Executive Dysfunction and Everyday Functioning Deficits in Parkinson's Disease

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Abstract
Everyday Dysfunction and Everyday Functioning Deficits in Parkinson’s Disease
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Cognitive impairment is increasingly recognized as a characteristic of Parkinson’s disease (PD). Executive dysfunction is recognized as a significant facet of cognitive impairment in PD across studies, while research in other cognitive domains, such as such as attention, memory, and visuo-spatial functioning, have had mixed results. Cognitive decline in PD patients may lead to impairments in everyday functioning, or the ability to perform activities of daily living, and decreased quality of life. Although the relationship between motor impairments and global cognitive impairment on everyday functioning in PD has been explored, the impact of domain-specific deficits is not well understood. The neuropathology of PD, including deficits in the basal ganglia and associated cortical feedback loops, has been suggested to play a role in executive dysfunction. These brain structures have been implicated in executive dysfunction and everyday functioning in normal aging samples as well.

Using a retrospective database, this study consisted of two specific aims; 1) to examine neuropsychological correlates of everyday functioning in PD, and 2) to examine the clinical utility of two commonly used measured of global cognitive status in relation to everyday functioning. It was hypothesized that initiation/perseveration and working memory, sub-domains of executive functioning, would demonstrate the strongest relationship to everyday functioning
in PD compared to other cognitive domains. It was hypothesized that two commonly used measures of global cognition would be significantly correlated with measures of everyday functioning.

The data used in this study was collected as part of an ongoing longitudinal cohort study, conducted through Parkinson’s Disease and Movement Disorders Center (PDMDC), an outpatient neurology clinic in Philadelphia, Pennsylvania. Demographics were coded, and the measures analyzed in the present study included: 1) neuropsychological measures of global cognition (Mini-Mental State Examination, MMSE; Dementia Rating Scale-2, DRS-2), attention (DRS-2 Attention subscale), memory (Hopkins Verbal Learning Test – Revised, HVLT-R, delayed recall; DRS-2 Memory subscale), visuo-spatial/visuo-perceptual functioning (Judgment of Line Orientation, JOLO; DRS-2 Construction subscale), and sub-domains of executive functioning (phonemic verbal fluency; clock draw copy; DRS-2 Initiation/Perseveration subscale); 2) everyday functional status via care-giver report (Alzheimer’s Disease Cooperative Study –Activities of Daily Living Inventory, ADCS-ADL); and 3) PD motor disability (Hoehn & Yahr).

In a sample of 181 participants with confirmed PD, partial correlation analyses indicated that measures of global cognition (MMSE, r=0.25, p<.01; DRS-2, r=0.27, p<.01), measures of visuo-spatial/visuo-perceptual abilities (JOLO, r=0.20, p<.05; DRS-2 Construction r=0.20, p<.05), and sub-domains of executive functioning including initiation/perseveration (DRS-2 Initiation/Perseveration, r=0.16, p<.05), and working memory/tasking monitoring (phonemic verbal fluency, r=0.18, p<.05), are related to everyday functioning in PD. Attention and memory were not
significantly related to everyday functioning. A multiple regression analysis of three
tests of executive functioning, including measures of working memory/task
monitoring (verbal fluency), planning/execution (clockdraw copy), and
initiation/perseveration (DRS-2 Initiation/Perseveration subscale), revealed the
model to have significant predictive value in everyday functioning in PD (R = .52, F
(3, 152) = 18.88, p < .001).

Several neuropsychological assessment tools that require 20 minutes or less
to administer demonstrated significant relationships with everyday functioning in
PD, including measures of sub-domains of executive functioning
(initiation/perseveration, working memory), visuo-spatial/visuo-perceptual
functioning, and two commonly used clinical measures of global cognition. High
correlations demonstrated between the MMSE, DRS-2 and everyday functioning
supports continued use in the clinic. Future research should further explore the
clinical utility of these measures, in an effort to inform everyday functioning status
and integrative treatment approaches for PD patients, and provide a foundation for
the development of PD-specific assessment measures of both global cognition and
everyday functioning.
1. Introduction

1.1 Specific objectives

The overarching goal of this research project was to examine the impact of differential neuropsychological domain deficits on everyday functioning in patients with Parkinson’s disease (PD). PD is a neurodegenerative disorder that is characterized primarily by a combination of cardinal motor impairments including resting tremor, rigidity, bradykinesia, and postural instability (Gelb et al., 1999). In addition to motor impairments, PD patients often exhibit some form of cognitive deficits (Janvin, Aarsland & Larsen, 2005; Troster & Woods, 2005; Bassett, 2005; Emre 2003). It is thought that both motor impairments and cognitive deficits can affect PD patients’ ability to perform everyday functional activities, also commonly referred to as activities of daily living (ADLs). However most empirical research has focused on studying the impact of motor impairment in isolation, through controlling for cognitive deficits (Fleischman, Wilson, & Schneider, 2007). The few studies that have addressed the contribution of cognitive deficits to ADL impairments in PD have focused primarily on the contribution of global cognitive impairments.

Research has shown that PD patients suffer from impairments not only in global cognition, but also in a variety of specific neuropsychological domains (Troster & Woods, 2005; Taylor & Saint-Cyr, 1995). Deficits in executive functioning, memory, attention, and visuo-spatial functioning have been reported in neuropsychological investigations of PD. The impact of these differential domain deficits on the performance of ADLs has not been well established. The aim of this
study is to elucidate the neuropsychological domain that best correlates with functional disability in PD patients, and suggest assessment measures that may be useful in predicting functional decline in clinical settings. The results are hoped to influence the rehabilitation literature and inform the development and implementation of interventions involving compensatory strategies and/or remediation techniques that may treat affected cognitive domains and improve everyday functional performance.

