LATERALITY OF MOTOR SYMPTOM ONSET, DISEASE PROGRESSION, AND COGNITION IN PARKINSON'S DISEASE

BY

Phuong M. Chau

Submitted to the graduate degree program in Psychology

and the Graduate Faculty of the University of Kansas

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Douglas R. Denney, Ph.D.
Co-Chair
Professor of Psychology

Brenda Hanna-Pladdy, Ph.D.
Co-Chair
Assistant Professor of Psychiatry
Landon Center on Aging

Committee members:

David K. Johnson, Ph.D.
Assistant Professor of Psychology
and Gerontology

Sarah B. Kirk, Ph.D.
Assistant Professor of Psychology

Vicki Peyton, Ph.D.
Assistant Professor of Psychology
and Research in Education

Date defended: July 12, 2010

The Dissertation Committee for Phuong M. Chau certifies
that this is the approved version of the following dissertation:

LATERALITY OF MOTOR SYMPTOM ONSET, DISEASE PROGRESSION, AND COGNITION IN PARKINSON'S DISEASE

Committee members:

Douglas R. Denney, Ph.D.
Co-Chair

Brenda Hanna-Pladdy, Ph.D.
Co-Chair

David K. Johnson, Ph.D.

Sarah B. Kirk, Ph.D.

Vicki Peyton, Ph.D.

Date approved: July 12, 2010

Abstract

The current study examined whether laterality of initial motor symptom onset (left-sided onset vs. right-sided onset) in Parkinson's disease (PD) would predict the pattern and/or severity of cognitive deficits measured at various stages of disease progression. We evaluated the relationship between initial motor presenting symptoms obtained at the time of PD diagnosis and current cognitive profiles across three different patient groups (early unilateral, late unilateral, late bilateral stages of PD). Findings lend some support for study hypotheses regarding a lateralization of cognitive deficits based on initial laterality of motor symptoms. That is, right-sided motor symptom onset in PD was associated with diminished performance on left hemisphere cognitive measures, but the data did not reveal a significant relationship between left-sided motor symptom onset and impairment on right hemisphere measures. The current study also revealed cognitive deficits consistent with hypothesized effects of disease progression, such that cognitive changes during the unilateral stages of PD seem restricted to executive dysfunction, whereas bilateral disease in PD (with greater than 5 years disease duration) is associated with more widespread cognitive decline.

Laterality of Motor Symptom Onset, Disease Progression, and Cognition in Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative movement disorder believed to be caused by nigrostriatal dopamine depletion and characterized by hallmark motor symptoms such as tremor, bradykinesia (i.e., slowness in voluntary movement), and muscular rigidity. In James Parkinson's original (1817) essay, he stated that "the senses and intellect were uninjured" in the illness that now bears his name, and PD has long since been characterized as a disorder restricted to the motor system. However, there is increasing awareness that this disease process also involves a non-motor symptom complex that can include cognitive difficulties. The cognitive difficulties associated with PD have not been well characterized. While it has been established that dopamine depletion is associated with PD motor deficits, the specific neuropathology underlying cognitive impairment remains unclear.

The research literature examining cognitive impairment in PD has grown considerably over the past two decades. Cognitive deficits are most consistently observed in frontal-executive functions (Duke & Kaszniak, 2000; Taylor, Saint-Cyr, & Lang, 1986; Zgaljardic et al., 2006), particularly on tasks of working memory, planning, and cognitive set shifting (Cools, Barker, Sahakian, & Robbins, 2001). These changes have been observed even early in the course of the disease (Cools et al., 2001). Impairments in verbal, visuospatial, and memory functions have also been described, even in PD patients without dementia (Levin, Tomer, & Rey, 1992; Dubois & Pillon, 1997), but reports have been inconsistent across studies. These mixed results may be related to differences in patient selection factors across studies, including differences in disease progression which may be reflective of different subtypes of PD with and without cognitive decline. In all, there appears to be significant heterogeneity in the cognitive course of PD. Estimates of dementia in PD vary widely depending on the disease characteristics of particular study samples, but large scale epidemiological studies suggest that approximately 20-40% of patients will develop dementia in later

stages of the disorder (Marder, Tang, Cote, Stern, & Mayeux, 1995; Mayeux et al., 1992; Tison et al. 1995). While some PD patients do not appear to demonstrate significant cognitive deficits throughout the course of their illness, frontal-executive impairments are present over the course of PD in many patients, even in those who do not develop frank dementia (Duke & Kaszniak, 2000; Emre, 2003).

Due to significant heterogeneity in the cognitive presentation of PD, there has been increasing interest in identifying which clinical variables may make patients more susceptible to cognitive decline and later development of comorbid dementia. Although there is no clear consensus, the following clinical characteristics have been reported in the literature as potentially associated with increased cognitive deficits in PD: increased age at disease onset (Locascio, Corkin, & Growdon, 2003; Mayeux et al., 1992), longer duration of illness (Biggins et al., 1992), the presence of bilateral as opposed to unilateral motor symptoms (Gasparoli et al., 2002; Viitanen, Mortimer, & Webster, 1994), the presence of postural instability and unsteady gait (Alves, Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006; Burn et al., 2006), and the severity of current motor symptoms (Locascio et al., 2003; Williams et al., 2007). These characteristics require further evaluation in studies of PD and cognition to elucidate their relative contributions to the disease course.

One clinical disease feature that has been investigated pertains to laterality of initial motor symptoms – that is, whether motor symptoms are present on primarily the right or left side of the body. In PD, a typical course of symptom progression involves unilateral onset of cardinal motor features (e.g., tremor, rigidity, bradykinesia), with a gradual progression to bilateral motor disease over the course of the disorder. Multiple studies have demonstrated that the asymmetrical onset of motor symptoms is associated with degeneration of nigrostriatal dopaminergic neurons contralateral to the affected body side (Kempster, Gibb, Stern, & Lees, 1989; Nahmias, Garnett, Firnau, & Lang, 1985, Rinne et al., 1993). Therefore, initial side of motor symptom onset and current predominant

side of symptoms may be important markers of the underlying neuropathology. However, research findings addressing neuropsychological disturbances on the basis of motor symptom laterality have been mixed. Some studies have identified specific patterns of neuropsychological deficits in PD patients with right vs. left unilateral motor symptoms, while others have found minimal or no differences. The effects of motor symptom asymmetry on cognitive profiles remain unclear, and consequently there is uncertainty whether the neuropathology in PD responsible for motor symptoms is also responsible for cognitive deficits.

This paper will first briefly discuss the neuropathology of PD and review current hypotheses about the neuropathological basis of cognitive decline in this disorder. We then evaluate the existing literature on the association between laterality of motor symptoms and cognition in PD and address methodological problems in previous studies (including failure to control for disease progression) that may account for the inconsistent findings. Lastly, results of the current study, which addresses some limitations of past research, are reviewed and discussed.

Neuropathology associated with different stages of Parkinson's disease

The neuropathological hallmark of PD is neuronal degeneration in the pars compacta of the substantia nigra, one of the nuclei clusters of the basal ganglia (Jellinger, 2001; Paulus & Jellinger, 1991). Neurons in the substantia nigra are the origin of the nigrostriatal pathways, which are responsible for both the excitatory and inhibitory dopaminergic innervation of the caudate and putamen (known collectively as the striatum) of the basal ganglia. The striatum and associated regions contain more than 80% of the total dopamine in the brain, and the degree of striatal dopamine deficiency appears to be correlated with the severity of motor symptoms in PD (Leenders et al., 1990; Wang et al., 2007). There are multiple complex pathways that connect the striatum to the frontal cortex, and much evidence has accumulated for the role of these frontal-striatal circuits in movement, cognition, and behavior (see Lichter & Cummings, 2001 for a detailed review of these frontal-striatal circuits).

At the earliest stages of PD, mild cognitive abnormalities, when present, are hypothesized to be primarily the result of dopaminergic disruptions to frontal-striatal circuitry (Owen, 2004; Zgaljardic et al., 2006). This is supported by functional neuroimaging studies showing selective underactivity in striatal and frontal lobe regions in the brains of early PD patients as compared to healthy controls during tasks of attention, working memory, and verbal fluency (Lewis, Dove, Robbins, Barker, & Owen, 2003; Rinne et al., 2000). Additionally, neuropsychological studies (Dubois & Pillon, 1997; Lees & Smith, 1983) show that cognitive deficits during early stages of PD are relatively subtle and restricted primarily to tests of frontal networks dysfunction (e.g., executive function, working memory). As the disease advances, however, more widespread cognitive deficits typically become apparent, even in the absence of dementia (Green et al., 2002). This is consistent with evidence that other neuropathological mechanisms can also be involved in later stages of the disease. These include diffuse Lewy body disease, comorbid Alzheimer's pathology, and/or degeneration in non-dopaminergic (e.g., cholinergic, noradrenergic and serotonergic) neuronal systems (Braak et al., 2003, Dubois & Pillon, 1992; Emre, 2003; Galvin, 2006; Jellinger, 2001; Zdaljardic, Foldi, & Borod, 2004). Consequently, in later stages of the disease, differential diagnosis can be challenging due to similar clinical presentations of PD with comorbid dementia (PDD), Alzheimer's disease with Parkinsonian features, and dementia with Lewy bodies (Galvin, 2006; Jellinger, 2001). Thus, when examining the neuropathology of PD, duration and stage of illness are believed to be highly relevant, since additional non-dopaminergic pathology is more likely to be present as the disease advances.

The relationship between motor symptoms and cognition in PD

The precise pathophysiological mechanisms underlying cognitive impairments in PD, as well as the relationship between motor and cognitive symptoms, are not well understood. A number of studies have documented a significant relationship between motor disability and cognitive difficulties. For example, severity and progression of current motor symptoms, as indexed by Hoehn

and Yahr stages or Part III of the Unified Parkinson's Disease Rating Scale (UPDRS), have been associated with greater cognitive impairment, even after controlling for age and disease duration (Huber, Freidenberg, Shuttleworth, Paulson, & Christy, 1989; Locascio et al., 2003; Williams et al., 2007). Additionally, some researchers have demonstrated that patients with bilateral motor symptoms have more global cognitive impairment than patients with unilateral symptoms (Gasparoli et al., 2002; Starkstein & Leiguarda, 1993; Viitanen et al., 1994). However, because of the increased likelihood of having additional non-dopaminergic pathology in later stages of the disease, it is unclear whether the cognitive impairment associated with disease progression is indeed related to the same dopaminergic pathology underlying motor symptoms. Although some investigations suggest a close connection between motor symptoms and cognitive performance, other studies have reported weak or nonsignificant correlations. For example, Cooper, Sagar, Jordan, Harvey, and Sullivan (1991) studied patients with newly diagnosed PD and found a strong association between UPDRS motor scores and depressive symptoms, but a weak correlation between motor disability and cognitive impairment. The authors concluded that cognitive dysfunction, even in early PD, may reflect neuropathological changes that are distinct from the nigrostriatal dopamine depletion underlying motor symptomatology. Although many studies suggest a significant association between motor disability and cognition, the predictive value of motor symptoms for subsequent cognitive decline remains controversial at present. It would be important for future studies to clarify this relationship.

For many patients, motor symptoms begin on one body side and remain unilateral for some time prior to bilateral involvement. As noted previously, it is commonly believed that PD patients exhibit motor symptoms on the body side that is contralateral to the site of brain dysfunction (Blumenfeld, 2002). Kempster et al.'s (1989) post mortem study found that asymmetrical motor symptomatology is associated with greater neuronal loss in the substantia nigra contralateral to the affected body side. Nahmias et al. (1985) demonstrated the hypothesized asymmetry of

dopaminergic activity in patients with unilateral motor symptoms using positive emission tomography (PET), revealing that patients with right side motor symptoms had a significantly lower levodopa reuptake in the left striatum, and patients with left sided motor symptoms had decreased reuptake in the right striatum. However, it is uncertain how these dopamine asymmetries may influence the cortex and cognitive functions. If degeneration of the substantia nigra and striatal dopamine depletion remain largely asymmetrical for a period of time in PD, then these neuropathological asymmetries may have effects on cognition as well. Because of the multiple complex frontal-subcortical pathways that originate from the striatum, it is plausible that these subcortical asymmetries could exert a distinct pattern of deficits in higher cortical functions. Thus, examining the relationship between motor symptom asymmetry and cognition may help further our understanding of the pathophysiological basis of cognitive decline in PD. There have been a number of studies examining this relationship, and these are reviewed in the next section.

Previous research examining laterality of motor symptoms and cognition

Research examining the relationship between motor symptom asymmetry and cognition can be divided into two categories: 1) studies that relate laterality of motor symptoms *at the time of disease onset* to cognition later in the disease course, and 2) studies that examine the relationship between *current* motor symptoms and current cognitive functioning. Results from the latter category are discussed first.

Studies investigating associations between current laterality of motor symptoms and current cognitive deficits have utilized a similar research design in that PD pati ents are typically divided on the basis of their motor symptom laterality. That is, differences in neuropsychological performance are examined in patients with either right or left motor symptom predominance. These investigations have yielded very mixed results. Some researchers have found a clear lateralized cognitive profile, such that patients with predominantly right-sided motor symptoms (implying greater left hemisphere involvement) were more impaired on tests of language and verbal ability, and patients with

predominantly left-sided motor symptoms (implying greater right hemispheric disease involvement) performed more poorly on visuospatial tasks (Bentin, Silverberg, & Gordon, 1981; Blonder, Gur, Saykin, & Hurtig, 1989; Starkstein, Leiguarda, Gershanik, & Bertheier, 1987). Other studies have found only partial support for the expected lateralized profile, such that right-sided motor symptoms were associated with greater impairment on tests of left hemisphere function, but no group differences were observed on tests assessing right hemisphere function (Huber, Miller, Bohaska, Christy, & Bornstein, 1992; Spicer, Roberts, & LeWitt, 1988). Williams et al. (2007) found that a predominance of right-sided motor symptoms is associated with increased overall cognitive impairment, whereas another study found that patients with left-sided motor symptoms performed more poorly across a broad range of neuropsychological test measures (Direnfeld et al., 1984). Further complicating the picture, another set of studies show no significant differences between patients with unilateral right and unilateral left motor symptoms (Huber, Freidenberg, Shuttleworth, Paulson, & Clapp, 1989; St. Clair, Borod, Sliwinski, Cote, & Stern, 1998). Consequently, it remains unclear whether motor symptoms are predictive of the severity and profile of cognitive deficits in patients with PD.

