SOURCE MEMORY AND FRONTAL FUNCTIONING IN PARKINSON’S DISEASE

by

Lauren L. Kong

A Dissertation Submitted to the Faculty of the DEPARTMENT OF PSYCHOLOGY
In Partial Fulfillment of the Requirements For the Degree of DOCTOR OF PHILOSOPHY
In the Graduate College
THE UNIVERSITY OF ARIZONA

2008
The University of Arizona
Graduate College

As members of the Dissertation Committee, we certify that we have read the dissertation prepared by Lauren L. Kong entitled Source Memory and Frontal Functioning in Parkinson's Disease and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

__________________________________________ Date: 4/25/08
Elizabeth Glisky, Ph.D.

__________________________________________ Date: 4/25/08
Alfred Kaszniak, Ph.D.

__________________________________________ Date: 4/25/08
John JB Allen, Ph.D.

__________________________________________ Date: 4/25/08
Steve Rapcsak, M.D.

__________________________________________ Date: 4/25/08
Linas Bieliauskas, Ph.D., University of Michigan

Final approval and acceptance of this dissertation is contingent upon the candidate’s submission of the final copies of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

__________________________________________ Date: 4/25/08
Dissertation Director: Elizabeth Glisky, Ph.D.
STATEMENT BY AUTHOR

This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this dissertation are allowable without special permission, provided that accurate acknowledgment of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: Lauren L. Kong
Acknowledgements

This project would not have been possible without the selflessness of the study volunteers, who donated their time and efforts in hopes of helping the Parkinson’s community. Special thanks to the Lansing Area Parkinson’s Support Group and Mr. Donald Hitko for their inspiring words and crusading spirit. I also thank Dr. Nico Bohnen and his research team for generously providing laboratory space.

My dissertation committee has been nothing but enthusiastic and supportive throughout this entire process. Both Dr. Steve Rapcsak and Dr. Alfred Kaszniak were instrumental in the conception, development, and design of this study. I am so grateful for the help of Dr. Linas Bieliauskas, who provided me with a “home away from home” and supplied the resources needed to complete this project in Michigan. I owe a heartfelt thank you to my advisors, Dr. John Allen and Dr. Elizabeth Glisky, not only for their help with this study, but for the support they have provided throughout my entire graduate school experience. I credit the success of my graduate career to their encouragement and guidance, and I am grateful to call them my advisors, colleagues, and friends.

I attribute my career path to the inspiration of my college advisors, Dr. William Banks and Dr. Richard Lewis, who gave me my first glimpse into the wonderful world of the human brain. I also give thanks to the faculty, staff, and students of the University of Arizona Department of Psychology, including Beth Owens, Elizabeth Dyckman, and the members of the Amnesia and Cognition Lab, to name a few.

I am so thankful for the love and support of Capt. Daniel Drag, who has been my solid ground throughout the last three years. He truly is my biggest fan. Lastly, I would not be where I am if it were not for the unwavering and unconditional love and support of my parents. I cannot thank them enough for providing me the roots with which to grow and the wings with which to fly.
# TABLE OF CONTENTS

LIST OF FIGURES...........................................................................................................6
LIST OF TABLES.............................................................................................................7
ABSTRACT.....................................................................................................................8

CHAPTER 1: Introduction.................................................................................................9
  Biological Changes Associated with PD.................................................................10
  Parkinson’s Disease and Cognition......................................................................15
  Dopamine and Executive Functioning: Frontostriatal Circuitry.......................20
  Dopamine and Executive Functioning: Pharmacological Challenge...............22
  Source Memory and Parkinson’s Disease............................................................24
  The Relation amongst DA, Source Memory, and Executive Functioning...........30
  The Current Study................................................................................................32

CHAPTER 2: Methods....................................................................................................37
  Participants.............................................................................................................37
  Materials...............................................................................................................39
    Neuropsychological Tasks..................................................................................39
    Memory tasks.....................................................................................................40
  Procedure..............................................................................................................42

CHAPTER 3: Results......................................................................................................44
  Medication and Memory Effects.........................................................................44
  Neuropsychological Effects.................................................................................46
  Correlational Analyses.........................................................................................47
  Logistic Regression.............................................................................................50
  Mediator Analysis.................................................................................................51

CHAPTER 4: Discussion...............................................................................................54
  Source Memory and Dopamine..........................................................................55
  Source Memory and Executive Functioning.....................................................61
  Depression and PD...............................................................................................65
  Conclusions, Caveats, and Future Directions....................................................66

REFERENCES..............................................................................................................68
LIST OF FIGURES

FIGURE 1, Scatterplot of FFAC and Source Scores Labeled by Group......................49
FIGURE 2, Scatterplot of PFAC and Source Scores Labeled by Group .....................50
FIGURE 3, Correlations amongst Group, Executive Functioning, and Source Memory..52
LIST OF TABLES

TABLE 1, Demographic Information for Control Participants and PD Patients........44
TABLE 2, Mean (SD) Scores from Memory and Motor Tests On and Off Medication..46
TABLE 3, Neuropsychological Data and Memory Scores.................................47
TABLE 4, Correlations Between FFAC, PFAC, and Memory Scores
   for All Participants....................................................................................48
TABLE 5, Correlations Between FFAC, PFAC, and Memory Scores
   for the PD Group .....................................................................................49
TABLE 6, Correlations Between FFAC, PFAC, and Memory Scores
   for the Control Group ...............................................................................49
Abstract
Parkinson’s disease (PD) is a neurodegenerative disorder characterized by dopamine dysregulation in several regions of the brain, including the striatum. Because of the intimate connections between the striatum and the frontal lobes, individuals with PD often demonstrate impairments on those tasks relying on the prefrontal cortex (e.g. tests of executive functioning). Source memory, or memory for context, is believed to rely on the prefrontal cortex and has been previously associated with executive functioning performance, although it has received little attention in the PD literature. Executive functioning and source memory were measured in a group of non-demented PD patients and healthy control participants. Within the PD group, an anti-Parkinson’s medication withdrawal manipulation was used to examine whether source memory was affected by phasic changes in dopamine levels. Compared to healthy control participants, PD patients were impaired in source memory (both on and off medication) and on two composite measures of executive functioning. Within the PD group, medication administration improved motor performance but did not have a significant effect on source memory, suggesting that source memory may not rely on the dopamine system.
CHAPTER 1: Introduction

Parkinson’s disease (PD) is a neurodegenerative disorder characterized by the presence of abnormal motor movements stemming from disturbances of the dopamine system. The hallmark triad of symptoms associated with PD is tremor at rest, rigidity, and bradykinesia. A diagnosis of PD is based on the presence of at least two of these symptoms as well as an improvement in symptoms with dopaminergic medication. Other typical symptoms include hypokinesia, akinesia, drooling, a paucity of normal facial expression, micrographia, shortened stride length, and hypophonia.

While PD has traditionally been thought of as primarily a motor disease, recent emphasis has been placed on the cognitive sequelae that may accompany the disorder. PD is associated with increased risk for dementia, although non-demented patients often demonstrate cognitive impairments on certain tasks. Dopamine dysregulation, such as that found in PD, can have significant effects on those aspects of cognition that depend on an intact dopaminergic system. One area of brain with extensive dopaminergic innervation is the frontal lobes, and research has consistently found PD-related impairments on certain tasks thought to rely on the frontal lobes. Source memory, or memory for context, is thought to rely at least in part on the frontal lobes, but has received very little attention in the literature on PD. The current study examined source memory and executive functioning in individuals with PD and examined how cognition is affected by both static and phasic alterations in dopamine levels.
Biological Changes Associated with PD

The dopamine dysregulation implicated in the pathophysiology of PD is thought to result from a loss of pigmented cells in the pars compacta region of the substantia nigra, resulting in dopaminergic hypofunction in pathways projecting from this area. Disruption of these pathways can account for many of the motor and cognitive symptoms that often accompany PD. One destination of efferent projections from the substantia nigra is the ventral tegmental area, which is closely connected to cortical regions. This pathway, termed the mesocorticolimbic pathway, is affected less severely and later on in disease progression (Agid, Javoy-Agid & Ruberg, 1987) and thought to be responsible for the neuropsychiatric pathology that can manifest at later stages of the disorder. The main projection from the substantia nigra is to the basal ganglia, namely the putamen and caudate which comprise the striatum. These projections are termed the nigrostriatal pathway. Because of the interconnectivity between these two regions, disease-related cell atrophy in the substantia nigra results in dopamine depletion in the striatum, and it has been demonstrated that dopamine uptake in the substantia nigra is highly correlated to striatal uptake (Scatton et al., 1983). Substantia nigra pathology has a great impact on basal ganglia functioning, thus much focus has been placed on this nigrostriatal pathway and its efferent connections.

The basal ganglia are part of a network that shares information with the cortex and thalamus via afferent and efferent projections. These basal ganglia-thalamocortical projections are highly organized in both a functional and anatomical manner. Five main dopaminergic circuits transmit information from the striatum to other cortical and
subcortical regions. Each circuit interconnects the cortex, striatum, globus pallidus, and thalamus and results in a bidirectional communication between the neocortex and the striatum. Each of these loops innervates anatomically distinct areas of these structures, allowing specific areas of the brain to communicate via separate pathways. The basic structure of each of these circuits is similar, in that the circuit originates from frontal regions, passes through the striatum and globus pallidus, and then projects back to the frontal regions by way of the thalamus. These five frontostriatal circuits can be separated into motor circuits, consisting of the motor and oculomotor loops, and non-motor circuits, consisting of the dorsolateral prefrontal, anterior cingulate, and orbitofrontal loops (Alexander, Delong & Strick, 1986). The motor loop connects the putamen to motor, supplementary motor, and somatosensory cortices. PD-related alterations to this pathway are thought to be responsible for the motor abnormalities that are the hallmark symptoms of the disorder. The four other nigrostriatal pathways project through various areas of the caudate. The oculomotor circuit connects the frontal eye fields to the caudate and plays a role in reflexive and voluntary eye movements. The anterior cingulate circuit encompasses anterior cingulate projections to and from the ventral striatum and is thought to underlie motivational states. The lateral orbitofrontal circuit connects the ventromedial head of the caudate with the lateral orbitofrontal cortex and is responsible for socially critical restraint and empathy. The dorsolateral prefrontal circuit connects the dorsolateral prefrontal cortex (DLPFC) and the dorsolateral head of the caudate and mediates executive functioning (Alexander, Delong & Strick, 1986, Mega, Cummings & Jeffrey, 1995). Dysfunction in the caudate can lead to impairments in cognitive processes
relying on the frontal lobes mainly via the lateral orbitofrontal and DLPFC circuits (Rinne et al, 2000).