1.2 Background: Parkinson's disease

Parkinson’s disease (PD) is one of the most common neurodegenerative movement disorders. Dopamine depletion throughout the brain, a result of neuropathological changes in the basal ganglia, particularly the substantia nigra, contributes to PD progression. The substantia nigra is the brain’s main source of dopamine. Throughout the progression of PD, dopamine depletion adversely affects fronto-striatal systems and cortico-subcortical feedback loops involving multiple brain regions.

A 1993 study by Zhang and Roman reported worldwide prevalence rates to vary from 18 to 418 per 100,000; however, in more recent studies, prevalence rates have varied depending on the geographical areas studied, and estimated worldwide prevalence rates have increased in range. In a literature review by von Campenhausen and colleagues (2005), prevalence rates in Western countries were reported to range between 65 and 12,500 per 100,000. The researchers also reported annual incidence rates ranging from 5 to 346 per 100,000. Gender and race differences in prevalence rates are controversial and widely differ across studies,
however it is generally accepted that PD is more common in men than women (Troster & Woods, 2005). Differences in methodologies and diagnostic criteria across clinics and geographical areas may contribute to the wide ranges of prevalence and incidence rates. It is important to note that across studies, incidence rates increase for older age groups.

PD is diagnosed based on the presence of a combination of four cardinal motor symptoms; tremor, rigidity, bradykinesia and gait/posture disorder. Two common assessment instruments measure PD severity. The most commonly used measurement of overall disease disability is the Hoehn and Yahr (Hoehn and Yahr, 1967), a 5-point scale that rates the overall “stage” or current severity of PD, with 1 being less severe and 5 being the most severe and disabling. The Unified Parkinson’s Disease Rating Scale (UPDRS; Fahn & Elton, 1987) is a more detailed assessment consisting of structured questionnaires (Parts I, II and IV) and an assessment of motor symptoms (Part III). Parts I and II is a structured interview, querying patients concerning mental status and activities of daily living, respectively. Part III is a motor assessment performed by a neurologist to investigate the presence and severity of the four cardinal symptoms as well as other common symptoms of PD. Part IV is a structured interview collecting patient-reported effects of PD medication therapy.

Since the latter half of the 1980s, non-motor symptoms of Parkinson’s disease have received considerable attention in the literature. Psychiatric symptoms such as depression, anxiety, hallucinations and cognitive decline have been investigated. Cognitive studies of Parkinson’s disease have been primarily
focused on those diagnosed with Parkinson’s disease with dementia (PDD). The risk of developing dementia in PD has been studied using both cross-sectional and longitudinal designs. In the 1970s and 1980s, percentage estimates varied greatly, from 3% to 80%; more recent studies have yielded an annual incidence rate of 95 per 1,000 (Aarsland et al., 2000) and have reduced the risk range estimates to between 20% and 40% (Aarsland et al., 2003), but these are still controversial. The research on PDD led to a current effort in the literature to examine cognition in PD across the spectrum of the disease. Considering the risk of developing dementia in PD, examination of cognitive functioning and potential deficits in non-demented PD will further inform the literature and shed light onto cognitive deficits that may be precursors to PDD.

1.3 Cognitive deficits in PD

1.3.1 Global cognitive deficits

As it is accepted that PD patients may suffer from some level of cognitive impairment throughout disease progression, global cognitive assessment measures are often used in the clinic to determine if impairment is present or absent. The most commonly used assessment tool is the Mini-Mental Status Examination (MMSE; Folstein et al., 1975). Administration of the MMSE is quick to perform in neurology clinics, where the majority of PD patients seek treatment. While the MMSE has been shown to be sensitive in distinguishing between Parkinson’s patients who do and do not have dementia, it has been criticized for its lack of specificity in non-demented PD. Janvin, Aarsland and colleagues (2003), found that two groups of PD patients with varying levels of impairment detected by a
comprehensive neuropsychological battery both scored an average of 28 on the MMSE. Azuma and colleagues (2003) conducted a longitudinal study of neuropsychological testing in non-demented PD, and found that of the 69 participants with MMSE scores in the normal range (28-30) at the beginning of the study, 12 patients had an average of 4 points lower on the MMSE two years later, placing participants in the mild range of impairment on average. The remaining subjects maintained their original MMSE scores.

The MMSE has been described as having a ceiling effect in PD, likely because it does not measure a wide range of neuropsychological domains (Athey & Walker, 2006). In a recent study, the MMSE and a comprehensive neuropsychological battery were administered to three groups; 1) PDD, 2) Parkinson’s disease with mild cognitive difficulties, and 3) a control group. Group assignment was determined using standard MMSE cutoff scores. While differences were found between groups in the neuropsychological battery, the MMSE scores did not differ between the mildly cognitively impaired PD group and the controls, indicating that it may not sufficiently detect the domains of cognition affected in PD, particularly in early stages of cognitive decline (Song et al., 2008).

The Dementia Rating Scale-2 (DRS-2; Mattis, 1988) is a more detailed cognitive assessment scale that yields a total score, as well as scores on five subscales assessing differential cognitive domains (attention, initiation/perseveration, conceptualization, construction, and memory). Earlier research focused on the use of the total DRS-2 score as a global measure of cognition in PD. The DRS-2 has been found to detect more variation in cognitive functioning
in PD than the MMSE; however, the global score is not as descriptive of cognitive deficits as the subscale scores (Brown, et al., 1999). Koven and colleagues (2007) found that the initiation/perseveration subscale was impaired in PD, but did not significantly affect the total score to provide insight into a global cognitive profile. There exists a need to further investigate the utility of the DRS-2 in non-demented PD patients, and to look more closely at the neuropsychological domains it encompasses.