These discrepant findings may be due to a number of methodological factors including small sample sizes, lack of control for disease progression, and inadequate selection and/or interpretation of neuropsychological measures. In past studies, patients classified as "unilateral" may have also included patients who had progressed to the bilateral disease stage – but were nevertheless classified as unilateral patients due to a continuing motor asymmetry that was consistent with their initial presentation of motor symptoms. In other words, they had more severe motor symptoms on one side than the other, but at the time of cognitive testing, their motor symptoms affected both sides of the body. Because the relationship between laterality of motor symptoms and cognition may depend upon stage of disease, it would be important for future investigations to control for disease progression. Additionally, studies have differed in their interpretations of what constitutes right vs.

left hemisphere cognitive tasks, and therefore may misinterpreted cognitive profiles with respect to hemispheric specialization. For example, the Stroop Test was used in one study as a task of right hemisphere function (St. Clair et al., 1998) based on an earlier demonstration (Hietanen & Teravainen, 1989) that PD patients with primarily left-sided motor symptoms performed more poorly on the Stroop task than patients with right-sided motor symptoms. In addition to the obvious visual nature of the task, the Stroop test also requires reading and rapid speech output (tasks often ascribed to the left hemisphere) as well as a strong attentional and executive component (functions that are not as lateralizing). Additionally, verbal fluency has been included in previous studies as a measure of left hemisphere function (Blonder et al., 1989; Huber et al., 1989b; St. Clair et al., 1998), but it is also a task that is highly dependent upon intact attention and speed of processing. Consequently, when interpreting hemispheric profiles reflective of asymmetric brain dysfunction, it is important to consider the multiple cognitive functions measured by each task.

Some investigators have chosen to study whether laterality of motor symptoms at disease onset predicts cognitive deficits later in the disease course. Tomer, Levin, and Weiner (1993) employed this research design with a mixed PD sample (average disease duration of six years) that included patients with both unilateral and bilateral disease at the time of neuropsychological testing. Tomer et al. found that, when examined later in the disease course, patients with initial left-sided motor symptoms consistently performed more poorly across a range of cognitive measures compared to patients with right-sided motor symptom onset. Yet, another investigation (Viitanen et al., 1994) evaluated the cognitive profiles of PD patients in unilateral and bilateral stages (with an average disease duration of nine years), and found no significant pattern of differences between the performance of patients with right vs. left motor symptom onset. Since both studies utilized patients who had both unilateral and bilateral motor symptoms at the time of neuropsychological testing, failure to control for disease progression may have confounded results and limited interpretation of these findings.

Despite some drawbacks of the Tomer et al. (1993) and Viitaenen et al. (1994) studies, there may be some advantages to examining the relationship between initial side of motor symptoms and later cognitive impairment, rather than examining how cognitive performance relates to current motor symptom profiles. As noted by others (Katzen Levin, & Weiner, 2006; Tomer et al., 1993), one reason why it may be helpful to study side of motor symptoms at disease onset relates to the issue of medication usage in PD. The effects of dopaminergic medications (i.e., dopamine replacement drugs such as levodopa, or dopamine agonist drugs such as bromocriptine or ropinirole) on cognition have been hotly debated in the research literature. Investigations comparing medicated vs. unmedicated patients and those examining "on" and "off" medication states have indicated cognitive improvement, deterioration, or no changes, depending on the study (see Cools, 2008; or Pillon, Czernecki, & Dubois, 2003 for reviews on the complex relationship between dopamine and cognition). Because of multiple studies suggesting an association between the use of dopaminergic medications and cognitive deterioration, medication usage becomes a relevant issue here. Many PD patients begin dopaminergic drugs shortly after diagnosis and early in the course of their disease, and it is possible that these medications may contribute to the heterogeneity of cognitive symptoms observed in PD. Additionally, these medications are known to suppress many of the motor abnormalities associated with PD. After a period of time on these medications, it is possible that evaluation of current motor symptom severity may not accurately reflect the underlying neuropathology. Therefore, laterality of motor symptom at disease onset may be an important marker of the underlying neuropathological changes and cognitive change, possibly more so than current motor symptomatology.

Disease progression and cognition in PD

Because cognitive deficits may be qualitatively and quantitatively different at various stages of PD, studies in recent decades have examined the role of disease progression on cognition in PD. Disease progression has been operationally defined a number of ways in previous investigations.

Some studies have characterized disease progression simply as illness duration (i.e., years since initial PD diagnosis). Muslimovic, Schmand, Speelman, and De Haan (2007) conducted a meta-analytic review of 25 longitudinal studies (ranging from 2-8 years between initial and follow-up assessment) examining disease duration and cognition in PD. The authors examined aggregate differences between neuropsychological performance at baseline and follow-up, and reported small to moderate effect sizes across all cognitive domains examined. In addition to longitudinal studies, investigations have employed cross-sectional designs. These studies, examining differences between patients with varying levels of illness duration, also indicate that longer disease duration is associated with increased cognitive difficulties (Locascio, Corkin, & Growdon, 2003; Stern & Mayeux, 1986). However, one limitation with using illness duration as a marker of disease progression is that patients commonly progress at different rates due to the heterogeneity in PD. For this reason, disease progression has been alternatively studied by assessing severity of motor symptoms (either by examining Hoehn and Yahr scores reflective of unilateral versus bilateral disease stages, or UPDRS scales assessing motor disability). As discussed earlier, both Hoehn and Yahr stages and UPDRS scores appear to be associated with cognitive impairment in most studies (Gasparoli et al., 2002; Huber et al., 1989; Locascio et al., 2003; Starkstein & Leiguarda, 1993; Viitanen et al., 1994; Williams et al., 2007). The implicit assumptions of these research designs should be noted – namely, that bilateral motor disease is reflective of a more advanced PD stage than unilateral motor disease, and that higher motor disability scores on standardized scales indicate more advanced disease progression.

From the discussion thus far, it is clear that studies examining the relationship between motor symptoms and cognition in PD must control for disease severity/progression or otherwise consider how this might influence research findings. The underlying neuropathology during early and later PD stages may involve different neuronal mechanisms, and this is likely to influence observed patterns of cognitive impairment. However, disease progression has not been well controlled in

previous neuropsychological studies of PD. Many researchers have measured disease progression as a single construct or have examined motor symptom impairment, duration of disease, or stage of motor symptom progression (unilateral vs. bilateral) alone without considering the other variables. Thus, it may be helpful for future studies to tease apart specifically which dimensions of disease severity/progression (motor symptom severity, illness duration, or unilateral vs. bilateral motor involvement) are linked to cognitive difficulties.

Rationale for the current study

The current study examined whether laterality of motor symptom onset (left-sided onset vs. right-sided onset) in PD is related to the pattern of cognitive deficits observed at various stages of disease progression. In contrast to previous studies, we evaluated how initial motor symptoms predicted cognitive performance in patient groups that differ with respect to both disease duration and severity – specifically, in patients who were in either the early unilateral, late unilateral, or late bilateral stages of PD. By examining patients in three different current stages of disease progression, the present study may clarify whether disease progression can account for some of the heterogeneity in the results of previous studies. Findings from this study may provide predictive information regarding the relationships between laterality of motor symptom onset, disease progression, and subsequent development of cognitive impairment. These results may also shed light on the pathophysiological basis of cognitive impairment in PD.

Study hypotheses

The following hypotheses were derived from the previous discussion:

1. *The laterality of initial motor onset predicts the profile of cognitive impairment in the earlier stages of the disease.* We selected participants on the basis of either right or left unilateral motor symptom onset, and evaluated cognitive profiles at unilateral and bilateral stages of the disease (reflective of disease progression). We predict that PD patients will show a pattern of lateralized cognitive deficits consistent with expected dopamine asymmetries only while they

are still in the unilateral stage of the disease. Lateralized cognitive deficits are not expected for patients in the bilateral stage of disease progression.

2. *PD patients in the unilateral stage of the disease will display frontal-executive deficits, with the later unilateral group exhibiting more severe impairment than the early unilateral group.* Utilizing a cross-sectional design, we will evaluate the cognitive profiles of PD patients in the unilateral stage of the disease across two different ranges of disease duration. We predict that PD patients in the (early and late) unilateral stages will exhibit a pattern of frontal-executive, attention/working memory, and memory encoding deficits, consistent with the hypothesis of dopamine depletion as the primary pathology. We expect that the late unilateral group (2-5 years since diagnosis) will show greater severity of impairment than the early unilateral group (<1 year since diagnosis), consistent with the hypothesized effects of disease progression.
3. *PD patients in the bilateral disease stage will exhibit more global cognitive deficits than patients in the unilateral stage.* We expect that the cognitive performance of PD patients in the bilateral stage will be significantly lower than that of age-matched controls and PD patients in the unilateral stage across most or all cognitive domains, consistent with hypothesized involvement of additional non-dopaminergic pathology in the later stages of the disorder.

Method

Participants

Sixty participants with PD and 20 age-matched healthy adults were recruited for this study. All participants were between 51-77 years of age, were right handed as defined as by a score of >+60 on the Edinburgh Handedness Inventory (Oldfield, 1971), were native English speakers, and had completed at least a high school education. Demographic characteristics of PD and control groups are outlined in Table 1. Exclusionary criteria for all participants included the following: history of

CNS disease other than PD, history of DSM-IV major psychiatric disorder, history of concurrent, unstable or serious medical condition, history of major head trauma, or history of neurosurgery.

PD sample. PD participants were nondemented (score of 25 or greater on the Mini Mental Status Examination) and had a diagnosis of idiopathic PD, as confirmed by the study's collaborating neurologist (Rajesh Pahwa, M.D.), a movement disorders specialist. PD patients were recruited from the PD and Movement Disorders Clinic at the University of Kansas Medical Center (KUMC). The PD Clinic manages an IRB-approved research database consisting of approximately 1,000 patients who present with unilateral symptoms. These patients consented for storage of their clinical history in the database and also consented to be contacted for future PD-related research studies. Thus, information regarding side of disease onset (left vs. right) and date of PD diagnosis were archived in the database and available to study researchers during the recruitment process. Clinical information was further verified by participants during the recruitment process and prior to the experimental session.

Patients with right and left initial motor symptom onset were recruited into the following three PD progression groups:

1) Early Unilateral Group – participants with early unilateral disease (defined as one year or less from date of diagnosis), with motor symptoms currently in the unilateral stage.

2) Late Unilateral Group – participants with later unilateral disease (2-5 years from date of diagnosis), with motor symptoms still remaining in the unilateral stage.

3) Bilateral Group – participants with later bilateral disease (a minimum of 5 but no more than 13 years since PD diagnosis), with motor symptoms beginning as unilateral but affecting both sides of the body at the time of neuropsychological testing.

The Hoehn and Yahr (1967) index was used to determine the progression of PD motor dysfunction, and the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987) was utilized to determine motor severity. Ratings on these measures were given to PD patients within 6 months of

the experimental session by a study collaborator (Kelly Lyons, Ph.D.) trained by the Movement Disorder's Society to administer these scales. Of note, current UPDRS and formal Hoehn and Yahr ratings could not be obtained for 3 PD participants; however, because their reported unilateral vs. bilateral status at the time of neuropsychological evaluation was confirmed by notes from their recent clinical visits, they were retained in the study.

Patients in the two unilateral groups received a recent Hoehn and Yahr rating of Stage 1 (unilateral disease), while all patients in the bilateral sample received a Hoehn and Yahr rating of Stage 2 (bilateral disease without impairment of balance). See table below for an illustration of PD participants recruited in each group:

		Side of Initial Motor Onset	
Symptoms of PD	Progression	Right	Left
Unilateral (<1 year since diagnosis)	Early	10	8
Unilateral (2-5 years since diagnosis)	Middle	8	9
Bilateral (> 5 years since diagnosis)	Late	13	12

The current study design permitted an examination of two different aspects of disease progression: illness duration (defined as years since receiving the diagnosis of PD) and disease stage (defined as the presence of unilateral vs. bilateral motor symptoms). Current motor scores on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987) were also reviewed for each patient to determine motor symptom severity. The UPDRS motor scale examines the severity of speech, tremor, rigidity, deficits in facial expression, body bradykinesia, and other motor-related symptoms. Although PD participants were not selected on the basis of motor symptom severity, UPDRS scores between right-sided onset and left-sided onset groups were also examined to determine if there were significant differences in scores within the same classified disease stage.

Healthy control sample. Control participants were recruited from an IRB-approved research participant database consisting of healthy elderly adults and managed by staff at the Landon Center for Aging at the University of Kansas Medical Center (KUMC). Participants in the healthy control database were prescreened by Landon Center staff and classified as healthy aging older adults. However, participants were only included in the control sample if they met study inclusion criteria (described earlier), did not report current significant difficulty with activities of daily living, and obtained a score of 27 or higher on the Mini Mental Status Examination (MMSE).

Procedures and Data Collection

Individuals who indicated interest in the project were contacted via telephone to discuss the study and determine participant eligibility. Those who met full study inclusion criteria were scheduled for a 2.5 – 3 hour session to undergo neuropsychological testing at the Landon Center for Aging at KUMC.

Information regarding current medication regimen was recorded for all participants at the time of the neuropsychological evaluation. With respect to medications, all PD participants were tested during their *on* state. In order to reduce differences in dopaminergic modulation, time of day effects, and fatigue levels, most PD participants were scheduled for a morning session after their morning dose.