In PD, the neurodegenerative process first affects dopamine levels in the putamen before progressively affecting the caudate. This accounts for the early appearance of motor symptoms in the disorder, with subsequent cognitive changes. One imaging study examining uptake of f-dopa, a PET measure thought to reflect presynaptic dopamine function, found that uptake in the putamen of PD patients was 42% of the level of normal controls, while uptake in the caudate was at 76% (Nurmi et al., 2000). These findings of striatal dysfunction with greater putamen involvement have been supported by other imaging studies (Bruck et al., 2004; Leenders et al., 1990; Rakshi et al., 1999). Although the degenerative process affects the putamen first, once the caudate is affected the rate of progression in both the caudate and putamen are identical (Nurmi et al, 2001). Greater putamen involvement in PD explains why the cognitive symptoms of the disorder are much more subtle and considered secondary to the motor deficits.

In addition to the nigrostriatal tract, dopaminergic deficits have also been demonstrated in other areas of the brain, as changes in dopamine levels in PD eventually affect all regions receiving dopaminergic innervation. For example, dopamine depletion in cortical areas in postmortem brains of individuals with PD was found to range from 52-68% of normal levels (Scatton et al 1983). Dopaminergic hypofunction is found in the prefrontal cortex, albeit to a much lesser degree than the striatum. Apart from the frontostriatal pathway, the frontal lobes receive dopaminergic projections directly from the ventral tegmental area via the mesocorticolimbic pathway. Thus, dopamine
dysregulation in the frontal lobes can result from disturbances in innervations from both the frontostriatal pathways and the mesocortical pathway. However, the ventral tegmental area is less affected in PD and therefore the mesocortical pathway is most likely not the primary cause of the frontal deficits commonly found in the disorder (Lewis et al., 2003; Postle et al., 1997; Scatton et al., 1983).

While dopamine dysregulation is the primary pathophysiological mechanism of PD, considering PD solely a disorder of the dopamine system would be an overgeneralization; other neurotransmitter systems are affected by the disease, albeit to a lesser extent. The locus ceruleus suffers an average cell loss of 63% in PD patients compared to controls (McNamara & Durso, 2006). Cell loss in this region results in reduced cortical and limbic norepinephrine innervation. Scatton et al. (1983) studied autopsied brains of individuals diagnosed with PD and found a marked loss of norepinephrine in the hippocampus and cortical regions. Norepinephrine dysregulation can disrupt attentional processes and lead to heightened distractibility (Zgaljardic, Foldi & Borod, 2004). Reduced serotonin levels can also accompany the disorder (Castro, Pascual & Romon, 1998; Zhang et al., 2007). Serotonin modulates dopamine levels and plays an inhibitory role on presynaptic dopamine release. It has been hypothesized that a reduction in serotonergic activity may be a compensatory mechanism for reduced dopaminergic activity (Jacobs & Fornal, 1993). Serotonin dysregulation results in difficulties with behavioral and inhibitory control. Both the raphe nuclei (responsible for serotonin) and the locus ceruleus (responsible for norepinephrine) send projections to the striatum.
The cholinergic system is also affected by the disease process. Areas of the brain associated with cholinergic output (i.e. the basal forebrain and the nucleus basalis of Meynert) are degenerated in some patients, resulting in low levels of cortical acetycholine (ACh). Striatal ACh, on the other hand, is typically inhibited by stimulation of dopaminergic receptors. Given the lack of modulatory output from striatal dopamine, there is actually an affluence of ACh in the striatum, leading to a dopamine /ACh imbalance which can result in worsening of motor symptoms (Calbresi et al., 2006). A balance of striatal ACh and dopamine is thought to be important in normal motor functioning and thus this PD-related imbalance is thought to contribute to motor symptoms. Anticholinergics are often prescribed to regulate this imbalance and alleviate motor symptoms; however, these medications can paradoxically have a negative impact on cognition.

In addition to these neurotransmitter systems, Lewy Bodies are also related to disease pathology. While Lewy Bodies typically reside in the substantia nigra, they can also be found in other subcortical and cortical regions. Lewy bodies are thought to be involved in PD-related dementia. PD patients with a dementia diagnosis have nearly a ten-fold increase in Lewy Body inclusions in the cortex and limbic system than non-demented PD patients at autopsy (Apaydin et al., 2002). Concomitant AD pathology may also be present. In sum, the pathophysiological changes accompanying PD are not restricted solely to dopamine dysfunction and are thought to underlie some of the symptoms found in PD. However, it has been suggested that early PD pathology is relatively restricted for the most part to dopamine depletion in the striatum and therefore
it is believed that most non-dopaminergic abnormalities develop in the later stages of the disease (Cools, 2006).

*Parkinson’s Disease and Cognition*

While typically thought of as a motor disorder, recent research has focused specifically on the cognitive changes that can accompany PD. PD significantly affects the nigrostriatal system, and as expected, this has important consequences for those cognitive processes that rely on brain regions within this circuit. Cognitive deficits in PD are task-specific and dependent on the underlying neural substrates of each task. While the basal ganglia is a region greatly affected by PD, patients show impairments on only certain basal ganglia-dependent tasks, due to the anatomical segregation of this region. For example, in the early stages of the disease, PD is characterized by dopamine depletion in the dorsal striatum, whilst the ventral striatum remains intact. Accordingly, PD deficits in the earlier stages are restricted to those functions associated with the dorsal striatum, such as delayed spatial memory, while functions associated with the ventral striatum (such as reversal learning) remain intact (Cools, 2006).

The prefrontal cortex is also affected by the disease process and is thought to be responsible for the regulation of attention, planning, impulse control, mental flexibility, and the initiation and monitoring of actions. These types of higher-level processes are commonly termed executive functioning, which is a higher-order cognitive construct that is involved in the self-regulation of goal-directed behavior and important in the effective
organization and utilization of large amounts of information (Arnsten & Li, 2005, Uekermann et al., 2004).

Given the connectivity between the striatum and the frontal lobes, it is not surprising that numerous studies have found a range of executive functioning deficits in individuals with PD. One aspect of executive functioning that is affected in the earlier stages of the disease is working memory (Farina et al., 2000; Levin et al, 1989; Owen et al, 1992; Owen et al., 1995; Postle et al., 1997). Working memory tasks requiring manipulation and depending on DLPFC are often impaired in individuals with PD while the maintenance of information in short-term memory is usually intact, as maintenance relies more on the ventrolateral prefrontal cortex (Gilbert et al., 2005; Levi & Goldman-Rakic, 2000; Lewis et al., 2005; Rinne et al., 2000; Zgaljardic et al., 2006). Ventral prefrontal areas are typically not affected until later in disease progression.

Impairments have also been demonstrated on tests that assess planning and problem-solving ability such as tower tests (Culbertson et al., 2004; Hanes et al., 1996; Lewis et al., 2003;) and tests assessing inhibition, such as the Stroop Interference task (Gurd, 1995; Hanes et al., 1996; Hietanen & Teravainen, 1986; Janvin et al, 2002; Kensinger et al., 2003; McNamara et al., 2006). Verbal fluency is often impaired in individuals with PD, as this ability is thought to be circumscribed to the left DLPFC (Azuma et al., 2003; Bondi et al., 1993; Green et al., 2002; Gurd, 1995; Hanes et al., 1996; Steganova et al., 2001). The Wisconsin Card Sorting Task (WCST) is a set-shifting task that taps mental flexibility. It requires subjects to maintain attention to a reinforced stimulus dimension and then shift attention to a previously irrelevant dimension. Deficits
in set-shifting ability have been attributed to disruptions in frontostriatal circuitry (Purcell et al., 1997). As would be expected, individuals with PD often have difficulty on the WCST and other tasks measuring set-shifting ability (Bondi et al., 1993; Dirksen et al., 2006; Farina et al., 2000; Green et al., 2002; Lange et al., 1992; Lewis et al., 2005; Owen et al., 1992; Stamenovic et al., 2004; Stefanova et al., 2001).

Findings of frontal deficits in PD patients have not been entirely consistent, however. For example, some studies have found intact functioning on the WCST (Levin, Llabre & Weiner, 1989) and verbal fluency (Farina et al., 2000; Gabrieli et al., 1996; Rogers et al., 1998). One possible cause is the heterogeneity of the PD samples used in studies. For example, Levin et al. (1989) included a sample of PD patients with a wide range in disease severity who were taking some combination of dopaminergic and anticholinergic medication and demonstrated intact performance on the WCST. In contrast, Farina et al. (2000) only included patients in the early stages of the disease taking only dopaminergic medication and found a set-shifting impairment. These inconsistencies illustrate the need for future studies to take medication status and disease progression into account when examining cognitive status.

It has been suggested that PD-related frontal impairments stem from a failure to initiate mnemonic strategies and/or self-directed planning, processes that are important to successfully carry out tasks tapping executive functioning (Farina et al., 1994; Gabrieli et al., 1996; Knoke et al., 1998). When information to be spontaneously recalled exceeds the limits of normal memory span, individuals must impose an organizational strategy to effortfully encode information. Individuals with PD often fail to self-initiate these
strategies, resulting in poor performance on executive functioning tasks. It has also been hypothesized that PD patients have difficulty “keeping one’s place” in a situation where alternative possibilities need to be ignored (Taylor & Saint-Cyr, 1995). Such difficulties are thought to result in an inability to sort task-relevant from task-irrelevant information and to inhibit inappropriate thoughts or actions (Kensinger et al., 2003) An intact caudate has been proposed to act as a navigational guide, helping the prefrontal cortex favor one particular action over another. Caudate dysfunction means that the prefrontal cortex must act alone resulting in a shift from one strategy to another without the ability to lock onto the most successful one (Knoke et al., 1988). Thus, disease-related dysfunction in the caudate and frontal lobes can lead to an inability to generate and maintain a productive strategy while inhibiting task-irrelevant stimuli, which can significantly impact executive functioning abilities.

Cognitive impairments in PD are not universal, as the disease affects only certain areas of the brain. Other cognitive processes such as language, general intelligence, recognition memory, visuospatial construction, and semantic memory are generally unaffected by the disease process (Farina et al., 2000; Gabrieli et al., 1996; Green et al., 2002; Hsieh & Lee, 1999; Stefanova et al., 2001; Van Spaendonck et al., 1996; Vriezen & Moscovitch, 1990), illustrating the specific nature of PD-related cognitive effects.