The MMSE and DRS-2 were designed to assess dementia. Although these measures are useful for clinicians to detect cognitive impairment, recent research has been directed at developing new global cognitive assessments designed for PD patients. Brief global assessment measures such as the Scales for Outcomes of Parkinson’s disease – Cognition (SCOPA-COG; Marinus et al., 2003) and Addenbrooke’s Cognitive Examination (ACE; Mathuranath et al., 2000; Reyes et al., 2009) have been developed and have had preliminary positive results, correlating with MMSE and DRS-2 scores. Despite preliminary correlational results with the MMSE and DRS-2, these measures are in need of further validation. Each of these studies has discussed that the need for a PD-specific global assessment measure stems from the need to further isolate cognitive domains that are most affected in PD.

The existing literature concerning global cognitive assessment in PD suggests that a comprehensive neuropsychological battery composed of measures assessing differential domains would be more sensitive to the components of cognitive deficits most common in PD than a single global cognitive measure. Global measures are
useful for diagnosis of PDD, but there is a need for investigation of mild cognitive deficits and potential prodromal dementia. Neuropsychological studies have been prevalent in recent years and have identified key domains of cognitive impairment across the spectrum of PD, such as memory, attention, visuo-spatial functioning, and executive functioning.

1.3.2 Domain-specific cognitive deficits

Research concerning memory deficits in PD has varied in the sub-domains of memory investigated, and little consensus has been reached. Early studies focused on verbal recall and recognition abilities through word list learning tasks. Ivory and colleagues (1999) found that immediate recall for verbal information is impaired in PD, while verbal recognition in intact; these results were replicated in subsequent studies (Emre, 2003; Ong et al., 2005). A recent debate has emerged concerning recognition memory in PD, in which more recent studies have found recognition to be dependent on retrieval deficits, and the level of familiarity with task stimuli (Higginson et al., 2005; Davidson et al., 2006; Whittington, Podd, & Stewart-Williams, 2006). Studies have found that memory retrieval deficits persist throughout the progression of PD, which may affect longer-term recognition abilities (Faglioni et al., 1997; Zizak et al., 2005), although longitudinal research on long-term recognition decline is not currently available.

Studies of attention in PD have had similarly mixed results. Research on attention in PD has primarily focused on its role in motor symptoms, such as falling instances, and gait and posture disability (Yoge et al., 2005; Hausdorff et al., 2006; Allock et al., 2009). Studies focusing on the cognitive impact of potential attention...
deficits have been less frequent. Of the existing literature, earlier studies reported attention to be intact in PD (Faglioni et al., 1997). Attention to object and location shifting (Hsieh et al., 1997) and selective attention (Lee et al., 1999) were also found to be intact. Recently, however, attention deficits have been observed when participants are attending to the performance of actions (Rowe et al., 2002) and visual shifts and maintenance of attention (Pollux & Robertson, 2001). The nature and origin of attentional deficits in PD, although mediated in part by frontal lobe circuits, are not yet well defined.

Visuo-spatial deficits in PD have also yielded conflicting results. There was little agreement in earlier studies; visuospatial orienting was found to be normal in PD in some studies (Hsieh et al., 1996), and found to be moderately to severely impaired in others (Doyon, Bourgeois, & Bedard, 1996). Overall, recent studies suggest at least some level of visuo-spatial impairment, although proposed etiologies and qualitative descriptions vary (Lyros, Messinis, & Pапathanasopoulos, 2008; Kemps, Szmalec, Vandierandonck, & Crevits, 2005). A meta-analysis (Siegert et al., 2008) found that PD patients were impaired on both simple and complex visuospatial tasks across studies. Evidence for difficulties with executive tasks involving visual information have also been demonstrated (Nieoullon & Coquerel, 2003).

Executive functioning deficits have received the most attention in neuropsychological research with PD, and have also attained the most converging evidence concerning impairment in comparison to other cognitive domains. Literature reviews of studies of executive dysfunction in PD have found that patients
have difficulties in tasks involving the management of novel input, mental flexibility and set-shifting (Taylor & Saint-Cyr, 1995) and more recently also in working memory, initiation and perseveration (Troster & Woods, 2005). Consistent with the presence of initiation and perseveration errors, Henry and Crawford (2004) reported both phonemic and semantic fluency deficits in PD. Muslimovic, Post, Speelman and Schmand (2005) found that deficits in executive functioning and immediate recall ability had the greatest impact on total cognitive performance on a neuropsychological battery. Siegert and colleagues (2008) performed a meta-analysis of studies examining both simple monitoring and complex working memory tasks in PD and found a consistent pattern of impairment. Slower rates of neurocognitive speed in PD participants compared to age-matched healthy controls have also been observed (de Frias, Dixon, Fisher & Camicioli, 2007).

The literature concerning cognition in PD indicates that global scales are good indicators of the presence or absence of a dementia, and useful in the neurology clinic as a quick assessment of overall cognition. However, milder cognitive deficits encountered in PD may not be detected with global measures. Domain-specific neuropsychological assessment is important to isolate the facets of cognition affected most in PD.

