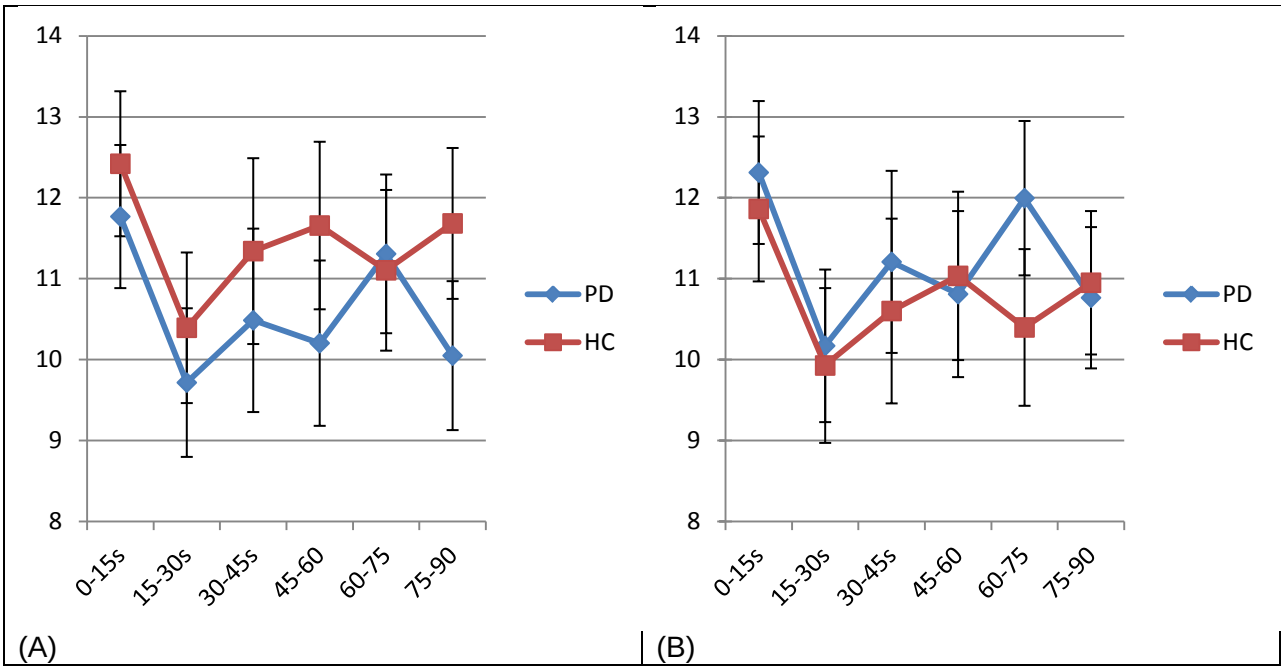

Figure 3-5. Means and 95% confidence intervals of between group differences in response output on Stroop Color-Word Interference before (A) and after (B) controlling for processing speed with the SDMT.