For the most part, individuals with PD are not impaired on memory tasks relying on the medial temporal lobes, as this area does not receive direct projections from the striatum (Farina et al., 1994; Mungas et al., 1990). While memory impairments have been found in some studies on tasks such as Logical Memory, Visual Paired-Associates, and
delayed recall from the Rey Auditory Verbal Learning Test, it has been suggested these deficits stem from underlying frontal pathology (Hietanen & Teravainen, 1986, Stefanova et al., 2001; Whittington, Podd & Stewart-Williams, 2006). Bondi et al. (1993) demonstrated that when frontal measures were covaried with memory measures, memory impairments failed to reach significance. Stefanova et al. (2001) also found that frontal performance explained much of the variance in memory performance in their PD sample. Higginson et al. (2003) demonstrated that working memory performance was predictive of recall deficits and concluded that frontal deficits underlie the memory deficits they found in their PD sample.

Memory deficits can stem from a failure of the frontal lobes to initiate strategies to help with both the encoding and recall of information. Gabrieli et al. (1996) found that although individuals with PD were impaired on a recall task, these deficits stemmed from a failure to implement a semantic clustering strategy, suggesting a specific deficit in the internally-guided use of strategic memory rather than a deficit in memory ability. Likewise, Knoke et al. (1998) concluded that PD-related impairments on the California Verbal Learning Test (CVLT) were due to a poor organization strategy. Pillon et al. (1993) demonstrated that PD-related deficits on the CVLT were ameliorated when patients were provided with a mnemonic strategy. In addition, memory scores were related to performance on executive functioning tasks. These studies suggest that while individuals with PD may have memory deficits, these impairments are often sequelae to the primary frontal deficits found in PD (but not always, see Davidson et al., 2006). These memory deficits are often thought to reflect a dysexecutive syndrome in that the
individuals have difficulty accessing memory traces because they fail to self-initiate a strategy, whether it be an encoding or at retrieval.

Dopamine and Executive Functioning: Frontostriatal Circuitry

Disruptions in the dopaminergic frontostriatal circuit are thought to underlie many PD-related impairments. It is widely accepted that deficits in executive functioning are one of the primary cognitive changes that can accompany PD. Executive functioning relies heavily on the DLPFC, an area of the prefrontal cortex innervated by the frontostriatal dopamine circuit. Lesions to the DLPFC can result in impairments in attentional set-shifting (Manes et al., 2002), holding information “online” (Wallis et al., 2001), and maintaining delay-related activity in the presence of distracting stimuli (Miller et al., 1993). Disturbances in the DLPFC loop are thought to underlie early PD-related executive functioning deficits as the dorsal head of the caudate, which is part of the DLPFC circuit, is affected early in disease progression (Emre, 2003; Vingerhoets et al., 2003). Illustrating the differential involvement of the DLPFC loop in PD, Zgaljardic et al. (2006) examined three different groups of cognitive tasks thought to depend on either the anterior cingulate cortex, the DLPFC, or the orbitofrontal cortex. These three regions are all highly connected to the striatum via anatomically segregated circuits. PD patients demonstrated impairments on all DLPFC tasks, including phonemic fluency and backwards digit span, and all anterior cingulate cortex tests, including the Stroop Interference task, but did not show any impairments on the orbitofrontal cortex tasks. A logistic regression analysis demonstrated that DLPFC performance was the only factor
that differentiated PD patients from controls, leading the authors to suggest that the DLPFC shows differentially greater levels of dysregulation than other cortical areas.

PD-related dysfunction at any point along the frontostriatal circuit can result in impairments in executive functioning. For example, f-dopa uptake in the caudate of individuals with PD has been correlated with performance on the Stroop Interference task (Bruck et al., 2001; Rinne et al., 2000). Another study found hypoactivation in both the basal ganglia and the prefrontal cortex of individuals with PD during a working memory task (Lewis et al., 2003). Set-shifting has been correlated with a marker of striatal dopamine demonstrating denervation in the caudate (Marie et al., 1999).

Even in a population of healthy adults, markers of dopamine have been found to correlate with executive functioning, illustrating the importance of the dopamine system in non-clinical populations. Volkow et al. (1998) found correlations between dopamine receptors and performance on the WCST and the Stroop Interference test even when age was statistically partialed out. Dopamine receptor density has been found to be a strong predictor of cognitive performance in normal aging (Backman et al., 2000), suggesting that age-related changes in striatal dopamine may be a mediator of the cognitive losses occurring during the normal aging process. A review of imaging studies by Cropley et al. (2006) demonstrated that in both healthy subjects and patient populations, presynaptic dopamine levels have been correlated with performance on a variety of tasks, including selective reminding, the Stroop Interference task, backwards digit span, verbal fluency, word recall, and the WCST. Post-synaptic dopamine levels in the striatum and prefrontal
cortex have correlated with verbal fluency, WCST, Stroop, trails, a tower task, and spatial span.

Individuals with MPTP-induced parkinsonism provide another means of examining the cognitive consequences of dopamine depletion. MPTP, a neurotoxin that induces biochemical and pathological changes similar to idiopathic PD, was self-administered by twelve individuals. Changes in the serotonergic and cholinergic systems have not been noted in these individuals, suggesting that MPTP-induced parkinsonism may be a purely hypodopaminergic condition (Stern & Langston, 1985). These individuals demonstrated impairments on tasks such as the Stroop Interference task, category naming, and reaction time tasks (Stern & Langston, 1985, Stern et al., 1990). The authors suggest that this pattern of performance is similar to that found in idiopathic PD, and hypothesize that changes in the dopaminergic system are responsible for at least some of the cognitive changes associated with idiopathic PD.

*Dopamine and Executive Functioning: Pharmacological Challenge*

Effects of dopaminergic medication can also speak to the role of dopamine in cognition. Processes that are impaired in PD patients and dependent on dopamine should be impaired when dopamine medication is withdrawn and improve with medication reinstatement. Studies examining dopaminergic effects using pharmacological challenge often utilize either l-dopa preparations or dopaminergic agonists. A dopaminergic agonist binds to dopamine receptors, mimicking the effects of endogenous dopamine and activating the receptor, resulting in increases in dopamine levels. Levodopa, or l-dopa, is
a dopamine precursor that crosses the blood brain barrier and then is metabolized into dopamine by decarboxylase enzymes. A dopamine precursor is needed because dopamine itself cannot cross the blood brain barrier. This metabolic process can also occur outside of the central nervous system, and thus it is standard for a decarboxylase inhibitor to be administered along with l-dopa (e.g. Sinemet). The administration of dopaminergic medication to PD patients in the form of l-dopa or dopamine agonists increases dopamine levels in the central nervous system and can improve motor symptoms as well as performance on executive functioning tasks such as verbal fluency, Stroop Interference, tower of London, WCST, digit span, planning, and spatial working memory (Brusa et al., 2002; Costa et al., 2003; Gotham et al., 1988; Hamel & Riklan, 1975; Lange et al., 1992; Lange et al., 1995; Luciana et al., 1998; Owen et al., 1995). Cools et al. (2002) demonstrated that in individuals with PD, l-dopa normalized blood flow to the DLPFC during planning and spatial working memory tasks. Even in healthy adults, the administration of Bromocriptine, a dopamine agonist, improves spatial working memory, while Fenfluramine, a drug that decreases dopamine transmission, leads to worsened performance (Luciana et al., 1998). These findings suggest that performance on many executive functioning tasks rely on dopaminergic functioning.

The administration of dopaminergic medication does not always have a beneficial effect, however, due to the regional specificity of the disease. Dopaminergic medications do not target specific brain regions and it has been demonstrated that l-dopa can affect both cortical and subcortical dopamine levels (Scatton et al., 1983). While dysregulation in some areas may be ameliorated with medication administration, other non-depleted
areas may actually be oversaturated, leading to a dissociable effect of dopamine medications on different tasks (Swainson et al., 2000). For example, medication leads to improvements in cognitive flexibility, which relies on the DLPFC, but worsened decision-making performance on a gambling task, which relies on the ventromedial prefrontal cortex (Cools et al., 2003). Medication can also have a deleterious effect on verbal memory, reversal learning, recognition memory and incremental learning (Ridenour & Dean, 1999; Shohamy et al., 2006; Swainson et al., 2000; Whittington, Podd & Kan, 2000). Thus, l-dopa can improve certain functions that are associated with significant dopamine dysregulation (e.g. DLPFC) while oversaturating those areas that are not as affected by the disorder (Cools, 2006). In addition, several studies have shown that medication can have no effects on certain cognitive processes such as visual learning, delayed match-to-sample, or visual discrimination (Lange et al., 1992; Lange et al., 1993; Ridenour & Dean, 1999). This suggests that some cognitive processes are impervious to fluctuations in dopamine levels, suggesting that dopamine is not important to all aspects of cognitive functioning.

Source Memory and Parkinson’s Disease

One area of cognitive functioning that has received very little attention in the PD literature is source memory. Source memory is thought of as memory for the characteristics of the specific conditions or context under which a memory is acquired. Memory for source can refer to the spatial, temporal or social context of an event, or the modalities through which it was perceived (Johnson et al., 1993). Source memory has
implications not only for cognitive testing in the lab (e.g. do I recognize this word because it was on the list I was supposed to remember, or did I hear it before I came into the memory experiment?) but also for everyday life (e.g. I recognize this woman, but do I know her from church or from the library?).

It has been suggested that context retrieval is related to the integrity of the frontal lobes, more specifically the DLPFC. The frontal lobes are thought to be responsible for binding information in memory to the various aspects of its context (Janowsky et al., 1989; Squire, 1987). This is in contrast to item memory which is typically ascribed to the medial temporal lobes. Lesion studies provide further evidence for the role of the frontal lobes in source memory, as patients with frontal lesions show impairments in memory for contextual information despite intact memory for the actual event (Trott et al., 1999). A study by Kopelman, Stanhope, and Kingsley (1997) found that a temporal context memory task was impaired in patients with DLPFC lesions. Patients with medial prefrontal lesions or other large lesions sparing the DLPFC performed normally on this task in this study. Neuropsychological evidence also provides support for frontal involvement, as correlations between frontal lobe functioning and source memory have been found in healthy older adults (Craik et al., 1990; Glisky, Polster & Routhieaux, 1995; Glisky, Rubin, & Davidson, 2001). Neuroimaging has also contributed to the growing body of evidence as studies have found that compared to item memory, retrieval of source information leads to increased activation in the left prefrontal cortex (Dobbins et al, 2002; Nolde et al, 1998).
Source memory and item memory are typically thought to be orthogonal, suggesting that source memory demands additional processes that are not needed for item recognition. Kuo and Van Petten (2006) suggested that the prefrontal cortex is needed to aid in the recovery of weakly encoded relationships and is engaged in source memory retrieval when the context of the stimulus is weakly encoded. These authors demonstrated that if explicit instructions were given to integrate the context with the item, source memory improved and previously-elicited prefrontal event-related potential activity was eliminated. They suggested that prefrontal brain regions are involved in the memory search for weakly-encoded links between contextual and item information. Similarly, Glisky et al. (2001) found that when subjects were oriented to the relationship between the item and its context at encoding, the source memory performance of those subjects with low frontal functioning and low source scores improved, while the performance of those subjects with high frontal functioning remained high and were unchanged. This suggests that the frontal lobes are involved in the self-initiation of encoding processes that integrate the item with its context.