All neuropsychological assessments were performed by a doctoral psychology student (Phuong Chau, M.A.) trained in the administration and scoring of the test battery, and supervised by a clinical neuropsychologist (Brenda Hanna-Pladdy, Ph.D.). The research protocol was fully approved by the Institutional Review Board (IRB) of the University of Kansas Medical Center. Written informed consent was obtained for all participants at the beginning of the experimental session.

Neuropsychological test battery

The following test battery was selected to evaluate a range of cognitive domains, and included tests that measure hemispheric specialization and frontal-striatal dysfunction.

Screening Measures

Beck Depression Inventory Second Edition (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a 21-item self-report questionnaire that measures characteristic attitudes and symptoms of depression. The BDI-II is one of the most widely used depression scales in clinical and research settings. Scores range from 0 to 63, with higher scores indicating increased depressive symptomology. Despite some concerns about the number of somatic items on the scale, the BDI-II appears to be a sensitive instrument to screen and measure the severity of depressive symptoms in patients with PD (Schrag et al., 2007).

Mini Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975). The MMSE is a brief cognitive measure often used in clinical and research settings as a quick screen for dementia. Items include questions on orientation, attention, and memory. Scores range from 0 to 30.

American New Adult Reading Test (AMNART; Grober & Sliwinski, 1991)**.** Intellectual functioning was estimated using a quotient based on the reading of irregular words that are acquired through experience and education. The AMNART shows a high correlation with the WAIS–R Verbal IQ Scale in nondemented patients (Grober & Sliwinski, 1991) and can be useful in generating a quick estimate of premorbid verbal intelligence.

Tests of Language

Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983). The BNT examines the ability to name pictured objects and evaluates for the presence of anomia. A stimulus cue is given if the examinee clearly misperceives the picture, and a phonemic cue is given if the examinee is unable to correctly name the picture within 20 seconds. The number of correct responses without phonemic prompts is recorded as the total correct score. Scores range from 0 to 15.

Verbal Fluency Test from the Delis-Kaplan Executive Function Scale (D-KEFS; Delis, Kramer, & Kaplan, 2001). Phonemic, semantic, and category switching tasks were administered. In the phonemic fluency task, examinees are given three letters of the alphabet and asked to generate as many different words as they can beginning with the letter, within a one minute interval for each letter. For the semantic fluency task, examinees are asked to quickly name different items from a single category (e.g., animals, boys' names). In the set switching condition, which is also frequently used as an executive function measure, participants alternate between naming different fruits and pieces of furniture. Discrepant performances across tasks can offer information as to whether difficulty results from fluency or cognitive shifting demands.

Visual-spatial Tasks

Judgment of Line Orientation (JLO; Benton, Sivan, Hamsher, Varney, & Spreen, 1994). The JLO is commonly used to assess visuospatial perception and judgment. For each item, examinees are shown a pair of lines on the top page and an array of 11 numbered lines on the bottom page. The task is to match the orientation and position of the numbered lines below with the two target lines on the top page. The shortened 15-item version of the JLO was used in the current study. Both lines must correctly be identified in each item in order to receive credit for that item. Scores range from 0 to 15.

Visual Form Discrimination Test (VFD; Benton, Hamsher, Varney, & Spreen, 1983). The VFD is a 16-item test that examines visuoperceptual discrimination. Examinees match a group of geometric figures from an array of choices. Scores range from 0-16, and errors can be further examined as complete distortional errors or minor rotational or peripheral errors.

Memory Tasks

California Verbal Learning Test Short Form (CVLT-II-SF; Delis, Kramer, Kaplan, & Ober, 2000). The CVLT-II-SF is a word-list learning task that provides information about acquisition, recall, retention, and retrieval of verbal information, as well as strategies used in

learning. Participants are asked to learn a 9-item list of words over four consecutive trials and asked to recall the list once again immediately following an interference trial. After a 20-minute delay, participants are asked to again recall words on the original list.

Visual Reproduction I & II Tests from the Wechsler Memory Scale Third Edition (WMS-III; Wechsler, 1997b). The Visual Reproduction Test measures visuoconstructive ability and non-verbal memory. Examinees are presented with five line drawings and must draw each picture immediately after viewing the picture and again after a 20-30 minute delay. Each item is scored according to standardized WMS-III criteria based on the presence, accuracy, and placement of various elements in the design. Immediate recall, delayed recall, and copy trials were administered in the present study, with scores for each trial ranging from 0 to 66.

Tests of Attention and Working Memory

Digit Span from the Wechsler Adult Intelligence Scale Third Edition (WAIS-III; Wechsler, 1997a). Digit Span measures simple auditory attention by having subjects listen to a string of numbers and recite the numbers in a specified order (forwards or backwards). Sequences of increasing length are administered for both the forwards and backwards conditions, and items correct across both conditions are summed for a total Digit Span score. Possible score ranges are as follows: 0-18 for Digit Span forwards, 0-16 for Digit Span backwards, and 0-34 for Digit Span total.

Spatial Span (from the WMS-III; Wechsler, 1997b). This test measures visuospatial attention. In Spatial Span Forward, the examiner taps the blocks in a specified order, and the examinee taps the blocks following the same sequence. In Spatial Span Backward, examinees tap the blocks in reverse order. Items correct for both conditions are summed for a total Spatial Span score. Possible score ranges are as follows: 0-18 for Spatial Span forwards, 0-16 for Spatial Span backwards, and 0-34 for Spatial Span total.

Letter-Number Sequencing (from the WAIS-III; Wechsler, 1997a). Letter-Number Sequencing measures auditory working memory and freedom from distractibility. Participants are given a mixed string of numbers and letters and are asked to recite the letter-number combination in a specified order. Responses are correct if there are no omissions of numbers or letters and if they are all recited in the specified sequence. Scores range from 0 to 21.

Trail Making Test (TMT, from the D-KEFS; Delis et al., 2001). The D-KEFS Trail Making Test consists of a visual scanning task (Condition 1) and a series of four connect-the-dot tests. These tests measure number sequencing, letter sequencing, number-letter sequencing, and motor speed (Conditions 2-5, respectively). Although performance on the TMT is highly dependent on attention and speed, the number-letter sequencing task (Condition 4) is considered to involve an executive component due to its set shifting demands. The multiple conditions further allow determination of whether poor test performance is attributable to visual search problems, sequencing speed, motoric speed, or the executive demands of the test. Higher scores indicate worse performance.

Tests of Executive Function and Reasoning

Wisconsin Card Sorting Test (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2005). The WCST examines abstract reasoning, concept generation, and perseverative responding. This task involves the sorting of cards according to one of three categories: color, number of elements, or shape. Examinees are never told the correct sorting category but only whether their responses are correct or incorrect. The sorting category changes unexpectedly when the examinee has figured out a particular solution. A computerized and shortened (64 cards) version of the WCST was used for this study. Test indices retained for analysis included the number of categories reached (with possible scores ranging from 0 to 5) and the number of perseverative errors committed.

Go-NoGo Test. A computerized Go-NoGo Test was developed for the current study. Go-NoGo paradigms examine response inhibition and impulsivity by requiring examinees to inhibit preprotent behaviors that were practiced and rehearsed in earlier segments of the task. There were

two main conditions in our Go-NoGo paradigm. In the first condition, participants were rapidly presented with one of two visual stimuli on the computer screen: either one red square or two red squares. Auditory stimuli accompanied each visual stimulus – one short beep occurred during each presentation of the single red square, and two short beeps during each presentation of two red squares. Examinees were asked to hit the space bar twice if they saw one red square, and to hit the space bar once if they saw two red squares. In the second condition, participants were again rapidly presented with the same stimuli as in the first condition. However, this time, they were instructed to hit the space bar twice when they saw one red square, and to inhibit any response each time they saw two red squares (the "no go" stimulus). Test indices for analysis included average reaction time per item and percentage of correct and incorrect responses in the second condition.

Sensorimotor Tasks

Subjects were asked to perform two speeded sensorimotor tasks using first their dominant and then their nondominant hand. Performance was scored separately for the right and left hand.

Finger Oscillation Test (Reitan & Wolfson, 1985). The Finger Oscillation Test, also known as Finger Tapping Test, was used to measure the speed of open looped movements. Participants place their hand on a finger tapping board (manufactured by the Lafayette Company) and are asked to tap as fast as they can. The apparatus records the number of taps, and the score is the mean number of taps in five 10 second trials for each hand.

Grooved Pegboard Test (Reitan & Wolfson, 1985). The Grooved Pegboard Test (also a Lafayette instrument) was used to assess closed loop movements for each hand. Participants rotate small grooved pegs and place them into a board filled with keyhole-shaped holes in various orientations. Test indices include task completion time and number of pegs dropped during the test. Higher scores (on either test indice) indicate worse performance.

The neuropsychological tests within the five cognitive domains (language, visuospatial, attention/working memory, memory, executive function) were used in the main analyses. The BDI-

II, MMSE, and AMNART were included in the battery as screening measures and were analyzed for descriptive purposes only. Sensorimotor tests were also included in the battery to examine the relationship between laterality of motor symptom onset and current asymmetries in fine motor skills. However, because assessment of fine motor skills was not a main focus of the study, performance on these tests was not included in the main analyses.

Study Design

Two independent variables (side of initial motor symptom onset and disease progression) were used as grouping variables in this study. As indicated previously, side of disease onset was established by classifying patients into groups based on the lateralization of their motor symptoms at the time of disease onset (left and right). Patients were assigned to groups based on their current disease progression (early unilateral, late unilateral, or late bilateral).

In order to examine hypothesis # 1 of a relationship between lateralization of motor and cognitive profiles for patients in the early stages of the disease, the following neuropsychological tests in the battery were evaluated:

- *Tests of left hemisphere function:* Boston Naming Test, Phonemic Fluency (Part I of the D-KEFS Verbal Fluency Test), Category Fluency (Part II of the D-KEFS Verbal Fluency Test), Digit Span, Letter Number Sequencing, California Verbal Learning Test Second Edition (CVLT-II).
- *Tests of right hemisphere function:* Spatial Span, Visual Form Discrimination Test, Judgment of Line Orientation, Visual Reproduction I & II, Visual Search (Condition 1) of D-KEFS Trail Making Test.

Study hypotheses #2 and #3 pertain to the performance of PD patients and healthy controls across multiple general domains of cognitive functioning. Because right-left hemispheric differences are less relevant for these analyses, the neuropsychological tests were regrouped into

cognitive functions that are considered to be more frontal-striatal in comparison to those that are believed to involve more medial temporal lobe and posterior cortical brain regions. These groupings are as follows:

- *Frontal-executive domain*: Go-NoGo Test, Wisconsin Card Sorting Test, D-KEFS switching conditions (of Trail Making and Verbal Fluency tests).
- *Attention/working memory*: Digit Span forwards, Digit Span backwards, Spatial Span forwards, Spatial Span backwards, Letter Number Sequencing.
- *Language*: Boston Naming Test, D-KEFS Verbal Fluency Test (phonemic and semantic tasks only).
- *Visuospatial skills*: Judgment of Line Orientation, Visual Form Discrimination Test, Visual Search (Condition 1) of D-KEFS Trail Making Test.
- *Information acquisition/memory encoding*: relevant information acquisition measures from the CVLT-II-SF and Visual Reproduction.
- *Memory retention*: relevant memory retention indices from the CVLT-II-SF and Visual Reproduction.

To review, it was expected that PD patients in the (early and late) unilateral stages would display attentional, frontal-executive, and memory encoding deficits, consistent with dopamine depletion as the primary pathology during early disease stages. Also, we predicted that the severity of impairment would increase with years of progression. That is, while the late unilateral group may be impaired relative to controls, it may be the case that early unilateral patients may be at too early a disease stage to detect significant changes. Finally, we expected bilateral patients to display more severe attentional and frontal-executive deficits, as well as additional deficits suggestive of greater cerebral involvement, including language, visuospatial, and memory retention deficits.

Results

Preliminary Analyses

Demographic and clinical characteristics of PD and control groups. Demographic and clinical data for the PD and control participants, including group means and standard deviations, are presented in Table 1. Sixty individuals (43 males, 17 females) comprised the PD sample, and there were 20 healthy controls (13 males, 7 females). The PD sample ranged from 51 to 77 years in age, and the control sample ranged from 51 to 76 years. There were no significant differences between PD and control groups with respect to current age (t (2,78) = 1.07, p =.29), years of education (t (2,78) = 1.00, p = .32), or gender ratio (X^2 (1, N = 80) = .32, p = .57). The PD group was found to exhibit more depressive symptoms (t (2,78) = 3.19, p < .01), lower MMSE scores (t (2,78) = 3.69, p < .01), and lower AMNART scores (t (2,78) = 3.17, p < .01) compared to controls. Since depressive symptomology and lowered mental status are known features of PD that may be closely connected to the disease process in PD (Frisina, Borod, Foldi, & Tenenbaum, 2008), they were not used as covariates in subsequent analyses. Despite its common use to achieve an estimate of premorbid intellectual function, the AMNART was also not used as a covariate in subsequent analyses due to its likely relationship to current cognitive decline (Taylor, Salmon, Rice, Bondi, Hill, et al., 1996). Thus, BDI-II, MMSE, and AMNART scores are reported for descriptive purposes, but were not used in further analyses comparing the neuropsychological performance of controls and PD groups.

Demographic and clinical characteristics of the different PD groups. Data comparing demographic and clinical characteristics between the right- and left-sided onset PD groups are presented in Table 2. No significant differences were found between these two PD groups on age (t (2,58) = 1.20, p =.24), years of education (t (2,58) = .11, p = .91), or gender distribution (X^2 (1,60) = 1.05, p = .31). The groups also did not differ in clinical characteristics such as age of disease onset (t (2,58) = 1.62, p = .11), disease duration (t (2,58) = 1.10, p = .28), or total UPDRS scores (t (2,58) = .58, p = .57). The left-sided onset group had been taking PD medications for a slightly longer period

of time on average (mean = 5.0 years, SD = 4.3) than the right-sided onset group (mean = 3.4 years, SD = 2.4), but this difference was not statistically significant, t (2,58) = 1.88, $p = .07$.