1.4 Everyday functioning in PD

The body of research on both global and domain-specific aspects of cognition in PD is now large and continually growing. However, less is known about the impact of cognitive deficits on everyday functioning in PD. Neuropsychological
examinations may help inform this issue, as domain-specific cognitive impairments may differentially contribute to deficits in everyday functioning. Cognitive problems are often a complaint in PD due to impediments in everyday activities, affecting quality of life. For instance, some patients complain of difficulty concentrating at work, word-finding problems in conversation, or trouble following directions (Poliakoff & Smith-Spark, 2008; Bassett, 2005; Troster & Woods, 2005).

There are several commonly used terms in the everyday functioning literature. Everyday functioning tasks are referred to as activities of daily living (ADLs). There are two subcategories of ADLs. Basic activities of daily living (BADLs) are routine tasks such as feeding oneself and maintaining proper hygiene. BADLs are also sometimes referred to as physical activities of daily living (PADLs) in the literature. Instrumental activities of daily living (IADLs) are considered more complex everyday activities that may rely on a combination of physical ability and cognition, such as balancing a checkbook or using household appliances. In PD, investigations of the impact of motor impairments on ADLs have been most common in the literature. These studies often control for cognitive deficits. Fleischman, Wilson and Schneider (2007) examined the contribution of motor impairments on functional disability in PD controlling for age, education, cognitive ability, depression, sex, and chronic medical conditions. The researchers found that more severe parkinsonian signs were associated with deficits in both PADL and IADL performance.
Only a small number of studies have examined relationships of non-motor variables to everyday functioning in PD. In a recent study examining everyday cognitive functioning, 24 PD patients and their significant others were asked to rate how frequently they encountered a wide range of everyday functioning errors with a cognitive component, including forgetting what they are about to say or incorrectly sequencing steps in a task. The data was compared to 24 healthy controls using the same scale. Results indicated a significant difference in which the PD group encountered a greater proportion of errors in specific domains of cognition including memory retrieval and attention processes than the control group (Poliakoff & Smith-Spark, 2008). In a study by Koven and colleagues (2007), perception of everyday functioning and cognition was explored in preliminary analyses of differential cognitive profiles and self-reported functional ability. Results suggested executive dysfunction as a primary contributor to functional deficits in PD patients. However, sample size was small (n=20), only the DRS-2 subscales and total were examined (not other neuropsychological measures), and it was not reported whether they controlled for motor deficits or duration of illness.

Cahn et al. (1998) designed a study with similar objectives and hypotheses as the present study. The researchers predicted executive functioning deficits would predict deficits in instrumental activities of daily living (IADLs) in a non-demented PD sample comprised of 39 participants. A secondary prediction was that PADLs would not be associated with cognition, but instead would correlate with motor symptoms only. The researchers used two tests, Trails B and Digit Ordering, to
measure executive functioning deficits. Correlation analyses were conducted between an executive composite score and each of the two executive measures with IADLs. The Dementia Rating Scale-2 (DRS-2; Mattis, 1988) was used as a global measure of cognitive impairment. Their results yielded significant correlations between DRS-2 total, the executive composite score, and both executive measures independently with IADLs, but not PADLs. Also consistent with their hypotheses, PADLs were correlated with motor deficits but not cognitive deficits. The overall results were consistent with the researchers’ hypotheses; however the study had a number of limitations. The DRS-2 total score was used in correlational analyses, but the specific domains examined by the test were not explored. This limits interpretability of the contribution of executive functioning deficits with regards to the DRS-2 because other cognitive domains were not examined. Additionally, participants in this study were all tested as candidates for pallidotomy, limiting generalizability to other PD patients.

The small number of studies examining everyday functioning and cognition in PD provide evidence for the impact of cognition, and particularly executive dysfunction, on everyday functioning deficits in PD. The results of Cahn et al. (1998) provide the most support for the rationale of the present study, however, replication of their findings and an examination of multiple cognitive domain associations with everyday functioning in PD have not been reported in the literature. It is important to examine multiple cognitive domains so that it can be established that executive
functioning contributes to more variability in everyday functioning deficits than other domains in PD.

1.5 Evidence from reports of the neuropathology of PD: Degeneration of fronto-striatal networks

The specific neuropathology of PD in the context of the disruption of fronto-striatal networks lends support for the differential contribution of executive functioning deficits in everyday functional impairments compared to deficits in other neuropsychological domains. Frontal systems deficits have been shown to relate to executive dysfunction in PD samples and samples with similar neuropathology (Troster & Woods, 2005; Zizak, 2005). In a literature review of neuropathology related to executive functions, Heyder, Suchan, & Daum (2004) described feedback loops between cortical and subcortical structures and the cerebellum that contribute to executive control. In the realm of the cortex, the researchers found that the prefrontal cortex (PFC), and particularly the anterior cingulate cortex, were involved in executive demands such as planning, inhibition and multi-tasking across the literature. The results of this study are supported by a meta-analytic review by Rajah & D’Esposito (2005). In this review, the researchers found working memory and episodic memory tasks in normal aging to be associated with a variety of region-specific changes in the prefrontal cortex as detected by fMRI and PET.

The role of feedback loops involving subcortical structures and the cerebellum imply that deficits in basal ganglia, thalamus and cerebellar processes,
although thought to contribute mostly to characteristic motor deficits in PD, may also interrupt fronto-striatal communication necessary for the maintenance of executive control. Monchi et al. (2006) performed an fMRI study to examine the role of the basal ganglia in the planning and execution of actions, and found that the caudate nucleus and putamen were of particular importance for the planning and execution of actions, as well as mental set-shifting. Chudasama and Robbins (2006) found that dysfunction of fronto-striatal networks distinguishes cognitive deficits in basal ganglia diseases like PD and Huntington’s disease (HD) from AD-type dementia or neuropsychological deficits that may signify pre-clinical stages of dementia.