Both of these studies support the idea that providing external support and strategies make the source memory task less frontally-dependent. Similarly, Spencer and Raz (1994) suggested that frontal functioning is important in source memory because when working memory capacity or speed of information processing decreases, as occurs in normal aging, cognitive resources are diminished. Thus, the resources that are remaining are focused on the target of the task (typically the item) and these intentionally-memorized aspects are given priority over the more incidentally-encoded
items, such as context. Thus, individuals with poor frontal functioning do not automatically bind an item and its context in memory during encoding due to poor strategy initiation and/or diminished cognitive resources. It has previously been hypothesized that the frontal lobes are involved in source memory tasks simply due to the difficult nature of the task. However, Glisky et al. (2001) equated item and source memory tasks for difficulty and found that source memory performance was still related to frontal functioning in older adults, suggesting that frontal involvement in source memory is not necessitated solely by the difficulty of the task.

Based on the frontal nature of the cognitive impairments found in PD, presumably individuals with PD should also show deficits in source memory. Tests assessing frontal functioning have been shown to predict source memory performance in non-clinical samples, suggesting that they rely on similar processes (Craik et al., 1990; Glisky et al., 1995; Glisky et al., 2001). In healthy older adults, source memory performance was predicted by a composite measure of tests thought to assess frontal functioning (Glisky et al., 2001). The frontal composite score was based on five executive functioning tasks: the WCST, a test of mental arithmetic, backwards digit span, verbal fluency, and a test of mental control. There is some evidence that individuals with PD may also show impairments on these tasks. PD-related impairments on the WCST and verbal fluency have widely been found (Azuma et al., 2003; Bondi et al., 1993; Farina et al., 2000; Green et al., 2002; Gurd, 1995; Hanes et al., 1996; Lange et al., 1992; Lewis et al., 2005; Stamenovic et al., 2004; Stefanova et al., 2001). One study demonstrated impairments in PD in mental control (Levin, Llabre & Weiner, 1989) while another found no deficits
(Hamel & Riklan, 1975). Only one study has specifically looked at backwards digit span in PD and demonstrated an impairment (Rinne et al., 2000). While no specific study has compared arithmetic performance of PD patients to controls, Kulisevsky et al. (2000) found that administration of long-term l-dopa therapy led to significant improvements in mental arithmetic, suggesting that dopamine plays a role in this ability. If this frontal composite score taps similar processes as those used in source memory (as suggested by the relation found by Glisky et al., 2001), PD patients who show impairments on these executive functioning tasks should also demonstrate an impairment in source memory.

Although source memory in PD has not been well-studied in the literature, there is evidence suggesting a disease-related source memory impairment. Individuals with PD show impairments in aspects of contextual memory, including temporal ordering and sequencing (Brown & Mardsen, 1990; Vermeule & Santens, 2005; Vriezen & Moscovitch, 1990), although this finding is not universal (Cooper, Sagar & Sullivan, 1993; Davidson et al, 2006; Vingerhoets, Vermeule, & Santens, 2003). Other studies have attempted to link source memory to basal ganglia and dopamine dysfunction. A study examining Huntington’s Disease, a neurodegenerative disease characterized by dysfunction of the basal ganglia, found that source memory was impaired despite intact memory for facts. Volume of the left caudate on MRI scans correlated with source memory (Brandt et al., 1995). In an attempt to link source memory to dopamine, Wittmann et al. (2005) demonstrated that source memory was better for reward-dependent stimuli in healthy adults. Because reward-dependent learning relies on the dopamine system, the authors suggested that reward-dependent stimuli led to increased
dopamine release which resulted in improved source memory for the stimuli. Thus, research findings have suggested that source memory may be dependent on dopaminergic frontostriatal circuitry, providing support for possible PD-related deficits in source memory.

Few published studies have specifically examined source memory in PD. Taylor, Saint-Cyr, and Lang (1990) examined source memory performance in unmedicated Parkinson’s patients using the CVLT. Patients were shown words and asked to determine whether the word was from a list previously presented five times, from a list presented once, or if it was an unlearned distractor word. Individuals with PD had difficulty localizing the source of words from the over-learned list. Hsieh and Lee (1999) examined different types of source monitoring in a group of medicated PD patients using three different experiments. They found that the ability to discriminate between two external sources and also between an external and internal source was intact. The authors concluded that PD patients were able to use distinctive cues to discriminate between the two different sources. In the external-external condition, participants heard male and female voices and were also simultaneously shown a picture of each speaker, increasing the distinctiveness of the sources. PD patients were, however, impaired in their ability to discriminate between two internal conditions – speaking a sentence or thinking about speaking the sentence. The authors suggested that the lack of discriminability between these conditions resulted in source impairments for the PD patients.
The Relation amongst DA, Source Memory, and Executive Functioning

The relation between executive functioning, dopamine, and the prefrontal cortex has been well-established in the literature. While it is possible that source memory may be an integrated part of this frontal network, the exact processes that interconnect executive functioning and source memory are unknown. It is also unclear whether dopamine plays a role in this relationship. It may be that both tasks require the initiation of strategy and/or inhibition of task-irrelevant information. Source decisions can at times be made rapidly and heuristically during the course of remembering. However, they sometimes involve more strategic processes, especially when contextual details are not automatically encoded with the item trace and when sources are not easily discriminable (Johnson et al, 1993). In the case of perceptually similar and overlapping sources (for example, sources in the same modality with close temporal proximity), it would be expected that a quick heuristic process would not be sufficient and a more systematic and deliberate strategic decision would need to be made in order to discriminate between the two sources and make an accurate source judgment. These strategic processes are thought to depend on the frontal lobes and are also critical to many executive functioning tasks, as strategy is important in planning, problem-solving, and organizing information within working memory. If dopamine allows an individual to focus on task-relevant features while ignoring irrelevant stimuli (as suggested by Kensinger et al, 2003), an intact dopamine system would be beneficial in discriminating between very similar items by focusing attention on the perceptual features of the stimuli that are needed for accurate discrimination. Ignoring distracting stimuli is also an important part of many executive
functioning tasks, including those assessing inhibition and set-shifting. Thus, both accurate source discrimination and executive functioning rely on self-initiated strategies and the inhibition of task-irrelevant characteristics, two processes thought to be subserved by the prefrontal dopamine system.

Another possibility stems from the cognitive control theory proposed by Braver et al. (see Braver, Barch & Cohen, 1999, Braver et al., 2001, Braver & Barch, 2002), who have suggested that the common element amongst many frontal tasks is that they require the internal representation, maintenance, and updating of contextual information. Context is described as any task-relevant information that biases performance processing in task performance. Contextual information is important in both executive functioning and source memory tasks. For example, contextual information in the form of goal representation is critical to many executive functioning tasks such as those measuring planning. Braver et al. also suggested that contextual information is particularly important to decision-making when there are competing responses, which is consistent with the notion that an important component of executive functioning is the inhibition of task-irrelevant stimuli. Contextual information is also critical to source memory, as source memory tasks require the representation of non-target information in memory (e.g. the sex of the speaker who spoke the sentence).

According to this cognitive control theory, certain tasks are frontally-dependent because contextual representations are updated and maintained within the DLPFC. Dopamine projections are responsible for regulating the updating and maintenance of these representations in the frontal cortex. Using computational modeling, Braver et al.
(2001) proposed that phasic changes in dopamine activity modulate the updating and maintenance of contextual information while inhibiting irrelevant information and interference. Thus, it is possible that both executive functioning and source memory rely on the prefrontal cortex and dopamine levels because of the context-dependent nature of both processes.

Therefore, there are several possible reasons that executive functioning and source memory may be dopamine-dependent, as they may both rely on context-processing, inhibition of task-irrelevant information, and/or the initiation of strategic processing. It is possible that dopamine dysregulation in PD leads to impairments in any or all of these processes, manifesting as impairments in both source memory and executive functioning. If changes in dopamine levels in the frontal lobes are responsible for these shared processes, it would be expected that performance on these tasks would be related and that dopamine would mediate this relationship.

**The Current Study**

Previous research has illustrated the specific nature of executive functioning deficits in PD, which are mostly thought to stem from dopaminergic deficits in the DLPFC circuit of the corticonigrostriatal pathway. Despite the burgeoning research on executive functioning in PD, source memory has been relatively ignored in the PD literature. Source memory is thought to be frontally-dependent and has previously been associated with executive functioning, suggesting that PD patients may demonstrate deficits in source memory. Two previous studies have examined source memory in this
population, and the current study aimed to extend their findings. Taylor, Saint-Cyr, and Lang (1990) used the CVLT, a list-learning task, to examine source memory. One list was read to the participants five times, while another list was read only once. Imbedded in a masked recognition task, participants were asked to judge whether words came from the first or second list. The lists were not presented an equal number of times, which would have resulted in differences in the strength of the memory trace. This can be problematic, as source memory judgments in such a task can be based on levels of familiarity or the strength of the memory trace rather than the actual memory for the source of the stimulus. Given that PD patients may have impairments in familiarity (Davidson et al., 2006), it is unclear whether poor performance on this task stemmed from a deficit in source memory or familiarity.

Hsieh and Lee (1999) also examined source memory in the PD population and found deficits only in the more difficult manipulation where patients were provided with fewer source cues. This study used a three-alternative forced-choice paradigm, where participants made source judgments only on items that they correctly recognized from the study phase. Given that it has been suggested that item and source memory are orthogonal, it is possible that contextual memory can exist independent of an accurate item judgment. Thus, in order to gain a better understanding of these contextual memory traces, it would be beneficial to test source memory for all studied stimuli, not just those that are recognized. The current study uses separate item and source stimulus presentation and tests in order to independently study item and source memory independent of each other. The Hsieh and Lee study also increased the distinctiveness of
the sources in the external-external condition by utilizing pictures of the speakers. It is possible that with less contextual cues (i.e. just the sound of a male or female voice) patients may show impairments in discriminating between two external sources.