Table 3 presents data on characteristics of the PD groups at different disease levels of disease progression (early unilateral, late unilateral, and bilateral stages). These three groups did not differ in demographic characteristics such as current age (F (2,57) = .59, $p = .56$), education (F (2,57) = .01, $p = .99$), or gender ratio (X^2 (1,60) = 1.41, $p = .49$). There were also no significant group differences in BDI-II (F (2,57) = 1.66, $p = .20$), MMSE (F (2,57) = .80, $p = .46$), or AMNART scores (F (2,57) = 1.32, $p = .28$). The groups significantly varied in PD characteristics such as years since initial diagnosis (F (2,57) = 57.87, $p < .001$), years since initial symptom onset (F (2,57) = 32.68, $p < .001$), and UPDRS score (F (2,54) = 16.14, $p < .001$) confirming appropriate characteristics for group assignment. Since PD groups were balanced with respect to current age, the trend was for patients with longer disease severity to display younger ages at initial diagnosis, although group differences in age at disease onset did not achieve statistical significance (F (2,57) = 3.12, $p = .052$).

Table 4 further presents demographic and clinical characteristics of the different PD groups by both side of initial symptom onset and current disease stage. Similar to above results, these six groups did not differ in demographic characteristics such as current age (F (5,54) = .61, $p = .72$), age at disease onset (F (5,54) = 1.90, $p = .11$), education (F (5,54) = .77, $p = .60$), or gender ratio, (X^2 (5,60) = 3.63, $p = .73$). They also did not significantly differ in BDI-II (F (5, 54) = 1.50, $p = .19$), MMSE (F (5,54) = .65, $p = .69$), or AMNART scores (F (5,54) = 1.45, $p = .21$). The six groups varied in PD characteristics such as years since initial diagnosis (F (5,54) = 27.86, $p < .001$), years since initial symptom onset (F (5,54) = 14.90, $p < .001$), number of years on PD medications (F (5, 54) = 16.1, $p = <.001$), and total UPDRS score (F (5,54) = 6.95, $p < .001$), with the direction of scores generally consistent with group assignment.

Medications. A qualitative analysis was performed to identify if there were differences between PD groups with respect to the types of medications taken at the time of the

neuropsychological evaluation. This information was examined in order to determine whether differences on the cognitive measures could potentially be accounted for by differences in treatment regimens between PD groups. The majority of PD participants (91.7%) were taking either a dopamine precursor (e.g., carbidopa-levodopa) or a dopaminergic agonist (e.g., ropinirole, pramipexole) medication, occasionally in combination with other drugs (such as COMT-I, MAOI, or anticholinergic drugs). Approximately 25% of the PD group was also taking an antidepressant and/or antianxiety medication. No strong trends were noted in medication regimen amongst the different PD groups. Numbers and percentages of PD participants prescribed each class of medication are presented in Tables 5 and 6.

Data preparation

Raw scores for all neuropsychological test indices were used in the analyses. Although normed scores were also available for use (age-corrected scores with published normative data serving as references, as well as computation of z scores for all participants based on the means and standard deviations of the control sample), raw data were employed for ease of presentation since similar patterns emerged regardless of whether raw or normed data were used.

Statistical assumptions for multivariate analysis of variance (MANOVA) were evaluated, including assumptions of normality, linearity, homoscedasticity, and the absence of univariate or multi-cell outliers (Tabachnik & Fidell, 2001). There was only one significant univariate outlier, which was omitted from further analyses. Some of the individual variables within groups had significant departures from normality as assessed by the Shapiro Wilk test. Because MANOVA and ANOVA tend to be robust to relatively minor violations of this assumption, results were reported without data transformation of the select variables. For the multiple MANOVAs performed in this study, Box's Test was significant for several, meaning that the covariance matrices significantly differed across the dependent variables for those analyses. For those select MANOVAs, the generally more conservative Pillai's Trace criterion was used rather than Wilks' Lambda, since the

former tends to be more robust to departures from the homoscedasticity assumption in the evaluation of multivariate effects. Dependent variables in each MANOVA were grouped according to a priori assumptions of the underlying constructs they are measuring. Correlations between DVs in each MANOVA were also examined to ensure they were measuring similar constructs, and were moderately but not too highly correlated with each other.

Significant MANOVAs were followed up with univariate tests, and significant ANOVAs were further examined with post-hoc comparisons. A few neuropsychological variables had unequal variances between groups based on Levene's Test; however, results were examined since ANOVA also tends to be quite robust to relatively minor violations of the homogeneity of variance assumption.

Main analyses

The relationship between side of initial motor symptom onset and current disease stage on right and left hemisphere neuropsychological measures. One of the primary aims of this study was to evaluate whether initial laterality of motor symptoms in PD would predict cognitive profiles at different stages of disease progression. In order to evaluate this, two 3 X 2 MANOVAs were calculated (one for left hemisphere measures, and the second for the right hemisphere measures), with disease progression group (early unilateral, later unilateral, later bilateral) and side of motor symptom onset (right or left) as the independent variables. If findings are congruent with our hypothesis that lateralization of cognitive deficits in PD vary as a function of disease progression (hypothesis #1), a significant interaction would be expected between side of motor symptom onset and disease progression in each of these two MANOVAs. However, the multivariate interaction was not significant for either the left hemisphere measures (Wilks' Lambda = .75, F (14,96) = 1.07, p =.39) or the right hemisphere measures (Pillai's Trace = .24, F (12,100) = 1.15, p = .33). For these sets of analyses, all multivariate main effects were also nonsignificant. Side of initial symptom motor onset was not found to be significantly related to the left hemisphere measures (Wilks'

Lambda = .85, F (7,48) = 1.21, p = .32), and disease progression was also nonsignificant as a main effect for the combined left hemisphere measures (Wilks' Lambda = .81, F (14,96) = .75, p = .72). For the combined right hemisphere measures, neither the side of initial symptom onset (Pillai's Trace = .08, F (6,49) = .68, p = .67) nor disease progression (Pillai's Trace = .16, F (12,100) = .74, p = .71) was significant. Table 7 lists the means and standard deviations of the PD groups (by disease stage and side of initial motor symptom onset) on all left and right hemisphere measures.

Comparisons between the controls and PD groups at different levels of disease progression. To establish whether PD patients display cognitive dysfunction relative to healthy controls, one way MANOVAs were performed to compare the four groups (controls, early unilateral group, later unilateral group, and bilateral group) on each of the six domains of cognitive function (frontal-executive, attention/working memory, language, visuospatial ability, memory encoding, and memory retention). Table 8 lists means and standard deviations of all groups on the test indices comprising the different cognitive domains, as well as p values for all multivariate and univariate analyses of group differences.

The multivariate effect was nonsignificant for the frontal-executive measures (Pillai's Trace = .26, F (12,216) = 1.69, p = .071), although it came close to reaching statistical significance. The multivariate effect was also nonsignificant for separate MANOVAs conducted for measures in the attention/working memory (Wilks' Lambda = .81, F (15,199) = 1.04, p = .42), language (Pillai's Trace = .14, F (9,228) = 1.22, p = .29), and visuospatial (Pillai's Trace = .14, F (9,228) = 1.25, p = .27) domains. Univariate analyses will thus not be examined for individual measures in these cognitive domains, although group means and standard deviations for these measures, as well as p values of univariate analyses, are presented in Table 7.

The MANOVAs performed to evaluate group differences on both the information encoding and retention aspects of memory were significant. The groups differed on the combined memory encoding measures, Wilks Lambda = .75, F (6,150) = 3.90, p = .001. Follow-up ANOVAs with

these measures revealed a significant difference on CVLT-II learning (F (3,76) = 7.61, $p < .001$), but not for Visual Reproduction learning (F (3,76) = 2.43, $p = .072$). Bonferroni post-hoc comparisons for CVLT-II learning yielded only one significant pairwise difference, between the controls and bilateral group ($p < .001$).

The groups also differed on the combined memory retention measures, Wilks Lambda = .76, F (6,150) = 3.73, $p = .002$. A follow-up univariate analysis revealed a significant overall group difference on CVLT-II delayed performance (F (3,76) = 6.88, $p < .001$), and paired comparisons revealed only a significant difference between controls and the bilateral group ($p < .001$). The follow-up univariate analysis applied to Visual Reproduction delayed performance was not significant, but came close to significance, F (3,76) = 2.67, $p = .053$.

Examination of a priori hypotheses concerning specific group differences. In order to improve detection of hypothesized differences between groups, a series of planned comparisons were conducted to investigate if there were significant predicted differences not previously revealed by the earlier analyses. Tables 9 and 10 illustrate results of all planned comparisons examined and their *p* values (one-tailed, since hypotheses were all directional) if significant. All planned contrasts were examined for statistical significance using the Bonferroni-Holm procedure to control for Type I error (Abdi, 2010).

Table 9 presents results of planned comparisons that examine the performance of healthy controls and 6 PD groups on designated right and left hemisphere measures, in order to evaluate the prediction that lateralized deficits are associated only with unilateral disease (hypothesis #1). These contrasts included comparisons between controls and each of the 6 PD groups, as well as those examining differences between right- and left-sided onset groups within each of the three disease progression stages. On the left hemisphere measures, controls outperformed the left-sided onset early unilateral group on CVLT-II learning, and no other differences were observed between controls and the right- and left-sided onset early unilateral groups. The right-sided onset late unilateral group

were more impaired relative to controls on category fluency and CVLT-II learning, and no other comparisons were significant between controls and the two late unilateral groups on the left hemisphere measures. The right-sided onset bilateral group demonstrated significantly weaker performances relative to controls on letter fluency, category fluency, WAIS-III letter number sequencing, and CVLT-II learning and memory retention. The left-sided onset bilateral were impaired relative to controls on CVLT-II learning and memory retention. On the left hemisphere measures, the right-sided onset bilateral group were also more impaired than the left-sided bilateral onset group on WAIS-III letter number sequencing; otherwise, no other contrasts were significant that examined right- and left-sided onset group differences within the same disease stage. For all planned contrasts with the right hemisphere measures, the only comparisons that were significant were between the controls and right-sided onset bilateral group on D-KEFS visual search speed and Visual Reproduction II.

Table 10 presents findings for the remainder of the planned comparisons, which compare the performance of controls and PD groups by disease stage. The first of these contrasts examined the performance of healthy controls and the unilateral patients groups in order to evaluate the prediction that unilateral PD disease would be associated with impairment in the frontal-executive, attention/working memory, and memory encoding domains (hypothesis #2a). For these comparisons, select planned contrasts (healthy controls vs. early unilateral, and healthy controls vs. late unilateral) were examined for individual neuropsychological measures in each of these three domains. After implementing Bonferroni-Holm corrections, the following contrasts were statistically significant: controls outperformed the early and late unilateral groups on Digit Span backwards, and controls also outperformed both groups on verbal memory encoding.

The next group of planned comparisons evaluated differences between the early unilateral and late unilateral groups to examine the prediction that the late unilateral group would show more severe impairment across measures of frontal-executive function, attention/working memory, and

memory encoding (hypothesis #2b). For this comparison, contrasts between the early and late unilateral groups were examined for all measures within these domains. However, none of these contrasts were found to be significant.

The final set of planned comparisons examined the hypothesis that PD patients in the bilateral disease stage would show impairment across all cognitive domains as compared to controls and patients in the earliest stages of PD (hypothesis #3). The bilateral group was compared to controls and the unilateral group on all measures in which Bonferroni post-hoc comparisons did not already reveal significant differences. In the frontal executive domain, the bilateral group performed significantly worse than controls on all four measures, and worse than the early unilateral group on DKEFS Trails switching only. For attention/working memory measures, the bilateral group was more impaired than the controls on Digit Span backwards. The bilateral group and controls came close to being significantly different on Letter Number Sequencing and Spatial Span backwards, but these contrasts were not significant after applying Bonferroni-Holm adjustments. No significant differences were observed between the bilateral and early unilateral groups on attention/working memory measures. In the language domain, controls outperformed the bilateral group on DKEFS Letter Fluency and DKEFS Semantic Fluency, and no significant differences were observed between the bilateral and early unilateral groups. For the visuospatial measures, controls significantly outperformed the bilateral group on the JLO only, and no other planned contrasts were significant. In the memory encoding domain, as reportedly previously Bonferroni post-hoc comparisons had revealed significant differences between the bilateral group and controls on verbal information encoding (CVLT-II total on learning trials). Planned contrasts additionally revealed a significant difference between the bilateral group and controls on nonverbal information encoding (Visual Reproduction I), as well as differences between the bilateral and the unilateral groups on verbal information encoding. The planned contrast applied to bilateral and unilateral groups on nonverbal information encoding came close to significance at $p = .046$. Within the memory retention domain,

post-hoc comparisons had earlier revealed differences between the bilateral group and controls on verbal memory retention (CVLT-II long delay performance). Planned contrasts between groups in the memory retention domain additionally revealed the following: significant differences between the bilateral group and controls on nonverbal memory retention (Visual Reproduction II), and significant differences between the bilateral and early unilateral groups on both verbal memory retention and nonverbal memory retention.

Additional comparisons between groups. Table 11 presents results of additional contrasts that were conducted, in order to further explore group differences on cognitive measures not examined in the planned comparisons. P values were evaluated for significance at the two-tailed level and after implementation of Bonferroni-Holm corrections. Results of these comparisons showed that the right-sided onset bilateral group performed worse than controls on the following additional measures: D-KEFS trails switching, Go NoGo contrasting motor condition, Digit Span backwards, and Spatial Span backwards. The right-sided onset bilateral group also performed worse than the left-sided onset group on the Go NoGo contrasting motor task. No other contrasts were significant in these additional comparisons.