These studies provide evidence that executive functioning is one of the most complex cognitive domains, requiring communication and activation of multiple brain areas. Many of these areas and structures, such as the basal ganglia, are known to be impaired in PD. Evidence of the association between these brain areas and the planning and execution of actions (Monchi et al., 2006) provides rationale for testing the association between executive dysfunction and everyday functioning deficits in PD.

1.6 Evidence from normal aging samples

In the literature, significant attention has been directed at the cognitive correlates of functional disability in normal aging populations. General cognitive impairment (using the MMSE as a global measure) was shown to be a strong predictor of functional disability in a sample of community-dwelling older adults
(Dodge et al., 2005). In a recent literature review, Royall et al. (2007) found that both general cognitive and executive measures explained more variance in functional status than other domains in normal aging (memory, attention, verbal abilities and visuospatial abilities). In the studies reviewed, those that used executive measures as predictor variables explained more of the variance in the performance of everyday tasks, suggesting that the association between cognition and everyday functioning is domain-specific.

The contribution of executive functioning in particular has received considerable support in empirical studies of normal aging. Executive functioning has been shown to decline in normal aging when compared to that of younger controls, including both young adults and younger elderly participants (Brennan, Welsh & Fisher, 1997). Cahn-Weiner, Boyle and Malloy (2002) and Bell-McGinty et al. (2002), found that executive measures predict functional performance in older adults. Johnson, Lui and Yaffe (2007) found that in a large sample of community-dwelling elderly women (n=7717), executive impairment better predicted functional decline than global cognition. Analyses were performed utilizing one measure for each variable; a modified MMSE was used for global assessment, and Trails B was used as a measure of executive functioning. Lewis and Miller (2007) tested 60 older adults in sub-domains of executive functioning to elucidate the contribution of specific executive skills on everyday functioning abilities. The sub-domains investigated were working memory, planning, task monitoring, verbal fluency, and mental flexibility. The results indicated that working memory, task
monitoring, and planning deficits best-predicted ADL decline in normal older adults in this sample.

In short, there is still debate as to whether global measures or executive measures are better predictors in the normal aging literature. There is support for both, but more recent studies support executive functioning as a better predictor than global cognition. The evidence from the normal aging population provides a rationale to explore domain-specific contributions and associations with everyday functioning impairment in PD and a comparison of global measures of cognition.

1.7 Purpose of the present study

Support for impairments in executive functioning have been demonstrated across the literature regarding cognition in PD. However, the impact of specific facets of executive functioning compared to other cognitive domains is not well understood. The neuropathology of PD, including damage to the basal ganglia and interruptions of fronto-striatal circuits, suggest a significant impairment in executive functioning skills in PD. Further rationale includes studies on normal older adults that exhibit associations between executive dysfunction and deficits in everyday functioning.

The current study consists of two specific aims: 1) to examine the neuropsychological correlates of everyday functioning in PD, and 2) to evaluate the relationship between everyday functioning in PD and two commonly used clinical measures of cognition. The researchers hypothesize that representative measures of executive functioning assessing initiation, perseveration and working memory will better predict functional deficits than measures of other cognitive domains and
global cognition. It is hypothesized that an executive measure of verbal fluency, assessing working memory, initiation, and word-list generation will demonstrate the strongest relationship with functional deficits compared with tests of other executive skills such as planning and execution, or initiation and perseveration.

This study will add to the literature in several ways. Analyses control for age, gender, education, global cognition, motor disability, and duration of illness in an attempt to isolate the contribution of cognition. Specific domains of cognition are examined through use of a more extensive neuropsychological battery than past studies. Through examination of multiple assessment measures, the goal is to suggest measures that may be most useful in informing and predicting everyday functioning in clinical settings. The present study includes the largest sample size of PD participants in the literature regarding cognition and everyday functioning in PD. Understanding the potential impact and nature of cognition’s contribution to deficits in everyday functioning may inform rehabilitation approaches, ultimately improving functional ability and quality of life for patients with PD.

2. Methods

2.1 Study overview

The data used in this study was collected as part of an ongoing longitudinal cohort study, conducted through Pennsylvania Hospital’s Parkinson’s Disease and Movement Disorders Center (PDMDC), an outpatient neurology clinic in Philadelphia, Pennsylvania. Access to the retrospective database was approved and analyzed under the supervision of Andrew Siderowf, MD of the PDMDC. The
retrospective database includes data collected on symptom type and severity, demographics, psychiatric/behavioral variables, motor disability and disease duration, everyday functioning abilities, and neuropsychological assessments. Using the retrospective database, the primary goal of the current study was to examine the relationship between data collected on cognitive abilities and everyday functioning abilities.

2.2 Participants

One hundred and eighty-one participants recruited between July 2007 and May 2009 were included in the present sample. A comprehensive and systematic medical and research chart review was conducted to identify eligible participants. Participants met the following inclusion criteria: 1) diagnosis of PD and 2) 60-years of age or older, as well as the following exclusion criteria: 1) no significant alcohol/drug history, defined by treatment or hospitalization and 2) no diagnosis of any movement disorder other than PD.

2.2.1 Power analysis

Due to the approximated sample size of the current study, the researchers used an alpha of .01 to determine statistical significance. Based on prior research, the effect size of this study was expected to fall in the medium range (Poliakoff & Smith-Spark, 2008; Koven et al., 2007; Cahn et al. 1998). Correlation analyses included 5 independent variables, and the regression analysis included 3 predictor variables. Power analyses were conducted according to Cohen’s (1988; 1992)
standards. Using correlation analysis with 5 independent variables at a power of .80 and an alpha of .01, the minimum sample size required to obtain a medium effect size is 126 participants. Using multiple regression analysis with 3 predictor variables at a power of .80 and an alpha of .01, the minimum sample size required to obtain a medium effect size is 108 participants. The current study's sample size meets these requirements for a power of .80 and a medium effect size for all analyses.