In addition, the PD patients tested by Hsieh and Lee (1999) study were all medicated and taking their anti-Parkinson's medication at the time of the study. Because of possible side-effects, it is important to test PD patients while in an off-medication state in order to gain an understanding of those specific deficits associated with the disease independent of medication. Based on findings that some cognitive processes are improved by medication, Lange et al. (1992) suggested that l-dopa therapy may be masking some of the cognitive deficits associated with the disease. The current study eliminated medication status as a confounding factor and actually used it as a variable of interest. Source memory was measured while patients were on their normal dose of anti-Parkinson’s medication, and also after a medication withdrawal period. This allowed for an examination of cognitive processes independent of medication effects and also allowed for a comparison of cognitive performance on and off medication.

The goals of the current study were multiple. Source memory performance of PD patients was compared to that of normal control participants while in the off-medication state, allowing for an examination of source memory abilities independent of medication effects. However, source memory was also tested in PD patients in an on-medication state, allowing for an examination of the effect of changes in phasic dopamine levels on source memory. Given the previous research linking source memory to both the DLPFC, an area innervated with dopaminergic projections from the striatum, and to other
dopamine-dependent executive functioning tasks, it is possible that the processes involved in source memory rely, at least in part, on the dopaminergic system. It was hypothesized that source memory performance would be affected by the withdrawal of dopaminergic medication.

To our knowledge, no studies have explored the relation between source memory and executive functioning in the PD population. The subset of executive functioning tasks administered in this study were divided into two composite factors, as indicated by principal components analyses: one thought to be related to executive functions in working memory (FFAC; see Glisky & Kong, in press) and one hypothesized to tap other aspects of frontal function, perhaps planning abilities (PFAC). These factors are thought to tap different aspects of executive functioning and have been validated on a large group of older adults. The FFAC is composed of five measures thought to reflect the self-initiation of integrative encoding in working memory, allowing for the binding of an item with its context during encoding. In support of this, Glisky et al. (2001) demonstrated that when integrative instructions were provided, the source memory performance of those older adults with low FFAC scores improved while the performance of those individuals with high FFAC scores were unchanged.

Exactly what aspects of executive function are captured by the PFAC is, at this time, still undetermined, although the tests were selected to reflect planning ability. As previously discussed, it has been suggested that planning ability is dependent at least in part on the DA system. PD-related deficits have been demonstrated on tower planning tasks and complex figure copy (Grossman et al., 1993; Uc et al., 2006). In addition, it has
been found that dopamine depletion impairs performance on a tower planning task (Mehta et al., 2005). Both a tower task and a complex figure copy are components of the PFAC. While no direct relationship between the tasks that comprise the PFAC and source memory has been demonstrated to our knowledge, it would be expected that PFAC and source memory should be related if both measures rely on the same cognitive processes (e.g. cognitive control) and/or biological processes (i.e. DA).

Based on previous findings of disease-related executive dysfunction, it was hypothesized that PD patients would demonstrate impairments on both the FFAC and PFAC. Given that source memory may rely on the same processes that subserve these executive functioning tasks, it was hypothesized that source memory would be related to the FFAC (as has been previously demonstrated in healthy older adults) and possibly also the PFAC.
CHAPTER 2: Methods

Participants:

Twenty-six individuals diagnosed with PD were recruited for the study from the VA Ann Arbor, the VA Tucson, the University of Michigan Neurology Clinic, and PD support groups in the Tucson, Lansing, and Ann Arbor areas. Patients were recruited via advertisements and referrals from physicians and other researchers. Of these 26 individuals, two patients were unable to complete the study (one could not stay awake during the study sessions and one reported that she didn’t feel like completing the memory tests and guessed randomly at all the answers) and thus data from 24 patients were used in the analyses. One patient had to leave a session early and did not complete two of the neuropsychological tasks. Demographic information and relevant medical history were obtained via structured background interview. Patients were excluded from the study if they had received surgical treatment for PD or received a PD diagnosis before the age of 50. All patients in the PD group had previously received a diagnosis of PD from their physician and were taking some form of dopaminergic medication (i.e. l-dopa or dopamine agonists). Of the 24 medicated patients, five were taking only l-dopa preparations (i.e. Sinemet), eleven were taking l-dopa in combination with other anti-Parkinson’s medication (e.g. dopamine agonists, MAO inhibitors, COMT inhibitors, or NMDA inhibitors), one was taking only a dopamine agonist, and seven were taking a dopamine agonist in combination with other anti-Parkinson’s medication. All PD patients participated in the study under the approval and supervision of their primary physician or neurologist. Disease severity ratings (Hoehn and Yahr stages; Hoehn & Yahr, 1997) were
determined by a trained member of the research team. Inclusion criteria limited disease severity to mild-to-moderate levels (i.e. Hoehn and Yahr Stages 1-3) in order to limit the heterogeneity of the patient sample and reduce incidences of dementia as much as possible. Of the 24 PD patients, ten met Hoehn and Yahr criteria for stage 1 or 1.5, thirteen for stage 2 or 2.5, and one for stage 3. The PD patients ranged in age from 56 to 80 ($M = 69.04$, $SD = 7.42$) with education levels ranging from a high school diploma to a doctoral degree ($M = 16.58$ years, $SD = 2.86$). Years since diagnosis ranged from one to ten ($M = 4.46$, $SD = 2.75$), although many patients reported experiencing symptoms prior to their official diagnosis. Average age at diagnosis was 64.62 ($SD = 8.05$).

Twenty-four control participants were recruited from the Ann Arbor community through the Claude D. Pepper Older Americans Independence Center at the University of Michigan. Control participants were recruited based on their demographic information in that each control participant was matched to a PD patient on sex, age, and education level. Mean age of control participants was 68.67 ($SD = 8.34$) with a mean education level of 17.08 ($SD = 3.03$). Paired samples t-tests revealed no significant differences between the PD and control groups in age ($t = .70, p = ns$) or education ($t = -1.2, p = ns$). Exclusion criteria for both groups included dementia (Mini-Mental Status Exam score < 26), a history of traumatic brain injury or a neurological disorder other than PD, medications believed to affect cognitive function, or a prior history of alcohol or drug dependence or a psychiatric disorder other than depression. Depression was not included as an exclusionary criterion, as depression is often a secondary result of underlying dopamine pathology and excluding for depression could possibly have reduced the power
to examine cognitive functions associated with dopamine depletion. One PD patient and two control participants had previously been diagnosed with depression.

Materials:

The Mini-Mental Status Exam (MMSE) was administered to exclude for dementia and the Geriatric Depression Scale (GDS) was given to assess depression. Sections II (activities of daily living) and III (motor examination) from the United Parkinson’s Disease Rating Scale (UPDRS) were used to determine Hoehn and Yahr disease stage and symptom severity.

Neuropsychological Tasks

A set of five neuropsychological tests traditionally associated with frontal functioning was administered: the FAS verbal fluency task (FAS), the modified Wisconsin Card Sort Task (mWCST), Backwards Digit Span (BDS) and Mental Control from the Wechsler Memory Scale-III, and Mental Arithmetic from the Wechsler Adult Intelligence Scale-Revised. Also included in the neuropsychological battery were three neuropsychological tests that measured a different set of functions associated with the frontal lobes, possibly planning ability: the Rey-Osterrieth Complex Figure Task (Rey-O), the zoo map planning test from the Behavioral Assessment of Dysexecutive Syndrome (BADS) and the Tower of Toronto. The finger tapping test (FTT) and the North American Adult Reading Test (NAART), an estimate of premorbid verbal IQ, were also administered.

A composite frontal factor score (FFAC) was computed from the total raw scores on the BDS, Mental Control and Mental Arithmetic, categories achieved on the mWCST,
and total words produced on the FAS. For more detail on the frontal factor scores, refer to Glisky et al, (1995; 2001). The raw scores from these tests were converted to z-scores based on the sample of 48 patients and controls. An FFAC score was computed for each participant by averaging their z-scores on the five tests. The other composite measure (PFAC) was computed in the same way and was based on a symmetry score from the Rey-O (Bennett-Levy, 1984), the raw score from the BADS Zoo Map 1 planning test, and planning time (time until the first move) from the Tower of Toronto.

**Memory tasks**

A total of 132 neutral sentences were used for the memory tasks, taken from Cook (2007). Each sentence was recorded by both a female and male speaker. Six lists of 20 sentences were formed along with a list of 12 sentences serving as practice and buffer items.

For the source memory task, participants were told that they would be hearing sentences spoken by a male and a female voice. They were instructed to rate each sentence as to how likely it would be that the sentence would be heard on the radio, using a likert-scale rating from 1 to 5. They were also told that they would be later tested on whether the male or the female spoke each sentence. Two practice sentences were given to ensure that each participant could hear the sentences and understood the rating instructions. The twenty sentences were presented aurally in randomized order, with two sentences added at both the beginning and the end of the list to serve as primacy and recency buffers. For each study list, half of the sentences were spoken by the male, and half were spoken by the female. The study list was presented twice, with the 20 sentences
presented in a different random order each time. After the study presentation, participants were given the source test. Each sentence was printed at the top of the screen, and participants were asked to decide whether the male or the female spoke that sentence by pressing the “M” or “F” key. Two practice sentences were given to ensure that the participants understood the test. The test was self-paced.

For the item memory task, participants were told that they would be hearing sentences spoken by one male voice. Presentation of the item study lists was identical to that of the source study lists except that all sentences were presented in a male voice. The participants were told that a memory test would be given later that would require them to recognize the sentences they just heard. After the item study presentation, participants were given a two-alternative forced choice test. Two sentences were printed on the screen, one above the other, labeled “A” and “B”. Participants were told to decide whether they previously heard sentence “A” or sentence “B” and to respond by pressing either the “A” or “B” button on the keyboard. Half of the previously-heard sentences were presented as sentence A and half were presented as sentence B. Two practice sentences were given to ensure that the participants understood the test. The test was self-paced. The source and item memory tasks were presented on a laptop screen using DMDX software (Forster, K. & Forster, J., 2003).

Of the six lists, the same three lists were always used for the first session and the same three lists were used for the second session (with medication status counterbalanced across the first and second sessions). Six counterbalancing conditions were created such that across subjects, each of the three lists served as the item study list, item distractor
list, and source study list, and that for the source study list, each sentence was spoken by both the male and female speaker. The order of the source and item tasks was counterbalanced across participants. Each PD patient and his or her matched control received the same counterbalancing condition and source/item sequence. Participants completed the source and item tasks a total of two times and heard a new non-overlapping set of sentences each session.