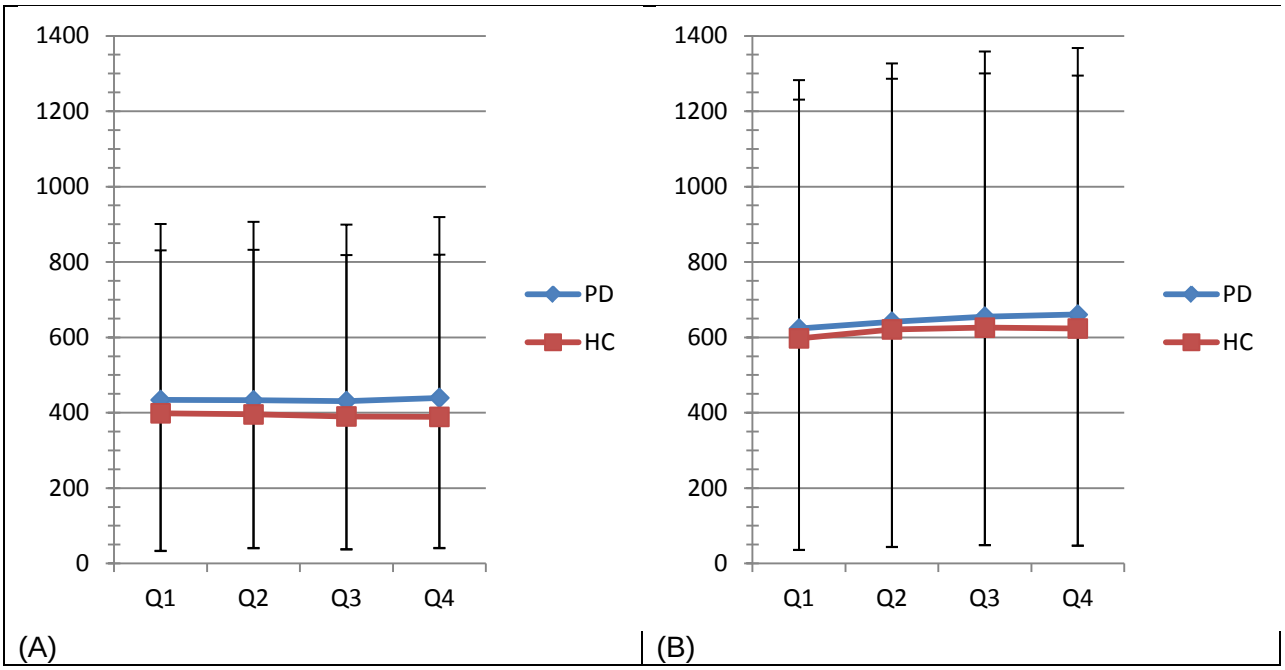

Figure 3-6. Mean reaction times (ms) and 95% confidence intervals of between group differences on the SRT (A) and CRT (B) tasks at each quartile.

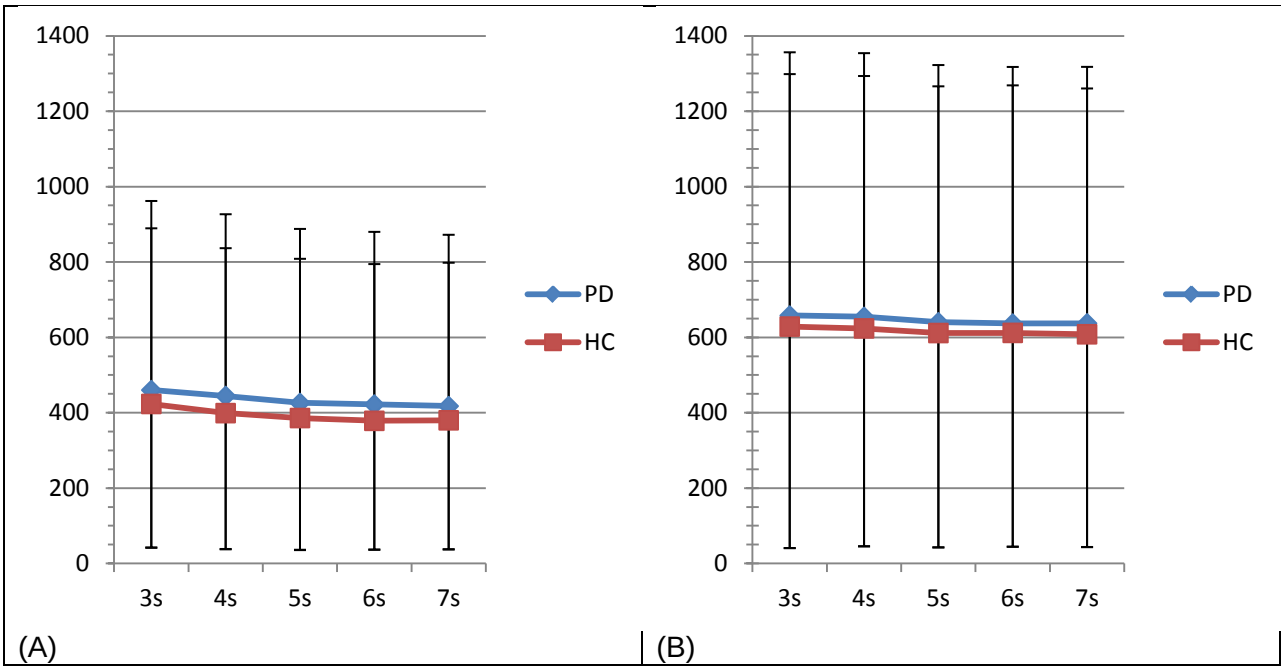

Figure 3-7. Mean reaction times (ms) and 95% confidence intervals of between group differences on the SRT (A) and CRT (B) tasks at each ISI interval.