2.3 Assessment measures

2.3.1 Sample characteristics

Age, gender, education, global cognition as measured by the Mini-Mental State Examination (MMSE; Folstein et al., 1975), motor disability as measured by the Hoehn and Yahr (Hoehn & Yahr, 1967) and duration of illness were collected and controlled for in all analyses. PD is more common in men than women, and the age of onset and duration of PD have been shown to affect the rate and type of progression in the disease. The goal of controlling for these variables and motor disability was to further isolate cognition's contribution to everyday functioning deficits. Participant self-reported data regarding psychiatric and behavioral symptomology, as well as nature and frequency of PD medication complications are also reported to further describe sample characteristics.
2.3.2 Motor measure

The Hoehn and Yahr is the most commonly used measure of PD motor disability and symptom progression. The Hoehn and Yahr ranges from stages 0 to 5, with higher scores indicating increasing disability level. In the present study, Hoehn and Yahr stage was determined and verified by participants’ respective treating neurologist at the PDMDC.

2.3.3 Neuropsychological measures

The neuropsychological measures included are well validated and commonly used in both clinical and neuropsychological assessment settings. The primary cognitive domains assessed were attention, memory, visuo-spatial perception, and sub-domains of executive functioning, as well as global cognition. The Mini-Mental State Examination (MMSE; Folstein et al., 1975) and the Dementia Rating Scale-2 (DRS-2; Mattis, 1988) total score, both measures of global cognition, were reported and analyzed. The sub-scales of the DRS-2 measure differential cognitive domains, and were utilized in several analyses. The attention measure analyzed was the attention subscale of the DRS-2. The construction subscale of the DRS-2 and the Benton Judgment of Line Orientation (JOLO; Benton et al., 1978) test were analyzed as measures of visuo-spatial perception and integration. It is of note that the construction subscale of the DRS-2 relies heavily on motor output, while the JOLO does not. The memory subscale of the DRS-2 and the Hopkins Verbal Learning Test – Revised (HVLT-R; Brandt, 1991) were utilized as measures of memory. The HVLT-
R is a 3-trial list-learning task; delayed recall of the word list was examined in the present study.

Three representative measures of executive functioning were utilized, which primarily target sub-domains of initiation/perseveration, working memory, and planning. The initiation/perseveration subscale of the DRS-2 is an executive measure of deficits in initiation and perseverative behaviors, assessing semantic word list generation, complex motor movements, and auditory articulation of vowel and consonant patterns. The copy condition of the clock-drawing test (Libon et al., 1996; Cosentino et al., 2004) requires participants to copy the face of a clock in which the hands are set to 10 after 11. This was examined as a measure of planning and execution. The copy condition of the clock-drawing task was analyzed as it has been theorized to rely more on executive processes and requires less of a semantic memory demand compared to the command condition (Libon et al., 1996). Phonemic verbal fluency is a word-list generation task, requiring participants to state as many words as possible beginning with a specific letter (e.g., F-A-S) within a limited period of time (60 seconds). Verbal fluency will be used as a measure of initiation and working memory. Refer to Table 1 in Appendix A for a list and descriptions of the neuropsychological measures used, the domain of cognition each targets, and associated references. All participants were administered the neuropsychological battery in the following order: MMSE, DRS-2, HVLT-R, Clock draw, JOLO, and verbal fluency word list generation (FAS).
2.3.4 Everyday functioning measure

Studies of everyday functioning in PD have focused on motor deficits, often controlling for cognitive impairment. A measure of everyday functioning examining the impact of motor and cognitive deficits was examined in the present study. Everyday functioning was assessed using the Alzheimer’s Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL; Galasko et al., 1997), a questionnaire filled out by a care-giver seeing the participant on a regular basis, such as a spouse, child, or close friend. The ADCS-ADL is a 23-item scale with a total possible score of 78, in which lower scores indicate greater impairment in everyday functioning. The first 6 items assess BADLs such as eating and hygiene maintenance, while the remaining items refer to IADLs such as, bill paying, shopping or operating the telephone. The scale was developed and validated for early and later stages of Alzheimer’s disease (Galasko et al., 1997; Desai et al., 2004; Li, 2006; Sarensen et al., 2008); therefore the present study is limited in that a scale developed specifically for PD was not used. Although scales concerning everyday functioning assessment in relation to motor symptoms exist, no comparable measures examining everyday functioning with an emphasis on cognitive abilities and IADLs in PD have been developed. In the present study, the total score of the ADCS-ADL was analyzed as a primary analysis. Secondary analyses explored the impact of cognitive domains upon the BADL and IADL subscales of the ADCS-ADL.
2.4 Procedures

Access to the retrospective database was granted under the supervision of Andrew Siderowf, MD of the PDMDC. Inclusion criteria required a diagnosis of PD, and a minimum 60 years of age. PD diagnosis is defined by the presence of a combination of four cardinal symptoms accepted in the literature; 1) tremor; 2) rigidity; 3) bradykinesia; 4) postural instability (Gelb et al., 1999). Diagnosis of PD was verified through a systematic medical chart review of diagnostic features reported by participants’ primary neurologist at the PDMDC.