Procedure:

The study was held in three different locations: the Amnesia and Cognition Laboratory at the University of Arizona, the University of Michigan Neuroimaging, Cognition, and Mobility Laboratory, and the Burcham Hills Retirement Home in Lansing, Michigan. Human subject approval for the study was granted by the University of Arizona, the University of Michigan, and the VA Ann Arbor. PD patients were asked to come to the laboratory for two sessions. For one visit, patients were asked to abstain from their PD-related medication for a period of at least 12 hours (the off-medication session). The average withdrawal period was 14.88 hours with a range of 12 to 21 hours. No patient reported any serious negative side-effects of this medication withdrawal and all were able to complete the off-medication session. For the on-medication session, patients were asked to take their medication as normal. The on-medication and off-medication sessions were scheduled at the same time of day, at least one day apart. The sequencing of the on/off medication sessions was counterbalanced across subjects. PD patients always gave informed consent and completed the background interview and the activities of daily living section of the UPDRS during the first session, regardless of
medication status. The motor examination of the UPDRS, FTT, and memory tests were given during both sessions. During the off-medication session, patients also completed the MMSE, the GDS, and the neuropsychological battery.

Control participants also came to the laboratory for two sessions, scheduled at the same time of day, at least one day apart. Each session was assigned to be either “on-medication” or “off-medication,” as determined by the sequence that was assigned to their corresponding PD patient. This was done for matching purposes, but no medication was administered to the control participants. Control participants completed the same tests in the on- and off-medication sessions as the PD patients, with the exception of the UPDRS, which was not administered to control participants.
CHAPTER 3: Results

Demographic information along with GDS, NAART, and MMSE scores for the PD group and control group are shown in Table 1. There were no significant differences in premorbid intelligence or mental status between the groups. The PD group endorsed significantly more depressive symptoms than the control group, $t(23) = 3.28, p = .003$. Seven PD patients met criteria for mild or moderate depression (i.e. GDS>10).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.67</td>
<td>69.04</td>
</tr>
<tr>
<td>Education</td>
<td>17.08</td>
<td>16.58</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.88</td>
<td>28.67</td>
</tr>
<tr>
<td>GDS</td>
<td>3.08</td>
<td>6.92</td>
</tr>
<tr>
<td>NAART</td>
<td>43.54</td>
<td>42.25</td>
</tr>
</tbody>
</table>

Medication and Memory Effects

Within the PD group, a paired-samples $t$-test indicated a significant difference between on and off medication conditions on the UPDRS motor exam, $t(23) = -7.07, p < .001$. As expected, UPDRS scores were lower in the on-medication condition, indicating that motor symptoms improved with medication administration. Source memory and item memory did not significantly differ between the two conditions, $t(23) = -1.16$, $t(23) = -0.93$, respectively. In order to examine whether the effects of medication on cognitive and motor performance in PD patients were significantly different than fluctuations that
normally arise in repeated testing, a multivariate repeated measures analysis of variance was conducted with group (PD/control) as the between-subjects factor, medication status (on/off) as the within-subjects factor, and source memory, item memory, and FTT scores as the dependent variables. Table 2 displays these scores separated by group and medication status. There was a significant interaction between group and medication status for dominant FTT scores, $F(1,46) = 4.11, p = .048, \eta^2_p = .08$, as scores improved with medication in the PD group, $t(23) = 2.58, p = .02$, but not the control group. There were no group-by-medication interactions for source memory, item memory, or non-dominant FTT. There was a significant main effect of group on source memory, $F(1,46) = 9.466, p = .004, \eta^2_p = .17$, as the PD group performed significantly worse than the control group. Item memory performance did not differ significantly between the PD group and the control group, $F(1,46) = 3.347, p = .07, \eta^2_p = .07$. A PD-related impairment in source memory but not item memory was further illustrated by a significant interaction in a repeated measures analysis of variance with group (PD/control) as the between-subjects factor and memory test (item/source) as the within-subjects factor, $F(1,46) = 5.25, p = .03$. Main effect analyses of medication status were not examined given that medication status was only of interest in the PD group.
Table 2

*Mean (SD) Scores from Memory and Motor Tests On and Off Medication*

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“On”</td>
<td>“Off”</td>
</tr>
<tr>
<td>UPDRS</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>domFTT</td>
<td>41.2 (7.0)</td>
<td>41.2 (6.9)</td>
</tr>
<tr>
<td>nondomFTT</td>
<td>36.8 (5.7)</td>
<td>36.8 (6.1)</td>
</tr>
<tr>
<td>Source</td>
<td>15.5 (3.2)</td>
<td>16.7 (2.9)</td>
</tr>
<tr>
<td>Item</td>
<td>19.6 (0.6)</td>
<td>19.7 (0.6)</td>
</tr>
</tbody>
</table>

**Neuropsychological Effects**

For comparisons between PD patients and controls, the off-medication neuropsychological performance of the PD group was compared to the “off-medication” performance of the control group in order to mitigate any medication effects. The means and standard deviations for each group on each of the neuropsychological measures are presented in Table 3. Paired-samples *t*-tests indicated that the PD group performed significantly worse on BDS (*t*[23] = -2.11, *p* = .046), Rey-O (*t*[23] = -2.88, *p* = .01), Zoo Map (*t*[23] = -4.98, *p* < .001), FFAC (*t*[23] = -2.67, *p* = .01), PFAC (*t*[23] = -4.35, *p* < .001), and dominant FTT (*t*[23] = -2.39, *p* = .03). The groups did not significantly differ on any of the other executive functioning subtests.
Table 3

Neuropsychological Data and Memory Scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Control</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFAC*</td>
<td>0.22 (0.62)</td>
<td>-0.22 (0.70)</td>
</tr>
<tr>
<td>FAS</td>
<td>46.13 (12.23)</td>
<td>41.00 (13.19)</td>
</tr>
<tr>
<td>BDS*</td>
<td>8.12 (2.68)</td>
<td>6.70 (2.22)</td>
</tr>
<tr>
<td>Mental Arithmetic</td>
<td>13.57 (3.55)</td>
<td>12.04 (3.88)</td>
</tr>
<tr>
<td>Mental Control</td>
<td>26.83 (4.36)</td>
<td>24.67 (4.62)</td>
</tr>
<tr>
<td>mWCST categories</td>
<td>4.67 (1.76)</td>
<td>3.83 (2.12)</td>
</tr>
<tr>
<td>PFAC**</td>
<td>0.32 (0.46)</td>
<td>-0.34 (0.59)</td>
</tr>
<tr>
<td>Rey-O**</td>
<td>8.83 (3.50)</td>
<td>6.25 (2.94)</td>
</tr>
<tr>
<td>°Tower of Toronto</td>
<td>12.22 (19.90)</td>
<td>10.96 (21.72)</td>
</tr>
<tr>
<td>°Zoo Map**</td>
<td>4.82 (3.58)</td>
<td>0.52 (2.94)</td>
</tr>
</tbody>
</table>

*n=23 in each group  *p<.05 **p<.01

Correlational Analyses

Correlations between source memory, item memory, and the neuropsychological measures for all 48 participants are presented in Table 4. Because source and item memory scores were not affected by medication status in the PD group, “on” and “off” medication memory scores were averaged for all participants to form composite scores for the correlational analyses. A correlational analysis with all participants demonstrated that source memory was significantly correlated with item memory ($r = .36, p = .01$), but this correlation was significant within the PD group ($r = .40, p = .05$) but not within the control group ($r = .18, ns$). Of particular interest were the correlations between source memory and the two factor scores. In the combined group of 48 individuals, both of these correlations were significant: for the FFAC, $r = .30, p = .03$, and for the PFAC, $r = $
.32, \( p = .03 \). Within each of the two groups, however, correlations between source memory and the factor scores failed to reach significance. Within group correlations for the PD group and the control group are presented in Tables 5 and 6, respectively. For the FFAC, correlations with source memory were \( r = .07, \ p = .76 \) for the PD group and \( r = .31, \ p = .15 \) for the control group. Correlations between the PFAC and source memory were \( r = -.09, \ p = .70, \ r = .36, \ p = .08 \) for the PD and control groups respectively. When “group” was entered into a regression equation with either the FFAC or the PFAC, the factor scores no longer accounted for a significant portion of source memory variance (\( p = .20, \ p = .38 \) respectively). Group membership was the only significant predictor for source memory, accounting for 12% and 9% of the variance in source memory. Thus, the overall correlations appear to be driven by group differences, as illustrated by the scatterplots showing the correlations between source memory and the two factors scores, FFAC (Figure 1) and PFAC (Figure 2). Specifically, the below-average scores are predominantly from individuals in the PD group whereas the above-average scores are predominantly contributed by normal controls.

Table 4

*Correlations Between FFAC, PFAC, and Memory Scores for All Participants*

<table>
<thead>
<tr>
<th></th>
<th>Source</th>
<th>Item</th>
<th>FFAC</th>
<th>PFAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>--</td>
<td>0.36*</td>
<td>0.30*</td>
<td>0.32*</td>
</tr>
<tr>
<td>Item</td>
<td>--</td>
<td>0.06</td>
<td>-0.03</td>
<td></td>
</tr>
<tr>
<td>FFAC</td>
<td>--</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFAC</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*\( p < .05 \)
Table 5

*Correlations Between FFAC, PFAC, and Memory Scores for the PD Group*

<table>
<thead>
<tr>
<th>Source</th>
<th>Item</th>
<th>FFAC</th>
<th>PFAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>--</td>
<td>.41*</td>
<td>.07</td>
</tr>
<tr>
<td>Item</td>
<td>--</td>
<td>-.07</td>
<td>-.32</td>
</tr>
<tr>
<td>FFAC</td>
<td>--</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>PFAC</td>
<td>--</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<.05

Table 6

*Correlations Between FFAC, PFAC, and Memory Scores for the Control Group*

<table>
<thead>
<tr>
<th>Source</th>
<th>Item</th>
<th>FFAC</th>
<th>PFAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>--</td>
<td>.18</td>
<td>.31</td>
</tr>
<tr>
<td>Item</td>
<td>--</td>
<td>.18</td>
<td>.28</td>
</tr>
<tr>
<td>FFAC</td>
<td>--</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>PFAC</td>
<td>--</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Scatterplot of FFAC and Source Scores Labeled by Group
Figure 2. *Scatterplot of PFAC and Source Scores Labeled by Group*

GDS scores were not significantly correlated to PFAC, FFAC, or either of the memory scores in the group of all 48 participants. Within the PD group, UPDRS scores were correlated to both dominant and non-dominant FTT scores in both medication conditions (all \( p \)'s<.01). Neither FTT scores nor any measure of disease severity (i.e. UPDRS scores, years since diagnosis, or Hoehn & Yahr stage) were significantly correlated with source memory, item memory, the FFAC, or the PFAC.