Supplementary Analyses

Discriminant function analyses. MANOVAs were followed with discriminant function analyses to evaluate the accuracy of the neuropsychological test measures in classifying different groups. The neuropsychological test indices that were used as predictors in these analyses were previously found to be significant either in the MANOVAs and follow-up ANOVAs or in the planned comparisons. Three discriminant function analyses were performed on the data. The first examined whether select test indices were effective in differentiating PD patients from controls in our sample. The second was performed to examine how accurately the predictor variables could group PD participants according to their level of disease progression (early unilateral, late unilateral, or late bilateral). The final discriminant function analysis investigated whether cognitive measures

could differentiate between PD patients with left-sided symptom onset vs. those with right-sided symptom onset.

For the first discriminant function analysis, there were two grouping variables (patient vs. control status) and the predictors entered into the model included the following: D-KEFS verbal switching, D-KEFS trails switching, WCST categories matched, Go NoGo contrasting motor condition, Digit Span backwards, Letter Number Sequencing, D-KEFS letter fluency, D-KEFS category fluency, Judgment of Line Orientation, CVLT-II learning total, CVLT-II delayed recall performance, Visual Reproduction I, and Visual Reproduction II. For this discriminant function analysis, a Wilks' Lambda of .68 was statistically significant ($p = .015$) and suggested that the model adequately discriminated between the control and patient groups. All predictor variables significantly discriminated between the two groups at least at the $p < .05$ level, with the exception of D-KEFS trails switching ($p = .062$), WCST categories sorted ($p = .069$), Letter- Number Sequencing ($p = .083$), and Visual Reproduction I ($p = .24$). The direct solution entering both variables simultaneously produced 76.3% correct classifications, with 7.5% false positives, and 16.2% false negatives. The classification matrix is presented in Table 12.

The second discriminant function analysis had three grouping variables (early unilateral, late unilateral, and bilateral) and included the following predictor variables: D-KEFS verbal switching, D-KEFS trails switching, WCST categories matched, Go NoGo contrasting motor condition, Digit Span backwards, D-KEFS letter fluency, D-KEFS category fluency, CVLT-II learning total, CVLT-II delayed recall performance, Visual Reproduction I, and Visual Reproduction II. However, these predictors were less accurate in grouping PD participants according to their level of disease progression, as results were nonsignificant (Wilks' Lambda = .67, $p = .56$), and only 51.7% of PD patients were correctly classified in their respective disease stage groups.

The final discriminant function analysis explored whether measures previously significant in the planned comparisons could adequately discriminate between the left- and right-sided onset PD

groups. The following predictor variables were entered simultaneously in the direct solution: D-KEFS letter fluency, D-KEFS category fluency, Letter-Number Sequencing, CVLT-II learning, CVLT-II memory retention, D-KEFS visual search, and Visual Reproduction II. Results were nonsignificant (Wilks' Lambda = .83, p = .17), with 63.3% of PD patients correctly classified.

Group differences on fine motor skills. Table 13 displays raw data means and standard deviations on the motor tasks for the PD groups. In order to evaluate group performances on fine motor measures, a 3 X 2 MANOVA was performed, with disease progression group (early unilateral, later unilateral, later bilateral) and side of motor symptom onset (right or left) as the independent variables, and right- and left-handed scores on the Grooved Pegboard and Finger Tapping tasks serving as the dependent variables. The multivariate interaction was not significant (Wilks' Lambda = .76, F (8,94) = 1.75, p =.10), and the multivariate main effect for current disease stage was also nonsignificant (Wilks' Lambda = .87, F (8,94), p = .58). However, there was a multivariate main effect for initial laterality, as side of initial symptom motor onset was found to be significantly related to the combined motor DV's (Wilks' Lambda = .56, F (4,47) = 9.37, p < .001). Further investigation with univariate analyses revealed that the left-side onset group performed worse than the right-side onset group on both of the left-handed measures (Grooved Pegboard left hand: F (1,50) = 5.51, p = .02, Finger Tapping left hand: F (1,50) = 17.14, p < .001). The two groups did not differ in their scores when performing on right-handed measures.

Motor asymmetry scores were computed by the formula (right hand performance – left hand performance / right hand performance). Higher asymmetry scores indicate superior performance on the right dominant hand, whereas lower asymmetry scores above zero indicate less skill superiority on the right hand. Scores that are in the negative range reflect nondominant (left hand) skill superiority on the specific motor measure, as all participants in the study were right hand dominant. The sign for the computed asymmetry score from Grooved Pegboard was reversed (e.g., if a (R-L)/R score was .17, it then became a -.17) in order to maintain consistency across the motor measures. To

examine whether patient groups display differences in observed asymmetries on motor skills, a 3 X 2 MANOVA was performed with disease progression and side of motor symptom onset as the independent variables, and with motor asymmetry scores on the Finger Tapping and Grooved Pegboard tests serving as the dependent variables. A significant interaction between initial side of motor symptom onset and disease progression was found for combined motor asymmetry (Wilks' Lambda = .74, F (4,98) = 4.00, p =.005). Follow-up ANOVAs reveal that the interaction was significant for both the Finger Tapping and Grooved Pegboard tasks. Figure 1 illustrates this interaction, which was similar for both motor tasks. Since the multivariate and univariate interactions between independent variables were significant, multivariate and univariate main effects were not examined.

Discussion

This study examined the effects of initial side of motor symptom onset and current disease stage on cognition in PD. Previous research examining the effects of motor symptom laterality on cognition has yielded mixed results; thus, the aim of the current investigation was to examine whether disease severity/duration could explain some of the heterogeneity of past studies and clarify the role of initial side of symptom onset in influencing later cognitive profiles. Present findings revealed a) some support for a significant relationship between initial laterality of motor symptoms and later cognitive pattern, and b) cognitive deficits in PD consistent with hypothesized effects of disease progression. Findings are further discussed below.

Initial laterality of motor symptoms and cognition in PD

Side of motor symptom onset in PD is believed to be an important clinical and neuropathological factor of the disease. Motor symptoms in PD typically begin on one side of the body, and patients whose symptoms begin on the left side of the body have greater nigrostriatal pathology in the right hemisphere whereas those with right side symptom onset have greater left hemisphere pathology (Kempster et al., 1989; Nahmias et al., 1985). Therefore, it was predicted

(hypothesis #1) that initial side of motor symptom onset would be associated with lateralized cognitive deficits only during the unilateral disease stage, and that lateralized deficits would not be observed in the bilateral disease stage.

The present dataset supported some aspects of our laterality hypothesis. In this study, individuals with right-sided onset unilateral disease demonstrated impaired performance relative to controls on some left hemisphere measures (i.e., category fluency and verbal memory encoding) that were not observed in the left-sided onset unilateral group, which is consistent with hypothesized lateralized deficits during unilateral disease in PD. Although the left-sided onset unilateral group did not significantly differ from controls or the right-sided onset unilateral group on any of the right hemisphere measures, the left early unilateral group did perform worse than controls on one of the left hemisphere measures (verbal learning/encoding). In the bilateral stage, those with initial right-sided motor symptoms demonstrated more pervasive impairment on left hemisphere measures (which extended beyond category fluency and verbal memory encoding to also include letter fluency, a task of auditory working memory, and verbal memory retention) and some right hemisphere measures (visual search and nonverbal learning/encoding), while the left-sided bilateral onset group were impaired relative to controls on verbal learning/encoding and retention.

Our results are consistent with some previous studies (Bentin et al., 1981; Blonder et al., 1989; Starkstein et al., 1987) suggesting a possible relationship between initial side of motor symptom onset and later lateralized cognitive deficits. In general, the right-sided onset group showed greater impairment on left hemisphere measures than the left-sided onset group, and particularly on tasks with a strong executive component. Somewhat contrary to our predictions, the lateralizing pattern was stronger for the right bilateral group than for the right unilateral group. Upon further reflection, this may not be entirely surprising, since unilateral disease is associated with deficits on primarily executive tasks, and executive dysfunction does not seem to consistently demonstrate a strong lateralizing pattern.

Another interesting finding was that the right bilateral group seemed to show greater cognitive impairment than all other groups (and more so than the left bilateral group) on both left and right hemisphere measures. Given that the groups were relatively balanced with respect to relevant demographic and PD characteristics, this could suggest that right-sided motor symptom onset is associated with more rapid cognitive decline than left-sided motor symptom onset, which has been posited by previous researchers (Williams et al., 2007). Alternatively, this finding may be an artifact of our small sample size.

Other past investigations have also documented a relationship between right-sided motor symptoms and diminished performance on tests of left hemisphere function, with no observed impairments for the left-sided individuals on tasks assessing right hemisphere function (Huber et al., 1992; Spicer et al., 1988). One distinct possibility for current null results with the right hemisphere measures is that the study simply lacked statistical power to detect significant group differences due to sample size. Some of these measures demonstrated a pattern consistent with the study's hypothesis regarding lateralization of deficits, but results did not achieve overall statistical significance. It is possible that the cognitive tasks utilized in our study (as well as previous studies with similar findings) were not as sensitive in detecting right hemisphere pathology. In any case, results suggest further exploration in this area. Future replication of this study with a larger sample may sufficiently increase statistical power to fully detect hypothesized differences.

Disease progression and cognition in PD

The current study also examined cognitive changes that occur as the disease progresses from the earliest stage after onset of clinical symptoms to later in the disease course when motor symptoms have become bilateral. Differences in neuropsychological performance were examined between age and education matched controls and the following three PD groups: early unilateral (< 1 year post diagnosis), late unilateral (2-5 years post diagnosis) and bilateral (over 5 years post diagnosis).

Cognitive deficits during early unilateral stages. It was predicted that PD in the unilateral stage would be associated with impairments in the frontal-executive, attention/working memory, and memory encoding domains (hypothesis #2a). Results were significant for differences between controls and the unilateral groups on two measures within these domains: Digit Span backwards, and CVLT information encoding. Although Digit Span backwards and CVLT list learning were not grouped within the frontal-executive domain, they can certainly be construed as executive abilities that involve efficiency in planning and simultaneous operation of a number of different cognitive processes. The Digit Span backwards trial involves internal control of attention, holding information in temporary storage for manipulation, and then reciting numbers in the reverse order that they were presented. And in order to effectively learn a list of auditory presented words, an efficient organizational strategy to aid encoding is necessary. Results on some other measures came close but were not statistically significant. These findings suggest that even at the earliest stage of PD, some changes can be observed in cognitive abilities that reflect frontal-striatal dysfunction. These results are consistent with the past findings suggesting a relationship between early stage PD and impairments in planning and working memory (Cools et al., 2001, Duke & Kaszniak, 2000; Muslimovic et al., 2005; Taylor et al., 1986; Zgaljardic et al., 2006), and suggest that signs of frontal-striatal circuitry dysfunction may be observed even within one year or less of receiving the PD diagnosis.

It was also predicted that the progression from early to late unilateral disease would be associated with increased deficits on measures sensitive to frontal-striatal dysfunction (hypothesis #2b). Although there was a trend for lower scores in the late unilateral group, no significant differences were found between the two unilateral groups on any of the measures examining frontal-executive, attention/working memory, and memory encoding. These nonsignificant findings may be at least partly due to the study's methodology and selection criteria. Average disease duration for the early unilateral group was .8 years, and average disease duration for the late unilateral group was 3.7

years. Thus, it may be the case that differences in disease duration between the two groups were not sufficiently varied in detect changes consistent with disease progression.

Cognitive deficits associated with later bilateral disease. Another study prediction was that PD patients in the bilateral disease stage with disease duration of at least 5 years would exhibit more global cognitive deficits than patients in the earlier unilateral stages, consistent with hypothesized involvement of additional non-dopaminergic pathology later in the disease course (hypothesis #3). Our results suggest that by the time PD progresses to the bilateral stage and beyond 5 years, deficits are observed in many cognitive domains, including frontal-executive function, attention/working memory, memory encoding, language, visuospatial skills, and memory retention ability.

Patients in the bilateral disease stage were more impaired than controls on all four measures of frontal-executive function (WCST, Go NoGo, Verbal Fluency switching, and Letter-Number switching tasks), one measure of attention/working memory (Digit Span backwards score), and both verbal and nonverbal information encoding (CVLT-II and Visual Reproduction learning). These executive and related deficits are certainly more pervasive than the changes observed in patients with unilateral disease, who displayed deficits compared to controls on only two of these measures (Digit Span backwards and CVLT-II learning). Notably, the bilateral group was also more impaired relative to the early unilateral group on select measures (verbal and nonverbal information encoding and D-KEFS Letter-Number switching task). The increased severity of executive impairments in the bilateral stage likely mirrors the progression of frontal-striatal pathology in PD over time. Also, increased executive impairments could also be due to additional cortical pathology at later stages that are believed to be part of the disease progression in PD (Braak et al., 2003; Braak & Braak, 2000) or due to comorbid pathology in later diseases that are unrelated to PD such as Alzheimer's disease or disruption of non-dopaminergic neuronal systems (Dubois & Pillon, 1992; Emre, 2003; Galvin, 2006; Jellinger, 2001; Zdaljardic et al., 2004).

The bilateral group also demonstrated impairments in language and visuospatial ability. The literature on language deficits in PD has been mixed (Grossman et al., 1991; Holtgraves, McNamara, Cappeart, & Durso, 2010; Levin, Tomer, & Rey, 1992), and it has been suggested (Murray, 2008) that basic language abilities (confrontation naming, sentence repetition, comprehension of basic commands) may be intact in PD but that more complex aspects of language processing and expression may be impaired. Our findings are consistent with this notion, as PD patients with bilateral motor disease displayed intact confrontation naming abilities but were impaired on tasks of phonemic and semantic fluency. The latter language tasks have a strong executive component, and thus deficits on these measures may reflect increased executive dysfunction (associated with greater disease duration and severity) rather than a true impairment in language abilities. Within the visuospatial domain, the bilateral group demonstrated impairment relative to controls only on a measure of spatial judgment and perception (Judgment of Line Orientation). This also supports previous observations that visuospatial impairments are inconsistently observed in PD (Spicer et al. 1988, Uc et al., 2005), and when observed they seem to be associated with advanced PD rather than earlier stages of PD (Huber et al., 1989a).