The research visit included collection of demographic and disease symptom information via participant report, a motor exam, and administration of the neuropsychological test battery. Caregivers who accompanied participants to the research visit filled out the ADCS-ADL during the visit. Caregivers not present for the research visit were mailed the ADCS-ADL, returning it to the PDMDC within three months of the research visit. After eligibility and the final sample of participants were determined, a new database containing the variables of interest to this study was created. Variables were included in the following categories: 1) demographic information, 2) illness duration; 3) motor disability; 4) neuropsychological data; 5) everyday functioning abilities. Participants’ with these variables were identified with a subject number in the study database to ensure protection of privacy.
2.5 Specific aims, hypotheses and plan of analysis

All analyses were performed using SPSS 18.0. The following factors were controlled for in each correlation analysis: 1) age; 2) gender; 3) education; 4) global cognition (MMSE total score); 5) motor disability (Hoehn & Yahr stage); and 6) duration of illness.

Specific Aim 1: The first specific aim of the present study was to examine the neuropsychological correlates of deficits in everyday functioning in PD, in an effort to explore whether differential cognitive domains have varying degrees of association with functional performance.

Hypothesis 1: Executive functioning sub-domains of initiation/perseveration and working memory will have the strongest association with everyday functioning in PD compared to other cognitive domains. A word-list generation task with executive demands of initiation and working memory will demonstrate the strongest correlation with the ADCS-ADL compared to representative measures of attention, memory, and visuo-spatial perception. The existing literature on the prevalence of executive dysfunction in PD, the neuropathology of PD which includes structures and neural networks necessary for these sub-domains of executive functioning, and evidence from the normal aging population supporting executive functioning as a predictor of everyday functioning provide justification for this hypothesis.
Planned Statistical Analysis 1: The association between neuropsychological test scores and the ADCS-ADL will be analyzed using partial correlations. A representative neuropsychological test from each cognitive domain will be utilized; memory will be measured by HVLT-R delayed recall, visuo-spatial perception by the JOLO, attention by the attention subscale of the DRS-2, and executive functioning skills of initiation and working memory by verbal fluency (F-A-S).

Hypothesis 2: Of the executive functioning tests included in this study, it is hypothesized that verbal fluency will have the strongest association with ADCS-ADL compared to the clockdraw copy and the initiation/perseveration subscale of the DRS-2. The rationale for this hypothesis is based on the extant literature concerning executive functioning sub-domains in PD. In the literature, working memory and initiation are well-established deficits in both demented and non-demented PD patients. The verbal fluency test loads on initiation, working memory and task monitoring skills. In contrast, the clock-draw copy loads on planning and execution, and the DRS-2 executive subscale measures initiation and perseveration.

Planned Statistical Analysis 2: This analysis will employ a multiple linear regression model comprised of the three executive tests (verbal fluency, clock draw copy, and initiation/perseveration DRS-2 subscale) as predictor variables and the ADCS-ADL as the outcome variable.
Specific Aim 2: The second aim of the present study is to evaluate the clinical utility of two commonly used clinical measures of cognition that may inform everyday functioning in PD.

Hypothesis 1: Two commonly used clinical measures of global cognition, the MMSE and DRS-2, will demonstrate strong associations with everyday functioning as measured by the ADCS-ADL. This is hypothesized in light of the extant literature supporting strong associations between these measures and measures of everyday functioning.

Planned Statistical Analysis 1: Partial correlation coefficients examining the association between the MMSE and ADCS-ADL, and DRS-2 and ADCS-ADL, will be calculated.

Hypothesis 2: The subscale of the DRS-2 representing a sub-domain of executive functioning (initiation/perseveration subscale) will have the strongest association with everyday functioning compared to subscales assessing other cognitive domains. The DRS-2 is a commonly used tool in cognitive assessment of PD, and determining which subscale is most associated with everyday functioning may be helpful in developing more targeted treatment recommendations, and rehabilitation plans. It is hypothesized that the initiation/perseveration subscale of the DRS-2, will demonstrate the strongest correlation with the ADCS-ADL compared to the other subscales. The remaining subscales target other cognitive domains: attention, memory, conceptualization/semantic knowledge and visuo-spatial reproduction.
Planned Statistical Analysis 2: The association between each of the DRS-2 subscales and ADCS-ADL will be analyzed through calculation of partial correlation coefficients.

Secondary Analysis: A secondary, exploratory analysis will be conducted to evaluate potential differential impact of deficits in basic versus instrumental ADLs in everyday functioning in PD.

Planned Statistical Analyses, Secondary Analysis: Partial correlations will be conducted between each DRS-2 subscale, and both the BADL and IADL subscales of the ADCS-ADL.

3. Results

3.1 Characteristics of the sample

3.1.1 General demographics

The sample consisted of 181 participants with a confirmed diagnosis of PD. Diagnosis of PD was determined by participants’ treating neurologist at the PDMDC. The sample was 30% female and 70% male, consistent with reported gender differences in Parkinson’s disease prevalence, indicating higher rates among males. Participants’ mean age was 72.79 years (SD = 6.99), and mean education 15.56 years (SD = 2.54). The sample was 96% white (n = 173), and comprised of less than 1% Asian (n = 3), African-American (n = 4), and multi-racial (n = 1) participants. The ethnicity of the sample was primarily non-Latino (Latino, n = 1).
3.1.2 Clinical demographics

Verified by records from their treating neurologist, 60% (n = 108) of participants had a confirmed diagnosis of non-demented Parkinson’s disease (PD), 23% (n = 42) had a diagnosis of Parkinson’s disease dementia (PDD), and the remaining 17% (n = 31) met criteria for PD and mild cognitive impairment (MCI).