CHAPTER 4
DISCUSSION

Findings and Implications

The purpose of this study was to examine the role of processing speed and executive demands on within-task performance over time in a group of individuals with idiopathic non-demented Parkinson's disease compared to a matched sample of healthy older adults. Using a top-down model of prefrontal functioning combined with the bottom-up influence of processing speed, we hypothesized that individuals with PD would be unable to sustain their behavioral output (i.e., task performance) over time compared to controls. This is based on the assumption that degeneration of the substantia nigra would disrupt specialized frontal-subcortical circuits that support executive functioning. We selected neuropsychological measures shown to be sensitive to frontal lobe dysfunction, some with varying levels of task complexity, to examine what factors might contribute to poor performance over time. We examined the effects of processing speed (i.e., bradyphrenia) on neuropsychological performance using the SDMT. The effects of depression and apathy were also considered.

The current study provided mixed support for declining within-task performance over time. Only on the task with the greatest dependence on the dorsolateral prefrontal cortex (i.e., letter fluency) did the PD group demonstrate the hypothesized differential decline in output relative to controls at the latter stages of the task. What quickly became apparent is that both groups had a decline in output over time on both letter and category fluency tasks as well as the three subtests of the Stroop. In fact, underlying processing speed appeared to explain nearly all observed effects. In terms of the inhibition component of the model, the Stroop Interference task was expected to

show a differential decline between groups that was not substantiated by these data. Furthermore, reaction time tasks revealed declines across early intervals regardless of group. Post hoc tests examining reaction time as a function of interstimulus interval demonstrated faster RTs as the ISI increased. A summary of each of these findings is detailed below.

Aim 1 – Verbal Fluency

Clinical observation of verbal fluency performance among patients with Parkinson's disease was the initial inspiration for the current research study. These results supported the original hypothesis that individuals with Parkinson's disease (but not controls) would demonstrate a decline in word generation during the last 15 seconds of letter fluency. Also as predicted, this pattern of results was not observed on category fluency. Taken together, this lends support to the theory that the longer a task requires sustained performance over time, there are increasing demands on executive resources (Fuster, 1997). When the task itself is executively loaded the effect is intensified.

In Parkinson's disease, the circuitry that connects areas of the prefrontal cortex with subcortical structures (e.g., caudate, thalamus) is compromised and this is the likely mechanism responsible for decreased executive functioning in these individuals. Upon closer inspection of group means and the overall pattern over time, it appears that the two groups begin to diverge in the third interval (i.e., 30-45 seconds). Even after controlling for the influence of processing speed, the performance over time effect remained significant. This is particularly interesting when one considers the current sample is highly educated and functioning particularly well in the early stage of their disease, which suggests that letter fluency may be particularly sensitive to early cognitive change in Parkinson's disease.

Although patients with PD did not show the same pattern of output on category fluency as seen on the letter fluency task, they did show an interesting pattern of decline over time. First, the PD patients generated significantly fewer animals overall than the matched controls. Second, they appeared to decline over time on category fluency except that their output diverged from the healthy controls between the first and second intervals—earlier in the time course than observed on letter fluency. One explanation for this pattern of results may be due to rapid word generation of an overlearned category during the first interval and then difficulty switching to a new cluster (e.g., switching from farm animals to animals found in the jungle). The role of switching and executive control has been well documented in category fluency (Troyer, Moscovitch, & Winocur, 1997). Previous research has shown that even neurologically intact individuals demonstrate some reduced word generation output over time. For example, in a sample of healthy young adults Crowe (1998) demonstrated that the greatest number of words were generated in the first 15s interval on both tasks of letter and category and these words also had higher frequency in the English language. Others have suggested that reduced category fluency in individuals with subcortical pathology is due to inefficient search and retrieval of relatively intact semantic stores (Carew, Lamar, Cloud, Grossman, & Libon, 1997).