Significant memory retention deficits, for verbal and nonverbal information, were also observed in the bilateral group. The pattern of memory deficits revealed impairment for both encoding and retrieval difficulties; therefore, memory difficulties in the bilateral group cannot be entirely attributed to encoding difficulties secondary to proposed frontal-striatal involvement in PD, as was evident in patients with unilateral disease. Braak et al. (2004) had asserted that in advanced stages of PD, the pathology often reaches the medial temporal lobes as well as other cortical structures. And interestingly, a recent MRI study (Ibarretxe-Bilbao, Tolosa, Junque, & Marti, 2009) found significantly reduced hippocampal and amygdala volumes in both demented and nondemented PD patients as compared to controls. Although the study authors did not specify disease stage/duration of their PD sample, their finding of medial temporal atrophy in PD is consistent with

our results demonstrating significant memory retrieval difficulties in bilateral PD. Medial temporal lobe structures, and particularly the hippocampus, are believed to play an important role in memory consolidation and retrieval, and therefore the atrophy of this cortical region may underlie the memory dysfunction associated with more advanced PD. Additionally, the finding of both verbal and non-verbal memory retrieval deficits in bilateral disease (as well as evidence of language and visuospatial difficulties) is suggestive of bilateral cognitive involvement that mirrors the bilateral motor symptom progression.

In short, present findings suggest that cognitive impairment in PD may be related both to laterality of motor symptom at disease onset and current disease stage. In the early unilateral stages within 5 years after onset, cognitive deficits when observed may be restricted mostly to executive tasks, and those with right-sided motor symptom onset seem to demonstrate diminished performance on executive tasks that are more verbal in nature. In contrast, PD in the bilateral stage exceeding 5 years disease duration appears to be associated with more widespread cognitive decline, with those with right-sided onset possibly showing more pronounced deficits than those with left-sided onset.

Motor skills and asymmetry in PD

Although motor skills in PD was not a primary focus of this investigation, we also examined fine motor performance and motor asymmetry as a function of initial motor symptom laterality in PD and current disease progression. Consistent with group classification, the left-sided onset group performed significantly worse than the right-sided onset deficits on both left-handed motor measures. However, groups did not differ in their performance on right-handed motor measures. For the left-sided onset group, there was a greater discrepancy between left and right hand motor performance (with higher scores on the right hand) early in the disease course that seemed to diminish over time, presumably as the disease progressed and the dominant right hand became increasingly affected. In contrast, patients with right-sided symptom onset showed an initial smaller asymmetry in motor performance, yet with greater disease severity the right-sided group appeared to demonstrate

increased motor asymmetry favoring the right hand (although the asymmetry was still less pronounced than for the left-sided group). The increased asymmetry over time in the right-side onset group likely parallels increased motor symptoms on the left side as the disease progresses. These results are also consistent with observations that compared to unilateral left hemisphere involvement, unilateral right hemisphere pathology tends to be associated with greater intermanual asymmetries (Hanna-Pladdy, Mendoza, Apostolos, & Heilman, 2002; Smutok et al., 1989). Findings in this study suggest that intermanual discrepancies in PD patients with initial left-side onset (implying greater right hemisphere) become less pronounced over time as the disease course progresses from unilateral to bilateral.

Study limitations and directions for future research

The current study has several strengths. First of all, this study uniquely examined the effects of both laterality of motor symptoms at disease onset and current disease progression on cognition. Secondly, our investigation was restricted to PD groups in the early and middle disease stages, and one advantage of studying PD groups earlier in the disease course is the likelihood of studying PD without the additional comorbidities that are typical of patients in more advanced disease stages. Other strengths of the investigation include use of an extensive battery of tests, inclusion of patient groups among three different stages of disease severity, and the utilization of well-matched and carefully screened participant groups.

However, there were some limitations to the current study. As noted earlier, the relatively small sample size may have lowered statistical power, and future similar studies may wish to employ larger sample sizes to increase chances of detecting significant differences. The present study also relied on a population of patients from a single Movement Disorders Center in the Midwestern U.S., and PD participants in this study were relatively well-educated, with an average of 16 years of formal education. Although PD participants were well-balanced with the controls in education, age, gender, and other demographic variables, it is possible that participants in our geographically restricted

sample are not representative of the general PD population. Also, it is important to note that significant findings reported in this study refer to statistical significance and are not necessarily suggestive of clinical significance.

In order to examine specific research questions of interest in this study, only select subgroups of the PD population were recruited (patients with unilateral disease and less than 5 years disease duration and those with bilateral motor disease and having had PD between 5-13 years). All PD participants were in the mild-moderate stage of PD (Hoehn & Yahr score of 1 or 2 only) and we did not assess patients at the more severe end of the motor symptom spectrum (e.g., patients with prominent balance/gait problems or requiring a wheelchair). Although there are advantages of such a research design as discussed above, study findings may not generalize to PD groups not evaluated in this investigation. Additionally, the current study did not examine differences between motor symptomatology subtypes (i.e., patients with tremor only, bradykinesia/rigidity only, or a combination of motor symptoms). Since different motor subtype profiles in PD could possibly involve varying pathological processes and foci (Jellinger, 2001), it may be helpful for future studies to clarify whether the relationship between laterality of motor symptoms and cognition is affected by motor symptom subtype.

Although this study was not designed to address medication effects, it is unclear to what extent PD medications may have affected findings in this investigation. Nearly all study participants were taking a dopamine precursor or a dopamine agonist medication, and the relationship between dopamine and cognition is complex and continues to be debated in the literature (Cools, 2008, Pillon et al., 2003). A few participants were also taking anticholingeric medications, which are expected to adversely affect cognition. However, steps were taken in the study to minimize the effects of medication differences. All participants were tested during their "on" state and pharmacological interventions employed appeared to be largely similar for the different PD groups of interest. Yet given the high frequency of polytherapy, switching of medications and doses by physicians and

patients, it would be helpful for future studies should carefully examine the effects of PD medications on cognition.

In summary, study results suggest the following: a) right-sided motor symptom onset in PD appears to be associated with diminished performance on left hemisphere tasks during both unilateral and bilateral disease stages, with the lateralizing pattern appearing relatively more pronounced during the bilateral stage than the unilateral stage, b) cognitive changes during the unilateral stages of PD (irrespective of laterality of motor symptoms) seem restricted to executive dysfunction, and c) bilateral motor symptoms in PD (with greater than 5 years disease duration) is associated with more widespread cognitive decline believed to reflect greater cortical involvement beyond frontal-striatal circuitry dysfunction. Even though our data was prospectively acquired, this was a cross-sectional investigation and more longitudinal studies are needed in order to confirm the nature of cognitive changes over the disease course. Future studies may address the neural basis of cognitive changes associated with motor symptomatology in PD. Neuroimaging data (e.g., functional magnetic resonance imaging, positron emission tomography) and post-mortem studies would further help shed light on the rate and severity of neurodegeneration in PD.

References

Abdi, H. (2010). Holm's sequential Bonferroni procedure. In: N. Salkind's (Ed.). *Encyclopedia of Research Design.* Thousand Oaks, CA: Sage Press.

Alves, G., Larsen, J. P., Emre, M., Wentzel-Larsen, T., Aarsland, D. (2006). Changes in motor subtype and risk for incident dementia in Parkinson's disease. *Movement Disorders, 21*, 1123-1130.

Bentin, S., Silverberg, R., & Gordon, H. W. (1981). Asymmetrical cognitive deterioration in demented and Parkinson patients. *Cortex, 17,* 533-544.

Benton, A. Hamsher, K., Varney, N. & Spreen, O. (1983). *Contributions to neuropsychological assessment: A clinical manual.* New York: Oxford University Press.

Benton A. L., Sivan, A. B., Hamsher, K., Varney, N. R., Spreen, O. (1994). Contributions to neuropsychological assessment, second edition. New York, NY: Oxford University Press.

Biggins, C. A., Boyd, J. L., Harrop, F. M., Madeley, P., Mindham, R. H. S., et al. (1992). A controlled, longitudinal study of dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 55,* 566-571.

Blonder, L. X., Gur, R. E., Ruben, C. G., Saykin, A. J., Hurtig, H. I. (1989). Neuropsychological functioning in hemiparkinsonism. *Brain and Cognition, 9,* 244-257.

Blumenfeld, H. (2002). Neuroanatomy through clinical cases. Sunderland, MA: Sinauer Associates, Inc.

Braak, H., & Braak, E. (2000). Pathoanatomy of Parkinson's disease. *Journal of Neurology, 247,* 3-10.

Braak, H., Del Tredici, Rub, U., De Vos, R., Steur, E. N. H. J., Braak, E. (2003). *Neurobiology of Aging, 24,* 197-211.

Burn, D. J., Rowan, E. N., Allan, L. M., Molloy, S., O'Brien, J. T., & McKeith, I. G. (2006).

Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *Journal of Neurology, Neurosurgery, and Psychiatry, 77,* 585-589.

Cools, R. (2008). Role of dopamine in the motivational and cognitive control of behavior. *Neuroscientist, 14*(4), 381-395.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). *Brain, 124,* 2503-2512.

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

Cummings, J. L. (1992). Depression and Parkinson's disease: A review. *American Journal of Psychiatry, 149,* 443-454.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. (2000). California Verbal Learning Test Second Edition (CVLT-II). San Antonio, TX: The Psychological Corporation.

Delis, D. C., Kramer, J. H., & Kaplan, E. (2001). *The Delis-Kaplan Executive Function System.* San Antonio, TX: The Psychological Corporation.

Direnfeld, L., Albert, M., Volicer, L., Langlais, P., Marquis, K., & Kaplan, E. (1984). The possible relationship of laterality to dementia and neurochemical findings. *Archives of Neurology, 41,* 935-941.

Dubois, B., & Pillon, B. (1992). Biochemical correlates of cognitive changes and dementia in Parkinson's disease. In: S. J. Huber & J. L. Cummings (Eds.). Parkinson's disease: Neurobehavioral aspects. Oxford University Press, pp. 178-198.

Dubois, B., & Pillon, B. (1997). Cognitive deficits in Parkinson's disease. *Journal of Neurology, 244,* 2-8.

Duke, L. M., & Kaszniak, A. W. (2000). Executive control functions in degenerative dementias: A comparative review. *Neuropsychology Review, 10,* 75-99.

Emre, M. (2003). What causes mental dysfunction in Parkinson's disease? *Movement Disorders, 18,* Suppl. 6, S63-S71.

Fahn, S., & Elton, R. L. (1987). The Unified Parkinson's Disease Rating Scale. In: S. Fahn, C. D. Marsden, D. B. Calne, et al. (Eds). *Recent Developments in Parkinson's disease: Volume 2*. Florham Park, NJ: MacMillan Healthcare Information, pp.153–163.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12,*189–198.

Frisina, P. G., Borod, J. C., Foldi, N. S., & Tenenbaum, H. R. (2008). *Neuropsychiatric Disease and Treatment, 4,* 81-91.

Galvin, J. E. (2006). Cognitive change in Parkinson's disease. *Alzheimer Disease and Associated Disorders, 20,* 302-10.

Gasparoli, E., Delibori, D., Polesello, G., Santelli, L., Ermani, M., et al. (2002). Clinical predictors in Parkinson's disease. *Neurological Sciences, 23 (Supplement 2),* S77-78.

Gladsjo, J. A., Heaton, R. K., Palmer, B. W., Taylor, M. J., & Jeste, D. V. (1999). Use of oral reading to estimate premorbid intellectual and neuropsychological functioning. *Journal of the International Neuropsychological Society*, 5, 247-254. 145.

Green, J., McDonald, W. M., Vitek, J. L., Evatt, M., Freeman, A., et al. (2002). Cognitive impairments in advanced PD without dementia. *Neurology, 59,* 1320-1324.

Grober, E., & Sliwinski, M. (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology, 13*(6), 933-949.

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

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression, and mortality. *Neurology, 17,* 427-432.

Holtgraves, T., McNamara, P., Cappaert, K., & Dorso, R. (2010). Linguistic correlates of asymmetric motor symptom severity in Parkinson's disease. *Brain and Cognition, 72,* 189-196.

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

Huber, S. J., Freidenberg, D. L., Shuttleworth, E. C., Paulson, G. W., & Clapp, L. E. (1989b). Neuropsychological similarities in lateralized parkinsonism. Cortex, 25, 461-470.

Huber, S. J., Miller, H., Bohaska, L., & Christy, J. A. (1992). Asymmetrical cognitive differences associated with hemiparkinsonism. *Archives of Clinical Neuropsychology, 7,* 471-480.

Ibarretze-Bilbao, N., Tolosa, E., Junque, C., & Marti, M. J. (2009). MRI and cognitive impairment in Parkinson's disease. *Movement Disorders, 24,* S748-753.

Jellinger, K. A. (2001). The pathology of Parkinson's disease. *Parkinson's Disease: Advances in Neurology, 86,* 55-72.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston Naming Test.* Philadelphia: Lee & Febiger.

Katzen, H. L., Levin, B. E., & Weiner, W. (2006). Side and type of motor symptom influence cognition in Parkinson's disease. *Movement Disorders, 21,* 1947-1953.

Kempster, P. A., Gibb, W. R. G., Stern, G. M., & Lees, A. J. (1989). Asymmetry of substantia nigra neuronal loss in Parkinson's disease and its relevance to the mechanism of levodopa related motor fluctuations. *Journal of Neurology, Neurosurgery, and Psychiatry, 52,* 72-76.

Kongs, S. K., Thompson, L. L., Iverson, G. L. & Heaton, R. K. (2005). Wisconsin Card Sorting

Test 64 Card Version. Odessa, Florida: Psychological Assessment Resources, Inc.

Leenders, K. L., Salmon, E. P., Tyrell, P., Perani, D., Brooks, D. J., et al. (1990). The nigrostriatal dopaminergic system assessed in vivo by positron emission tomography in healthy volunteer subjects and patients with Parkinson's disease. *Archives of Neurology, 47,* 1290-1298.