*Logistic Regression*

Given that the PD group demonstrated impairments in source memory, the FFAC, and the PFAC, a logistic regression was conducted to determine whether a combined profile of the three scores could differentiate patients from controls. The combined model
significantly predicted group membership, $\chi^2(1, N = 48) = 21.92, p < .001$, correctly classifying 88% of cases. PFAC scores were most predictive, followed by source memory and then FFAC scores. A model using only the PFAC and source memory correctly classified 83% of the cases while the PFAC alone correctly classified 81% of cases. There were no significant differences in goodness of fit amongst the three-predictor, two-predictor, or single-predictor models.

*Mediator Analysis*

Given the significant group differences in source memory and executive functioning and the significant relation between executive functioning and source memory, a mediator analysis (Baron & Kenny, 1986) was conducted to explore whether executive functioning mediated group differences in source memory. Correlations amongst the executive functioning measures, source memory, and group membership (PD or control) are displayed in Figure 3.
As necessary for a mediator analysis, group membership was significantly correlated with both source memory and the executive functioning measures. However, when either the FFAC or PFAC were entered into the regression equation with the independent variable of group, group membership still accounted for a significant portion of source memory variance, ($p = .02$ and $p = .04$, respectively). Neither the FFAC nor the PFAC significantly
predicted source memory variance, \( p = .20, p = .38 \), demonstrating that executive functioning did not mediate group differences in source memory.
Ch. 4 Discussion

As expected, PD patients demonstrated deficits on two composite measures of executive function replicating previous findings and adding to the growing literature on PD-related frontal dysfunction. Group differences in executive functioning suggested a disease-related deficit on processes measured by the FFAC and PFAC, thought to be processes involved in working memory and possibly planning, respectively. Patients demonstrated the greatest impairment on the PFAC, with 21 of the 24 patients scoring lower than their matched control participant. While a dopaminergic basis is possible given previous findings specifically linking dopamine to several of the tasks comprising the composites (or similar tasks), this cannot be confirmed in the present study as this hypothesis was not directly tested. Of note, patients demonstrated significantly impaired performance on only three of the individual subtests, suggesting that executive functioning deficits are subtle at the individual test level. However, composite measures of frontal functioning were sufficiently sensitive to demonstrate executive dysfunction that might have otherwise been overlooked, illustrating the utility of using a composite measure.

The PD group was also impaired in source memory but not item memory. This source memory deficit was demonstrated fairly consistently across 18 of the 24 matched patient-control pairs. These results extend previous findings of disease-related frontal deficits to include source memory, an area that has received little attention in the literature. One study by Hsieh and Lee (1999) found that a sample of medicated PD patients only demonstrated deficits on a difficult source memory task requiring
discrimination between two internally-generated sources. Performance on an external source memory task requiring patients to discriminate between a male and female speaker was unimpaired. The authors hypothesized that the ability to monitor sources was dependent on the distinctiveness of the cues, and thus patients only demonstrated deficits on those tasks where insufficient perceptual cues were provided. They argued that presenting voices of different genders provided enough perceptual detail for accurate contextual discrimination (although they also provided a visual picture of each speaker). The current findings suggest that patients can in fact demonstrate impairments on an external source memory test even with perceptually-distinct sources. Although the PD group was impaired in both source memory and executive functioning, executive functioning did not mediate PD-related source memory impairments.

Source Memory and Dopamine

It was previously hypothesized that the discrepancy between the current findings and those of Hsieh and Lee may be due to differences in medication states. It is possible that anti-Parkinson’s medications may have masked potential source memory impairments in their patient sample. The current study implemented a medication withdrawal period to examine source memory independent of possible medication effects, an important manipulation given previous findings that dopaminergic medication can have significant effects on cognition. Source memory was also examined while in a medicated state to further explore the effects of changes in phasic dopamine levels on source memory. Executive functioning was not measured while on medications because
of test-retest confounds. Medication withdrawal did not affect source memory in the present study despite having significant effects on motor abilities as measured by finger tapping and the motor subscale of the UPDRS as equivalent source memory impairments were observed in patients both on and off medication. Cognitive tasks may be less sensitive to phasic dopamine changes than are motor tasks, possibly related to the greater severity of dopamine depletion in motor versus cognitive areas.

It may also be that dopamine fluctuations only affect cognition in a subset of patients. Kimberg, D’Esposito and Farah (1997) examined the effects of Bromocriptine (a dopamine receptor agonist) administration on a variety of neuropsychological tasks including source memory, working memory, and the WCST. They found no main effect of medication status on source memory. However, they demonstrated that the effect of medication on the WCST was dependent on working memory ability, as those individuals with high working memory capacity performed more poorly on the WCST while on the drug while the performance of individuals with low capacity actually improved with drug administration. This suggested that dopaminergic medications can have differing effects on various subsets of patients. This is consistent with the suggestion of Cools (2006) that different individuals may have different baseline levels of dopamine, resulting in differential sensitivity to the effects of dopaminergic drugs. In the current study, only eight of the 24 PD patients demonstrated an improvement in source memory with medication reinstatement and these patients did not differ significantly in any measured variable (e.g. age, age of onset, disease stage, factor scores) from those patients who showed no medication effect.
In addition, heterogeneity in dopaminergic medication may have masked possible medication effects. Patients were included in the study if they were taking either l-dopa preparations or dopamine agonists. However, the half-life of agonists is longer than that of l-dopa, raising the possibility that the withdrawal period used in the study may not have been sufficiently long enough to eradicate medication effects in the central nervous system. For example, Tavares et al. (2005) extended their medication withdrawal period to over 24 hours for long-acting dopaminergic medication to demonstrate changes in fine motor control. While a withdrawal period of 12 hours has previously been used in the literature to demonstrate significant medication effects, future studies would benefit from extending the withdrawal period and limiting the patient sample to those only taking l-dopa. Cools (2006) has previously suggested that the shorter half-life of l-dopa makes it more suitable to the withdrawal procedure than receptor agonists. Although limited by small and uneven sample sizes, post-hoc multivariate analyses of variance revealed no differences in medication effects amongst groups of patients on l-dopa, dopamine agonists, or a combination of the two. Five of the 24 patients were taking only l-dopa preparations and none of these patients demonstrated improvement in source memory with medication administration.

Another possibility is that dopamine affects cognition via a threshold process rather than a continuum. This would suggest that cognition is affected once dopamine levels pass a certain threshold level (as occurs via the normal disease process), but is not affected by more subtle changes such as those that would occur with short-acting phasic changes in medication. This threshold hypothesis was proposed by Stern et al. (1990),
who found no significant differences in cognition between individuals exposed to MPTP with motor symptoms and individuals exposed to MPTP without motor symptoms. Because those individuals with motor symptoms presumably had a greater degree of dopamine loss, these authors suggested that dopamine affects cognition in a threshold rather than linear fashion.

Alternatively, source memory may not be dopaminergically-mediated, which would explain why dopaminergic medications had no effect on cognitive performance. While dopamine is the primary pathophysiological alteration in PD, several other neurotransmitter systems are affected by the disorder and certain cognitive impairments in PD may result from a non-dopaminergic process. Studies are not in agreement as to the extent to which dopaminergic medications alleviate the non-motor symptoms of PD. Several studies have found that dopamine therapy has no effect on performance on certain cognitive tasks (Brusa et al., 2002; Brusa et al., 2005; Lange et al., 1992; Lange et al, 1993). PD-related source memory impairments may be due, in part, to the contributions of other neurotransmitter systems, concomitant Alzheimer's Disease pathology, and/or Lewy Bodies. Support for non-dopaminergic cognitive contributions comes from Pillon et al. (1989) who demonstrated that neuropsychological test performance only correlated to those motor symptoms that are typically unresponsive to l-dopa therapy, namely gait and dysarthria. The authors suggested that cognitive problems in PD are related to non-dopaminergic lesions.

Other neurotransmitter systems are possible candidates for cognitive changes in PD. The prefrontal cortex is innervated with serotonergic projections from the raphe
nuclei, although there have been variable findings of serotonin dysregulation on prefrontal functioning. Serotonergic manipulations have regional specificity and typically affect the DLPFC. Using acute tryptophan depletion as a way to reduce central serotonin levels, Fusar-Poli et al. (2006) demonstrated that serotonin dysregulation affects reversal learning and memory recall in healthy individuals. However, this acute tryptophan depletion did not affect performance on the Stroop Interference task or verbal working memory, more frontal-based processes. Suggesting that serotonin may not play a direct role in cognition, Scholtissen et al. (2006) administered Citalopram, a selective serotonin reuptake inhibitor, and Buspirone, a serotonergic agonist, to PD patients. This pharmacological manipulation did not affect tasks assessing memory, cognitive speed, or cognitive flexibility. The authors concluded that cognitive functioning in PD patients does not appear to be susceptible to acute increases in serotonergic activity. Control participants in that study demonstrated a similar pattern of results with medication administration, suggesting that while the serotonin system may not be functioning optimally in PD, it does not seem to play a direct role in the cognitive changes associated with the disease. It is unknown whether source memory or those tasks that comprise the FFAC and PFAC are affected by serotonin depletion and if so, whether the PD-related cognitive impairments demonstrated in this study are due, at least in part, to serotonergic dysregulation. Acetylcholine has also been implicated in cognition as cortical ACh is affected in PD. Bohnen et al. (2006) demonstrated that cortical ACh activity correlated with performance on a digit span task. However, patients differed from controls more
strongly on measures other than digit span, again illustrating the multi-factorial nature of PD deficits.

Another method of examining dopaminergic contributions to cognition is to examine the relation between motor and cognitive symptoms in PD. If cognitive impairments result from the same processes that underlie motor symptoms (which are known to be dopamine dysregulation), there should be a correlation between the severity of motor symptoms and the degree of neuropsychological deficit. Fern-Pollack et al. (2004) has demonstrated that disease stage correlates with cognitive measures, although in the current study, Hoehn and Yahr staging did not predict performance on any of the cognitive measures, suggesting that cognitive abilities were not related to disease severity (although the range of disease severity was limited in this sample). There were no significant correlations between any of the motor scores and the neuropsychological scores in the PD group.

In sum, the frontal lobes, along with cognitive abilities that rely on the frontal lobes, can be affected in many ways by a variety of processes. As Chudasama and Robbins (2006) suggested, frontal dysfunction can be mediated by independent and interacting neural systems that may be affected by pathological processes other than dopamine dysregulation. While source memory and two executive functioning composites, all thought to be dependent on frontal processes, were impaired in the PD group, it is difficult to disentangle the possible contributions of other additional non-dopaminergic factors (e.g. Lewy bodies, cholinergic dysregulation). Thus, while it is
possible that dopamine plays a role in source memory, short-term effects of dopaminergic medication administration on source memory were not demonstrated in the current study.