In hindsight, the pattern of decline observed in the current sample is actually consistent with the model that suggests any task that requires sustained performance requires increasing support by the frontal lobes, it just occurs earlier in the trial than predicted. This may be due at least in part to the smaller range of available words in the category. Furthermore, there are methodological differences between the category and

letter fluency tasks. Letter fluency data was summed from three trials (F, A, and S) whereas there was only one trial for category fluency (animals). In fact, secondary analyses of performance over time on individual letters revealed no significant differences at all. Perhaps the use of a composite made up of all three trials resulted in a more reliable letter fluency variable by collapsing the three trials into one and averaging out the standard deviation. Alternatively, the use of a single trial on Animal Fluency could have resulted in a floor effect that may have masked further between-group divergence in output over time. Future studies should consider using an equal number of trials for both letter and category fluency to minimize the potential effect of this discrepancy. When underlying processing speed was controlled in these two models, the differences between groups across intervals were eliminated on category fluency; however, it did not fully explain the rapid decline in output by the PD group in the last interval on letter fluency.

Aim 2 – Stroop

The Stroop task was selected primarily to examine patterns over time on a measure of inhibition but also because the three subtests introduce increasing levels of complexity. Word reading is a relatively automatic, over-learned skill. In contrast, color naming is more novel and it is this novelty that makes it more challenging compared to word reading. As such, it was expected that Color Naming would require more executive resources than simple Word Reading. The third subtest is the most difficult and dependent on executive control to complete the task, which involves naming colors while inhibiting the automatic tendency to read the (incongruent) word. Given these differences in executive demands, it was hypothesized that the performance pattern of

interest would only appear on the most difficult Interference task. Inhibition has been linked to ventral medial regions of the caudate and prefrontal cortex.

The results on Word Reading and Color Naming were quite similar. In both cases, the PD group produced fewer words than the HC group overall, and both groups' response output declined significantly over the first two intervals. Controlling for the significant effects of processing speed on these two subtests explained the between group differences but the decline in performance over time remained. Surprisingly, there was no difference between the two groups on the number of responses produced on the more the difficult Stroop Color Word Interference trial. There was however, a significant interaction in which the output by the PD group dropped relative to the controls during the last interval (i.e., 75-90s.) Although this seemed to lend some support for the hypothesis, the effect was completely explained by underlying processing speed.

Aim 3 – Reaction Time Tasks

One aspect of this study that makes it unique is examining both clinical neuropsychological tests and experimental reaction time tasks in tandem. While reaction time tasks are uncommon in most clinical settings, in theory, using a computer to record reaction time to the millisecond could make it a sensitive measure of difference between and within individuals. Furthermore, reaction time tasks themselves are measures of processing speed, eliminating the need for additional covariates. When examining performance over the duration of the SRT in the current sample, however, there were no differences between groups or interval. Reaction times for both groups were slower on the CRT task than on the SRT but the groups were statistically similar. There was an increase in reaction time (i.e., slowing) between the first and second intervals regardless of group.

In hindsight, there is a methodological problem in these data. Both the SRT and CRT tasks were designed using random interstimulus intervals across all trials. In other words, each of the four intervals could have any combination of reaction time scores between individuals introducing an additional source of error. This increase in error makes it increasingly difficult to reach statistically significance. Follow up analyses compared performance across each ISI and, consistent with the literature, reaction times became faster as a function of longer interstimulus intervals. This anticipation effect was observed for all ISIs longer than 3 seconds.

Aim 4 – Onset Laterality

One of the characteristic pathonomic signs of Parkinson's disease is unilateral onset of symptoms usually to an upper extremity. This suggests that degeneration of the contralateral basal ganglia is more advanced than the ipsilateral side. Some studies have found that symptom onset laterality predicts cognitive and emotional functioning in some patients. Unfortunately, side of symptom onset did not predict performance patterns on any of these tasks in the current sample. This may have been due, at least in part, to small and unbalanced sample size and insufficient power.