Lees, A. J., & Smith, E. (1983). Cognitive deficits in the early stages of Parkinson's disease. *Brain, 106,* 257-70.

Levin, B. E., Tomer, R., & Rey, G. J. (1992). Cognitive impairments in Parkinson's disease. *Neurologic Clinics, 10,* 471-484.

Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., Owen, A. M. (2003). Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *Journal of Neuroscience, 23,* 6351-6356.

Lichter, D. G., & Cummings, J. L., Eds. (2001). Frontal-subcortical circuits in psychiatric and neurological disorders. New York: Guilford Press.

Levin, B. E., Tomer, R., & Rey, G. J. (1992) Cognitive impairment in Parkinson's disease. *Neurology Clinic, 10,* 471-485.

Levy, G., Tang, M. X., Cote, L. J., Louis, E. D., Alfaro, B., Mejia, H., Stern, Y., & Marder, K., et al. (2000). Motor impairment in PD: Relationship to incident dementia and age. *Neurology, 55,* 539-544.

Locascio, J. L., Corkin, S., & Growdon, J. H. (2003). Relation between clinical characteristics of Parkinson's disease and cognitive decline. *Journal of Clinical and Experimental Neuropsychology, 25,* 94-109.

Marder, K., Tang, T. X., Cote, L., Stern, Y., & Mayeux, R. (1995). The frequency and associated risk factors for dementia in patients with Parkinson's disease. *Archives of Neurology, 95,* 695-701.

Mayeux, R., Denaro, J., Hemenegildo, N., Marder, K., Tang, M., Cote, L. J., & Stern, Y. (1992). A population-based investigation of Parkinson's disease with and without dementia. Archives of Neurology, 49, 492-497.

Murray, L. L. (2008). Language and Parkinson's disease. *Annual Review of Applied Linguistics*, 28, 113-127.

Muslimovic, D., Schmand, B. Speelman, J. D., & de Haan, R. J. (2007). Course of cognitive decline in Parkinson's disease: a meta-analysis. *Journal of the International Neuropsychological Society, 13,* 920-932.

Muslimovic, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology, 65,* 1239-1245.

Nahmias, C., Garnett, E. S., Firnau, G., & Lang, A. (1985) Striatal dopamine distribution in Parkinson's patients during life. Journal of Neurological Sciences, 69, 223-230.

Oldfield, R. (1971). The assessment and analysis of handedness: The Edinburgh Handedness Inventory. Neuropsychologia, 9, 97-113.

Owen, A. M. (2004) Cognitive dysfunction in Parkinson's disease: The role of frontostriatal circuitry. *The Neuroscientist, 10*, 525-537.

Parkinson, J. (1817). *An essay on the shaking palsy*. Full document available on the following website: http://www.allaboutparkinsons.com/essay-on-the-shaking-palsy.html

Paulus, W., & Jellinger, K. A. (1991) The neuropathologic basis of different clinical subgroups of Parkinson's disease. *Journal of Neuropathology and Experimental Neurology, 50,* 743-755.

Pillon, B., Czernecki, V., & Dubois, B. (2003). Dopamine and cognitive function. *Current Opinion in Neurology, 16 Supplement 2,* S17-22.

Reitan, R.M. & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation.* Tucson: Neuropsychology Press.

Rinne, J. O., Laihinen, A., Rinne, U. K., Nagren, K., Bergman, J. et al. (1993). PET study on striatal dopamine D2 receptor changes during the progression of early Parkinson's disease. *Movement Disorders, 8,* 134-138.

Rinne, J. O., Portin, R., Ruottinen, H., Nurmi, E., Bergman, J., et al. (2000). Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. *Archives of Neurology, 57,* 470-475.

Schrag, A. Barone, P., Brown, R. G., Leentjens, A. F. G., McDonald, W. M., et al. (2007)**.** Depression rating scales in Parkinson's disease: Critique and recommendations**.** *Movement Disorders, 22 (8*), 1077-1092.

Smutok, M. A., Grafman, J., Salazar, A. M., Sweeney, J. K., Jonas, B. S., & DiRocco, P. J. (1989). Effects of unilateral brain damage on contralateral and ipsilateral upper extremity function in hemiplegia. *Physical Therapy, 69,* 195-203.

Spicer, K., Roberts, F., & Lewitt, P. (1988). Neuropsychological performance in lateralized Parkinsonism. *Archives of Neurology, 45,* 429-432.

St. Clair, J., Borod, J. C., Sliwinski, M., Cote, L. J., & Stern, Y. (1998). Cognitive and affective functioning in Parkinson's disease with lateralized motor signs. *Journal of Clinical and Experimental Neuropsychology,* 20, 320-327.

Starkstein, S., Leiguarda, R., Gershanik, O., & Berthier, M. (1987). Neuropsychological disturbances in hemiparkinson's disease. *Neurology, 37,* 1762-1764.

Starkstein, S., Mayberg, H. S., Leiguarda, R., Preziosi, T. J., & Robinson, R. G. (1992). A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 55(5*), 377–382.

Stern, Y., & Mayeux, R. (1986). Intellectual impairment in Parkinson's disease. *Advances in Neurology, 45,* 405-408.

Tabachnik, B. G., & Fidell, L. S. (2001). *Using Multivariate Statistics: Fourth Edition.* Allyn & Bacon: Needham Heights, MA.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Frontal lobe dysfunction in Parkinson's disease: The cortical focus of neostriatal flow. *Brain, 109,* 845-883.

Taylor, K. I., Samon, D. P., Rice, V. A., Bondi, M. W., Hill, R. L., et al. (1996). Longitudinal examination of American New Adult Reading Test (AMNART) performance in dementia of the Alzheimer's type (DAT): Validation and correction based on degree of cognitive decline. *Journal of Clinical and Experimental Neuropsychology, 18,* 883-891.

Tison, R. Dartigues, J. F., & Auriacombe, S. (1995). Dementia in Parkinson's disease: A population based study in ambulatory and institutionalized individuals. *Neurology, 45,* 705-708.

Tomer, R., Levin, B. E., & Weiner, W. J. (1993). Side of onset of motor symptoms influences cognition in Parkinson's disease. *Annals of Neurology, 34,* 579-584.

Trahan D. E., & Larrabee, G. J. (1988). Continuous Visual Memory Test. Odessa, Florida: Psychological Assessment Resources, Incorporated.

Uc, E. Y., Rizzo, M., Anderson, S. W., Qian, S., Rodnitsky, R. L., & Dawson, J. D. (2005). Visual dysfunction in Parkinson disease without dementia. *Neurology, 65,* 1907-1913.

Viitanen, M., Mortimer, J. A., & Webster, D. D. (1994). Association between presenting motor symptoms and the risk of cognitive impairment in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 57,* 1203-1207.

Wang, J., Zuo, C. T., Jiang, Y. P., Guan, Y. H., Chen, Z. P., Xiang, J. D., et al. (2007). 18F-FP-CIT PET imaging and SPM analysis of dopamine transporters in Parkinson's disease in various Hoehn & Yahr stages. *Journal of Neurology, 254,* 185-190.

Wechsler, D. (1997a). *Wechsler Adult Intelligence Scale Third Edition (WAIS-III).* New York: Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale Third Edition (WMS-III).* New York: Psychological Corporation.

Williams, L. N., Seignourel, P., Crucian, G. P., Okun, M. S., Rodriguez, R. L., Skidmore, F. M., et al. (2007). Laterality, region, and type of motor dysfunction correlate with cognitive impairment in Parkinson's disease. *Movement Disorders, 22,* 141-145.

Zgaljardic, D. J., Borod, J. C., Foldi, N. S., Mattis, P. J., Gordon, M. F., Feigin, A., et al. (2006). An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology,* 28, 1127-1144.

Zgaljardic, D. J., Foldi, N. S., & Borod, J. C. (2004). Cognitive and behavioral dysfunction in Parkinson's disease: Neurochemical and clinicopathological contribution. *Journal of Neural Transmission, 111,* 1287-1301.

Table 1

Demographic and clinical data for PD and Control Participants

	PD participants (n = 60)		Control participants (n = 20)	
	Mean	SD	Mean	SD
Age	63.9	6.1	65.6	6.8
Education	16.0	2.3	17.0	1.8
Gender	71.7% male		65% male	
BDI-II score*	9.1	6.3	3.3	4.0
MMSE score*	28.6	1.3	29.6	0.7
AMNART IQ estimate*	117.2	8.6	123.4	3.0
Age at disease onset	59.5	6.1		
Years since PD diagnosis	4.4	3.5		
Years since initial symptom onset	6.3	3.9		
UPDRS motor subscore	19.0	5.8		
UPDRS total score	29.9	10.5		

* $p < .01$

Table 2

Demographic and clinical data for right-sided onset and left-sided onset PD groups

	Right-sided onset (n = 31)		Left-sided onset (n = 29)	
	Mean	SD	Mean	SD
Age	64.8	6.2	62.9	5.9
Education	16.0	2.3	16.0	2.4
Gender	77% male		66% male	
BDI-II score	8.3	5.3	9.9	7.2
MMSE score	28.5	1.4	28.7	1.1
AMNART IQ estimate	116.8	8.6	117.7	8.7
Age at disease onset	60.8	6.4	57.9	7.3
Years since PD diagnosis	4.0	2.7	5.0	4.2
Years since initial symptom onset	6.0	3.4	6.6	4.5
Years on PD medications	3.4	2.4	5.0	4.3
UPDRS motor score	18.5	5.6	19.4	5.6
UPDRS total score	29.1	10.0	30.6	10.4

All above comparisons, including chi square comparisons for gender differences, were n.s. at $p > .05$

Table 3

Demographic and clinical data for PD groups at different disease progression stages

	Early unilateral (<1 year post diagnosis) (n = 18)	Middle unilateral (2-5 years) (n = 17)	Bilateral (5 years or greater) (n = 25)
	Mean (SD)	Mean (SD)	Mean (SD)
Age	62.6 (5.7)	64.4 (7.1)	64.5 (5.8)
Education	16.1 (2.5)	15.9 (2.7)	16.0 (2.0)
Gender	61 % males	76% males	75% males
BDI-II score	7.1 (6.4)	9.1 (6.7)	10.6 (5.8)
MMSE score	28.7 (1.1)	28.8 (1.3)	28.4 (1.4)
AMNART IQ estimate	119.2 (7.2)	118.1 (9.4)	115.1 (8.9)
Age at disease onset	61.7 (5.7)	60.7 (7.1)	56.9 (7.1)
Years since PD diagnosis**	0.8 (.4)	3.7 (1.1)	7.6 (3.0)
Years since initial symptom onset**	2.7 (2.1)	5.5 (1.8)	9.4 (3.6)
Years on PD medications**	0.9 (0.2)	3.5 (1.1)	6.8 (3.7)
UPDRS motor score**	17.7 (4.1)	15.8 (3.9)	22.6 (5.9)
UPDRS total score**	24.2 (6.5)	25.8 (6.7)	37.5 (10.1)

* $p < .05$
** $p < .01$

Table 4

Demographic and clinical data for different PD groups, by initial side of motor symptom onset and disease progression

	Early unilateral		**Late unilateral**		**Bilateral**	
	Right onset (n = 10)	**Left onset** (n = 8)	**Right onset** (n = 8)	**Left onset** (n = 9)	**Right onset** (n = 13)	**Left onset** (n = 12)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	63.2 (6.3)	61.8 (5.2)	66.6 (6.6)	62.3 (7.3)	64.9 (6.2)	64.1 (5.5)
Education	16.3(2.5)	15.8 (2.7)	16.6 (2.4)	15.3 (2.8)	15.3 (2.1)	16.8 (1.8)
Gender	70% male	50% male	87% male	66% male	77% male	75% male
BDI-II score	7.4 (6.3)	6.6 (7.1)	5.4 (1.8)	12.3 (7.8)	10.9 (5.2)	10.3 (6.5)
MMSE score	28.9 (1.1)	28.5 (1.2)	29.1 (1.4)	28.2 (1.7)	28.2 (1.7)	28.6 (1.0)
AMNART IQ estimate	121.0 (4.5)	117.0 (9.5)	119.2 (6.9)	117.1 (11.5)	112.0 (10.0)	118.5 (6.3)
Age at disease onset	62.2 (6.3)	61.2 (5.4)	63.0 (6.0)	58.7 (7.7)	58.4 (6.5)	55.3 (7.7)
Years since PD diagnosis*	1.0 (.4)	.6 (.4)	3.6 (1.2)	3.7 (1.0)	6.4 (1.9)	8.8 (3.6)
Years since initial symptom onset*	3.2 (2.5)	2.0 (1.3)	5.8 (2.1)	5.2 (1.7)	8.3 (3.1)	10.7 (3.7)
Years on PD medications*	.9 (.2)	.9 (.3)	3.3 (1.3)	3.7 (.9)	5.3 (2.2)	8.5 (4.4)
UPDRS motor score*	17.5 (4.7)	17.6 (3.4)	14.6 (4.4)	16.9 (3.3)	22.0 (5.3)	23.2 (6.9)
UPDRS total score*	24.9 (7.5)	23.3 (5.4)	22.6 (6.1)	28.7 (6.2)	36.8 (9.1)	38.3 (11.6)

* $p < .01$

Table 5

Medications prescribed at time of neuropsychological evaluation, for right- and left-sided onset PD groups

	Right-sided onset (n = 31)	Left-sided onset (n = 29)
	number (%)	number (%)
PD medications:		
Synthetic DA and/or DA agonist only	15 (48.4%)	13 (44.8%)
MAOI only	1 (3.2%)	2 (6.9%)
COMT-I only	0 (0%)	0 (0%)
Anticholinergic drug only	0 (0%)	0 (0%)
Combination of dopaminergic and other medication(s)*	15 (48.4%)	12 (41.4%)
None	0 (0%)	2 (6.9%)
Psychotropic medications:		
Antidepressant only	4 (12.9%)	4 (13.8%)
Antianxiety only	2 (6.5%)	2 (6.9%)
Both antidepressant/anxiety	2 (6.5%)	1 (3.4%)
None	23 (74.1%)	22 (75.9%)

* other classes of PD drugs prescribed for the PD sample in conjunction with synthetic dopamine (DA) or DA agonists included monoamine oxidase inhibitors (MAOIs), catechol-o-methytransferase inhibitors (COMT-Is), anticholinergic drugs, and the experimental drug Creatine.