**Source Memory and Executive Functioning**

While FFAC and PFAC scores correlated with source memory in the combined group of patients and controls, this correlation was not significant within the groups. Regression analyses demonstrated that this significant correlation was driven by group differences, as the patient group was impaired in all three measures. Within the PD group, FFAC scores did not predict source memory \( (r = .07) \), as was expected based on previous findings in healthy older adults. One possible explanation is the uneven distribution of scores within the group. FFAC scores ranged from -1.77 to 1.02 with bias towards the lower FFAC scores \( (M = -0.22) \). Sixteen of the 24 patients had low FFAC scores (below zero) while only eight patients had high FFAC scores (above zero). It is also possible that the FFAC tasks and the source memory task did not engage the same processes in PD patients as in healthy older adults. This would suggest that PD patients are recruiting different processes than older adults for one or both of these types of tasks. However, we were unable to confirm that FFAC scores were uncorrelated with source memory due to the uneven distribution of scores.

FFAC performance was not significantly correlated with source memory in the control group either \( (r = .31) \), but this might reflect a power problem. Like the PD group, there were uneven numbers of high FFAC and low FFAC control participants: 16 participants had above average FFAC scores while eight had low FFAC scores. Based on
previous research we would expect to find a significant correlation in healthy older adults if FFAC scores had been more evenly distributed across the entire range. The source memory paradigm used in this study was nearly identical to that used in a previous study by Cook (2007) that examined source memory in a group of older adults. An equal number of older adults were above and below the mean on FFAC scores and a significant effect of FFAC scores on source memory was found. In the current study selection on the basis of FFAC scores was not feasible given that FFAC scores were not obtained prior to memory testing.

Like the FFAC, PFAC scores were not significantly correlated with source memory in the PD group \( (r = -.09) \) or control group \( (r = .36) \), which also may be attributable to uneven group sizes (21 PD patients and seven control participants had low PFAC scores) and lack of statistical power. Here the range restriction is even more pronounced particularly in the PD group, and so the lack of correlation is uninterpretable. While it was previously hypothesized that executive functioning may mediate source memory impairments in the PD group, this could not be examined due to the restricted range in executive functioning scores in the PD group and shared variance between the factor scores and group membership.

We also have limited information about the PFAC and the latent construct that the composite may be measuring, and so interpretation of its relation to PD is speculative. The PFAC, as demonstrated by principal components analysis, was shown to measure an aspect of frontal functioning distinct from that measured by the FFAC, which was supported by the lack of significant correlation between these two factors in the current
study. The PFAC was originally conceived as a measure of planning ability, as the three
tests that comprise the factor are traditionally thought of as planning tests. Under this
assumption, it would be reasonable to expect that planning ability would be related to
source memory, given that they possibly share the same cognitive and/or biological
underlying processes. However, there are other alternatives. Given that the three PFAC
tasks are all visuospatial in nature, it may be that the PFAC specifically measures
visuospatial planning abilities. Another possibility is that it taps visuospatial working
memory, as these tests require the ability to organize and retain visuospatial information
in mind while executing the task. If the PFAC were tapping either of these visuospatial
processes, the PFAC might not predict source memory performance as the source
memory task used in this study was primarily verbal in nature. Future research could
examine whether the PFAC predicts performance on a spatial source memory task such
as the one used in Cook (2007).

It may also be that the PFAC taps some aspect of motor planning or the
sequencing of motor actions. All three of the tasks that comprise the PFAC require
individuals to formulate a plan of motor action and then execute this sequence of
movements. The pre-supplementary motor cortex and the supplementary motor cortex
proper are affected by disease-related changes in PD, resulting in impairments in the
planning of motor responses. Therefore, the effectiveness of the PFAC in predicting
group membership is consistent with the notion that the PFAC may be sensitive to
aspects of motor planning. This might also explain the lack of correlation with source
memory, as motor planning would not be expected to be a particularly good predictor of a verbal source memory task.

It may be that source memory in PD patients also relies on other frontal processes not tapped by the executive functioning tasks examined in this study. For example, traditional memory tasks direct the participant’s attention to the to-be-remembered information. In the current study, attention was focused on the item, not the source. Successful source memory performance was predicated on inhibiting the more salient but task-irrelevant information (i.e. the sentence) and focusing on the contextual details (i.e. the sex of the speaker). Therefore, PD-related source memory deficits may stem from a lack of inhibition, an executive functioning process that is part of many executive functioning tasks but may not be measured by either of the composite measures. This is consistent with the suggestion by Kensinger et al (2003) that DA dysregulation leads to difficulties sorting task-irrelevant from task-relevant information.

An alternative hypothesis relates to the significant correlation between item and source memory in the PD group. In previous research with healthy older adults, source memory and item memory were uncorrelated (Glisky, Polster, & Routhieaux, 1995; Glisky, Ruben, & Davidson, 2001; Glisky & Kong, in press), consistent with our findings in the control group, although in the present study performance on the item memory task was essentially on the ceiling in young adults. This suggests that unlike in healthy older adults, PD patients are utilizing a similar process to complete both the source memory and item memory test, and that this process may be unrelated to the processes tapped by the FFAC or PFAC tasks. This process may be sufficient for item recognition, but not for
recollection of source details. It may be that source memory in PD patients relies on a memory process dependent on the medial temporal lobes. Previous research has linked source memory to areas within the medial temporal lobes. For example, Davachi, Mitchell, and Wagner (2003) demonstrated using fMRI that encoding activation in the hippocampus and posterior parahippocampal cortex predicted later source recollection. Studies utilizing neuroimaging have suggested that medial temporal lobe decline may occur in PD (Double et al., 1996; Camicioli et al., 2003).

**Depression and PD**

Depression was measured in the current study as individuals with depression can demonstrate impairments on many tasks of executive functioning (Purcell et al., 1997; Merriam et al., 1999; Veiel, 1997). Depression is common in PD, with an estimated prevalence of approximately 40% (Norman et al., 2002). Depression was not an exclusionary criterion and eight patients and none of the controls met criteria for depression based on their scores on the GDS. Depression can have a negative effect on cognitive tasks, especially those relying on the frontal lobes. For example, Uekerman et al. (2003) demonstrated that depressed PD patients scored lower on backwards digit span and phonemic fluency than non-depressed patients. This raises the possibility that PD-related cognitive deficits may be due, in part, to the negative effects of depression. However, GDS scores were not significantly correlated with source memory or either composite factor score, suggesting that depression cannot account for the PD-related cognitive deficits demonstrated in the current study.
Conclusions, Caveats, and Future Directions

As hypothesized, individuals with PD demonstrated impairments in source memory and executive functioning. Neither the FFAC nor PFAC significantly predicted source memory performance in the PD group, but an uneven distribution of scores precludes any definitive conclusions regarding the relation between the frontal measures and source memory in PD. Increasing the size of the PD sample in future studies would increase the power to detect a significant relation (if one exists) between source memory and the factor scores.

While PD-related cognitive impairments were demonstrated at the group level, these comparisons do not imply that the disease process automatically leads to cognitive decline in all individuals. Within the PD sample, only a subset of patients demonstrated deficits in source memory and/or executive functioning, suggesting that not all patients suffer cognitive decline. Within the PD group, however, none of the demographic variables measured (e.g. age of disease onset, Hoehn & Yahr staging) was significantly related to cognitive performance. Future research should focus on identifying variables that discriminate those patients with cognitive deficits from those that are cognitively-intact.

In addition, sub par performance on laboratory measures does not necessarily translate to difficulties in everyday functioning, although the current findings do have possible real world implications. For example, the WCST, a task used in this study, has been found to be one of the neuropsychological measures most predictive of real world driving ability (Chatel et al., 1993). Also, verbal fluency has been shown to correlate
highly with competency, an issue that may be important later in the case of disease-related dementia (Marson et al., 1995). Given that it has been hypothesized that source memory impairments may stem from an inability to spontaneously integrate an item with its context at encoding, it would be interesting to examine whether PD-related source memory impairments would be ameliorated with explicit and integrative encoding instructions.

In addition, future studies should focus on better understanding the biological processes underlying source memory. Healthy older adults are impaired in source memory when compared to younger adults although the pathophysiological process that leads to this impairment is unclear. The dopamine hypothesis of aging posits that many of the cognitive change that accompany normal aging stem from declining dopamine levels (Postle et al., 1997; Erixon-Lindroth et al., 2005; Reeves, Bench & Howard, 2002; Ollat, 1992). It may be that the dopaminergic system underlies source memory abilities and future research utilizing pharmacological challenge and imaging in both clinical and non-clinical populations may help to better elucidate this relationship.
References


Bohnen, N., Kaufer, D., Hendrickson, R., Ivanco, L., Lopresti, B., Constantine, G.,
cortical cholinergic denervation in Parkinson’s disease and parkinsonian

System Dysfunction to Memory and Perceptual Abilities in Parkinson’s Disease.
*Neuropsychology, 7*(1), 89-102.

Memory in Huntington’s Disease and its Relation to Basal Ganglia Atrophy.
*Journal of Clinical and Experimental Neuropsychology, 17*(6), 868-877.

computational model of dopamine and prefrontal function. *Biological Psychiatry,
46*(3), 312-328.

Braver, T., Barch, D., Keys, B., Carter, C., Cohen, J., Kaye, J., Janoqsky, J., Taylor, S.,
Yesavage, J., Mumenthaler, M., Jagust, W., & Reed, B. Context processing in
older adults: Evidence for a theory relating cognitive control to neurobiology in

neuromodulation. *Neuroscience & Biobehavioral Reviews, 26*(7), 809-817.


dopaminergic neurons selectively vulnerable to Parkinson’s Disease. *Advances in
Neurology, 60*, 148-164.

Memory in Mild Alzheimer’s Disease and Early Parkinson’s Disease.
*Neuropsychology, 17*(2), 230-239.

subjects depend on working memory capacity. *NeuroReport, 8*, 3581-3585.

Recall in Parkinson’s Disease and Normal Subjects. *Brain and Cognition, 38*,
261-274.

memory in patients with focal frontal, temporal lobe, and diencephalic lesions.
*Neuropsychologia, 35*(12), 1533-1545.

Kulisevsky, J., Garcia-Sanchez, C., Berthier, M., Barbanoj, M., Pascual-Sedano, B.,
Replacement on Cognitive Function in Parkinson’s Disease: A Two-Year Follow-

depends on the prior encoding task. *Journal of Cognitive Neuroscience, 18*(7),
1133-1146.