Limitations

The biggest problem with the current study is the clear range restriction issue. The current patient sample was particularly bright (the average education among participants was a bachelor's degree), they were quite early in the disease process (the majority of patients were rated 1 to 1.5 on the 5 point Hoehn and Yahr staging model), and had little to no comorbid health concerns other than PD. It is important to examine a broader range of disease severity in future samples. While it is useful to know that a selective decline in performance over time is generally not present in the current PD

sample (except for letter fluency), it is still unknown whether the hypothesized patterns would emerge if the sample included individuals with a more advanced disease course and/or cognitive impairment.

Another limitation with the current study is the statistical methods used to analyze the data. Had we been able to control for processing speed over time (instead of just between groups) we may have had more sensitivity to detect subtle differences in change over time. One such approach would be to use a mixed multilevel modeling approach. In a recent study by McDowd and colleagues (McDowd, et al., 2011) such an approach was used to isolate slope and intercept data between groups and various fluency tasks. Furthermore, this approach would facilitate use of a time varying predictor of processing speed (e.g., SDMT data recorded in 15-second intervals) that would allow control of processing speed in the first 15-second interval in the same interval of the dependent variable. This approach would provide a better approximation of the error variance by interval, allowing potentially significant findings to be revealed.

Another consideration is that successful performance on verbal fluency requires *internal generation* of responses, whereas the Stroop and reaction time tasks provide a visual cue that may facilitate sustained performance over time. This internal generation component likely requires additional executive resources to perform mental search of semantic networks while maintaining task set and tracking previous responses. Future studies may consider examination of performance over time on other measures that require fluent generation of responses (e.g., action fluency, design fluency). Other research has emphasized the importance of within task clustering and switching

(Troyer, et al., 1997). Furthermore, analyzing the variety of errors that occur among and between groups may further elucidate the mechanisms for impersistent performance.

The current study proposes that the breakdown of frontal subcortical circuits is the underlying mechanism for the executive dysfunction and processing speed deficits seen in Parkinson's disease. However, no direct neuroimaging evidence was provided to support this assumption in the current study. Structural neuroimaging data, particularly diffusion tensor techniques that examine the integrity of these circuits, are essential to confirm and quantify this assumption. Volumetric measurements of critical subcortical structures such as the caudate and thalamus would be useful as well, as it may allow us to formally connect neuropsychological function with underlying neuroanatomy.

Taken together, the current study provides mixed support for slowing over time that was only partially explained by processing speed. Furthermore this pattern was only evident in tasks requiring internally generated responses. These findings suggest the potential benefit of examining performance patterns over time during standard neuropsychological evaluations as this may be a measure sensitive to early cognitive decline.

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BIOGRAPHICAL SKETCH

Sandra (Sykes) Mitchell was born in Merced, California and received her bachelor's degree in psychology from California State University at Fresno. Her interests in aging and memory developed while working as an undergraduate research assistant on the California Project on Successful Aging laboratory under the research mentorship of Matthew Sharps, Ph.D. She gained additional research experience at the Rocky Mountain Taste and Smell Center at the University of Colorado Health Sciences Center under the supervision of Miriam Linschoten, Ph.D. while completing her master's degree in clinical psychology at the University of Colorado at Denver. During her graduate work at Colorado, she was mentored by Jose Lafosse, Ph.D. while working on his White Matter Dementia project. She successfully defended her master's thesis entitled *Acquisition vs. Retrieval Deficit: The Nature of Verbal Memory Impairment in Relapsing-Remitting Multiple Sclerosis.* She received her doctoral training in clinical and health psychology with a special emphasis in clinical neuropsychology at the University of Florida under the mentorship of Catherine Price, Ph.D. Her dissertation entitled *Performance Over Time in Parkinson's Disease: The Influence of Processing Speed and Executive Control* was successfully defended in 2011. She completed her Clinical Psychology Internship at the Veteran's Administration Healthcare System in West Haven, Connecticut under the supervision of Dr. John Beauvais and Dr. Joseph Kulas in 2011. She will receive her postdoctoral training in clinical neuropsychology at the New Mexico VA Healthcare System in Albuquerque, New Mexico with Kathleen Haaland, Ph.D., Rex Swanda, Ph.D., and Joseph Sadek, Ph.D. Ms. Mitchell's current research interests continue in aging, dementia and the role of white matter disease in cognition.