Table 6

Medications prescribed at time of neuropsychological evaluation, for PD groups at different levels of disease progression

	Early unilateral (<1 year post diagnosis) (n = 18)	Middle unilateral (2-5 years) (n = 17)	Bilateral (5 years or greater) (n = 25)
	number (%)	number (%)	number (%)
PD medications:			
Synthetic DA and/or DA agonist only	9 (50.0%)	4 (23.5%)	10 (40.0%)
MAOI only	3 (16.7%)	0 (0%)	0 (0%)
COMT-I only	0 (0%)	0 (0%)	0 (0%)
Anticholinergic drug only	0 (0%)	0 (0%)	0 (0%)
Combination of dopaminergic and other medication(s)*	5 (27.7%)	12 (70.1%)	15 (60.0%)
None	1 (5.6%)	1 (5.6%)	0 (0%)
Psychotropic medications:			
Antidepressant only	1 (5.6%)	3 (17.6%)	4 (16.0%)
Antianxiety only	2 (10.2%)	0 (0%)	2 (8.0%)
Both antidepressant/anxiety	1 (5.6%)	1 (5.9%)	1 (4.0%)
None	14 (77.7%)	13 (76.5%)	18 (72.0%)

* other classes of PD drugs prescribed for the PD sample in conjunction with synthetic dopamine (DA) or DA agonists included monoamine oxidase inhibitors (MAOIs), catechol-o-methytransferase inhibitors (COMT-Is), anticholinergic drugs, and the experimental drug Creatine.

Table 7

Performance of PD groups on left and right hemisphere neuropsychological measures, by disease stage and initial side of motor symptom onset

	Early unilateral		**Late unilateral**		**Bilateral**	
	Right onset (n = 10)	**Left onset** (n = 8)	**Right onset** (n = 8)	**Left onset** (n = 9)	**Right onset** (n = 13)	**Left onset** (n = 12)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
LEFT HEMISPHERE MEASURES						
Boston naming test	14.60 (.70)	14.38 (.74)	14.38 (.92)	14.67 (.50)	14.08 (1.94)	13.92 (1.31)
DKEFS letter fluency	40.10 (14.46)	36.75 (11.12)	34.75 (12.78)	41.56 (12.02)	33.62 (8.89)	42.83 (15.04)
DKEFS category fluency	41.90 (12.01)	36.75 (7.25)	35.63 (13.06)	45.78 (7.86)	36.15 (6.71)	39.42 (8.60)
Digit span total	18.60 (2.32)	15.88 (3.98)	18.75 (4.74)	17.11 (4.49)	16.46 (3.80)	18.58 (3.66)
Letter number sequencing	10.10 (3.00)	9.38 (.92)	9.25 (1.49)	9.89 (1.45)	7.69 (2.93)	10.33 (3.28)
CVLT-II learning trials	27.90 (5.02)	24.38 (2.88)	24.88 (3.52)	26.33 (2.40)	22.92 (4.29)	24.17 (4.49)
CVLT-II delay free recall	6.30 (1.70)	6.63 (.92)	6.50 (1.77)	6.78 (1.20)	5.08 (2.10)	5.75 (1.36)
RIGHT HEMISPHERE MEASURES						
Judgment of line orientation	11.50 (4.30)	12.38 (3.11)	12.62 (1.41)	12.33 (1.12)	11.69 (2.14)	11.75 (2.18)
Visual form discrimination	30.40 (1.35)	30.00 (3.07)	30.38 (2.50)	29.11 (2.85)	29.54 (2.44)	29.67 (2.57)
DKEFS visual search (time completed in secs)	26.80 (4.44)	22.88 (3.27)	24.00 (3.63)	27.00 (8.60)	30.46 (10.35)	23.33 (8.78)
Spatial span total	15.40 (2.17)	14.75 (3.41)	15.25 (2.61)	14.11 (2.76)	13.38 (2.82)	15.75 (2.14)
Visual reproduction I	84.50 (11.02)	75.50 (12.31)	84.13 (9.98)	79.89 (15.79)	72.54 (14.72)	75.83 (10.33)
Visual reproduction II	72.60 (17.80)	55.38 (20.70)	60.25 (18.05)	61.56 (18.43)	53.92 (20.52)	58.08 (12.00)

Table 8

Neuropsychological performance of controls and PD groups at different levels of disease progression, within each cognitive domain – multivariate and univariate results

	Controls (n=20)	Early Unilateral (n = 18)	Late Bilateral Unilateral (n=17)	(n=25)	p value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
FRONTAL EXECUTIVE – F(4,70) = 1.69					**.070**
DKEFS verbal switching	14.63 (2.91)	12.89 (3.38)	13.00 (2.55)	12.35 (2.52)	.075
DKEFS trails switching	75.37 (25.48)	90.61 (44.07)	89.47 (37.84)	125.91 (86.22)	.030
WCST categories matched	3.68 (1.16)	3.17 (1.58)	3.29 (1.69)	2.39 (1.83)	.070
Go nogo condition 2	98.47 (1.58)	93.94 (5.86)	95.41 (4.68)	89.13 (17.96)	.041
ATTENTION/WORKING MEMORY – F(5,72) = 1.04					**.416**
Digit span forwards	11.25 (2.31)	10.78 (2.05)	11.00 (2.35)	10.84 (1.91)	.900
Digit span backwards	8.25 (1.94)	6.61 (1.61)	6.88 (2.40)	6.64 (2.27)	.045
Spatial span forwards	7.80 (2.07)	7.67 (1.57)	7.41 (1.73)	7.60 (1.71)	.929
Spatial span backwards	8.00 (1.81)	7.44 (1.46)	7.24 (1.35)	6.92 (1.82)	.188
Letter number sequencing	10.60 (1.85)	9.78 (2.29)	9.59 (1.46)	8.96 (3.27)	.170
LANGUAGE – F(3,74) = 1.22					**.285**
Boston naming test	14.65 (.93)	14.50 (.71)	14.53 (.72)	14.00 (1.63)	.225
DKEFS letter fluency	45.60 (9.80)	38.61 (12.83)	38.35 (12.49)	38.04 (12.86)	.148
DKEFS category fluency	45.20 (7.83)	39.61 (10.25)	41.00 (11.52)	37.42 (9.51)	.063
VISUOSPATIAL – F(3,74) = 1.22					**.269**
Judgment of line orientation	13.45 (1.32)	11.89 (3.74)	12.47 (1.23)	11.72 (2.11)	.074
Visual form discrimination	30.90 (1.74)	30.22 (2.21)	29.71 (2.69)	29.60 (2.45)	.253
DKEFS visual scanning	23.35 (6.60)	25.06 (4.34)	25.59 (6.72)	27.04 (10.11)	.444
MEMORY ENCODING – F(2,75) = 3.90					**.001**
CVLT-II learning trials	28.95 (3.00)	26.33 (4.47)	25.65 (2.98)	23.52 (4.34)	.000
Visual reproduction I	82.90 (10.30)	80.50 (12.16)	81.88 (13.15)	74.12 (12.65)	.072
MEMORY RETENTION – F(2,75) = 3.73					**.002**
CVLT-II delayed free recall	7.45 (1.36)	6.44 (1.38)	6.65 (1.46)	5.40 (1.78)	.000
Visual reproduction II	70.35 (15.29)	64.94 (20.53)	60.94 (17.69)	55.92 (16.77)	.053

Table 9

Results of planned comparisons between controls and PD groups, by initial side of motor symptom onset and disease progression

	Controls and REU	Controls and LEU	Controls and RLU	Controls and LLU	Controls and RB	Controls and LB	REU and LEU	RLU and LLU	RB and LB
LEFT HEMISPHERE MEASURES									
Boston naming test	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
DKEFS letter fluency	n.s.	n.s.	n.s.	n.s.	.003	n.s.	n.s.	n.s.	n.s.
DKEFS category fluency	n.s.	n.s.	.006	n.s.	.003	n.s.	n.s.	n.s.	n.s.
Digit span total	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Letter number sequencing	n.s.	n.s.	n.s.	n.s.	<.001	n.s.	n.s.	n.s.	.003
CVLT-II learning trials	n.s.	.003	.006	n.s.	<.001	<.001	n.s.	n.s.	n.s.
CVLT-II delay free recall	n.s.	n.s.	n.s.	n.s.	<.001	<.002	n.s.	n.s.	n.s.
RIGHT HEMISPHERE MEASURES									
Judgment of line orientation	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Visual form discrimination	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
DKEFS visual search (time completed in secs)	n.s.	n.s.	n.s.	n.s.	.004	n.s.	n.s.	n.s.	n.s.
Spatial span total	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Visual reproduction I	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Visual reproduction II	n.s.	n.s.	n.s.	n.s.	.005	n.s.	n.s.	n.s.	n.s.

Note. REU = Right-sided onset early unilateral, LEU = Left-sided onset early unilateral, RLU = Right-sided onset late unilateral, LLU = Left-sided onset late unilateral, RB = Right-sided onset bilateral, LB = Left-sided onset bilateral. All *p* values reported above were significant at the one-tailed level after Bonferroni-Holm adjustments to correct for Type I error.

Table 10

Results of planned comparisons between controls and PD groups, by disease stage

	Controls and EU	Controls and LU	EU and LU	EU and bilateral	Controls and bilateral
FRONTAL EXECUTIVE					
DKEFS verbal switching	n.s.	n.s.	n.s.	n.s.	.006
DKEFS trails switching	n.s.	n.s.	n.s. .025		<.003
WCST categories matched	n.s.	n.s.	n.s.	n.s.	.005
Go nogo condition 2	n.s.	n.s.	n.s.	n.s.	<.003
ATTENTION/WORKING MEMORY					
Digit span forwards	n.s.	n.s. n.s	n.s.	n.s.	
Digit span backwards	.009	.003	n.s. n.s.	.006	
Spatial span forwards	n.s.	n.s.	n.s. n.s.	n.s.	
Spatial span backwards n.s.	n.s.	n.s. n.s.		n.s.	
Letter number sequencing	n.s.	n.s.	n.s. n.s.	n.s.	
LANGUAGE					
Boston naming test	--	--	--	n.s.	n.s.
DKEFS letter fluency	--	--	--	n.s.	<.005
DKEFS category fluency	--	--	--	n.s.	.02
VISUOSPATIAL					
Judgment of line orientation	--	--	--	n.s.	.007
Visual form discrimination	--	--	--	n.s.	n.s.
DKEFS visual scanning	-- --	--	n.s.	n.s.	
MEMORY ENCODING					
CVLT-II learning trials .019	.005	n.s. <.001		*	
Visual reproduction I	n.s.	n.s.	n.s. n.s.	.009	
MEMORY RETENTION					
CVLT-II delayed free recall	--	--	--	.015	*
Visual reproduction II	--	--	--	.05	.004

* Contrast not examined because Bonferroni post-hoc comparison had already revealed significant pairwise difference.

Note. EU = early unilateral group , LU = late unilateral group. All p values reported above were significant at the one-tailed level after Bonferroni-Holm adjustments to correct for Type I error.

Table 11

Results of additional comparisons between controls and PD groups

	Controls and REU	Controls and LEU	Controls and RLU	Controls and LLU	Controls and RB	Controls and LB	REU and LEU	RLU and LLU	RB and LB
D-KEFS verbal switching	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
D-KEFS trails switching	n.s.	n.s.	n.s.	n.s.	.002	n.s.	n.s.	n.s.	n.s.
WCST categories matched	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Go nogo condition 2	n.s.	n.s.	n.s.	n.s.	<.001	n.s.	n.s.	n.s.	.002
Digit Span forwards	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Digit Span backwards	n.s.	n.s.	n.s.	n.s.	.007	n.s.	n.s.	n.s.	n.s.
Spatial Span forwards	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Spatial Span backwards	n.s.	n.s.	n.s.	n.s.	.005	n.s.	n.s.	n.s.	n.s.

Note. REU = Right-sided onset early unilateral, LEU = Left-sided onset early unilateral, RLU = Right-sided onset late unilateral, LLU = Left-sided onset late unilateral, RB = Right-sided onset bilateral, LB = Left-sided onset bilateral. All *p* values reported above were significant at the two-tailed level after Bonferroni-Holm adjustments to correct for Type I error.

Table 12

Classification matrix for discriminant function analysis of select neuropsychological measures, for control vs. patient group membership

	Predicted group membership		
Group	Control	PD patient	Total
Control	14	6	20
PD patient	13	47	60

Note. 76.3% of the cases were correctly classified.

Table 13

Performance of PD groups on fine motor tasks, by disease stage and initial side of motor symptom onset

	Early unilateral		**Late unilateral**		**Bilateral**	
	Right onset (n = 10)	**Left onset** (n = 8)	**Right onset** (n = 8)	**Left onset** (n = 9)	**Right onset** (n = 13)	**Left onset** (n = 12)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Grooved Pegboard Test						
Right hand	121.80 (49.96)	93.43(30.02)	102.25 (11.79)	100.44 (33.63)	117.30 (41.33)	123.67 (40.10)
Left hand	114.21 (43.60)	142.57 (49.66)	103.25 (18.20)	159.78 (55.59)	137.00 (58.95)	156.08 (67.66)
Finger Tapping Test						
Right hand	38.27 (40.89)	40.89 (13.13)	47.43 (39.64)	39.66 (7.32)	43.50 (7.70)	43.68 (11.27)
Left hand	43.17 (10.50)	28.91 (9.60)	45.88 (7.63)	34.56 (10.62)	44.40 (43.14)	34.84 (8.55)

Figure 1

PD group interactions on motor asymmetry scores