Motor disability as measured by Hoehn and Yahr stage revealed an average of 2.42 (SD = 0.75), indicating mild bilateral disability. This Hoehn and Yahr indication requires neurologist determination of bilateral symptom presentation, as well as recovery on a test of postural instability in which the shoulders are pulled back and proper balance must be maintained (referred to as the “pull test”). The range of stages 1 to 5 was normally distributed, indicating our sample was representative of the spectrum of motor disability in PD. Table 2 reports the sample distribution of Hoehn and Yahr accompanied by descriptions of each stage.

The average Geriatric Depression Scale (GDS; Yesavage et al., 1983; maximum total score of 30) score was 6.47 (SD = 6.10), suggesting the majority of participants were not depressed (GDS score of 0-9 indicates “normal” symptomology). The average score indicated a lack of depressive symptoms for the majority of participants, however it is of note that the range of scores was 0-28. Participants with varying levels of depression were included in the present sample as it commonly accompanies PD. Regarding other psychiatric symptoms, 24.5% reported experiencing visual hallucinations and mood fluctuations. Compulsive or impulsive behaviors, including gambling, hypersexual behavior, overeating, and
shopping, were reported by 21.6% of participants. These cognitive and behavioral symptoms are also commonly reported in the PD literature. One-third of participants reported experiencing daily fluctuations in efficiency and clarity of their thinking and cognition. Table 3 summarizes the frequency of psychiatric and behavioral symptoms relevant to PD in our sample by participants’ self-report.

Part IV of the UPDRS, entitled “Complications of Therapy (in the past week)” is a structured interview examining self-reported medication complications encountered within the week prior to the research visit. Seventy-six percent (n = 138) of participants did not experience dyskinesias. Of those that experienced dyskinesias, 21% (n = 38) experienced them less than 25% of the day. Less than 1% (n = 5) experienced dyskinesias more the 25% of the day. Early morning dystonia was reported by 33% (n = 60) of participants. Medication fluctuations refer to “on” states in which a patient feels medication effects, and “off” states in which medication effects significantly wear off. Forty-three percent (n = 77) of the sample reported experiencing such fluctuations.

3.2 Neuropsychological measures and ADCS-ADL

Descriptive statistics for all neuropsychological measures and the ADCS-ADL are summarized in Table 4. Data for the full sample was available for the DRS-2 and ADCS-ADL. Seventy-two percent (n = 131) of participants had data for the full battery of neuropsychological tests. The data utilized in this study is part of a larger longitudinal study. Due to the large span of time over which the study has been conducted, the neuropsychological battery was modified on several occasions. Table
4 specifies the number of participants with data for each measure. Also, a small number of PDD participants (n = 9) with severe cognitive deficits and difficulty tolerating the testing battery were administered an abbreviated version of the neuropsychological test battery (Moderate Impairment Battery; MIB) that included the MMSE and DRS-2 only. These participants were included to maximize generalizability of our findings; however, it is important to consider the significant impairment in motor, cognitive, and everyday functioning these participants demonstrated. These participants also tended to be older, and had longer disease duration. Demographic characterization of the sample, including information on motor, cognitive, and everyday functioning assessment, of participants receiving the MIB, and differences in sample size for each neuropsychological measure, will be taken into consideration in interpretation of our analyses.

3.3 Partial correlations: Neuropsychological measures and ADCS-ADL

Regarding the first aim of the study, to examine neuropsychological correlates of everyday functioning in PD, partial correlations were conducted between the ADCS-ADL and neuropsychological tests representing differential cognitive domains. Domains of attention (DRS-2 attention subscale), executive functioning sub-domains of initiation and working memory (verbal fluency), episodic memory (HVLT-R delayed recall), and visuo-spatial perception (JOLO) were correlated with the ADCS-ADL total score. Table 5 reports partial correlation coefficients for analysis of each measure of cognition and the ADCS-ADL.
It was hypothesized that initiation and working memory (verbal fluency) would be most significantly related to everyday functioning (ADCS-ADL) in comparison to other cognitive domains. Initiation and working memory (verbal fluency) were correlated with everyday functioning; however, in addition, visuo-spatial perception (JOLO) was also correlated with everyday functioning. Initiation and working memory as measured by verbal fluency was marginally significantly correlated with the ADCS-ADL utilizing an alpha of .01 to determine significance ($r = .18$, $p = .05$). Visuo-spatial perception as measured by the JOLO also approached significance ($r = .20$, $p = .03$). Memory (HVLT-R delayed recall) and attention (DRS-2 attention) did not demonstrate significant correlations with the ADCS-ADL.

3.4 Regression analysis: Executive functioning measures and ADCS-ADL

To further explore the relationship between neuropsychological deficits and everyday functioning in PD, a multiple linear regression was performed to determine which sub-domain of executive functioning might be most predictive of deficits in everyday functioning (ADCS-ADL). Three independent (predictor) variables measuring sub-domains of executive functioning were utilized; verbal fluency, clockdraw copy score, and the initiation/preservation subscale of the DRS-2. It was hypothesized that initiation and working memory as measured by verbal fluency would be most predictive of everyday functioning, as compared to planning/execution (clock copy) and initiation/perseveration (DRS-2 initiation/perseveration subscale). The overall regression model was significant ($R = .52$, $F (3, 152) = 18.88$, $p < .001$), demonstrating a large effect size ($f^2 = 0.37$) by
Cohen’s (1988) standards, suggesting measures of executive functioning predict everyday functioning. Analyses of beta values revealed verbal fluency ($b = .21, SE = 0.07, p = .01$), and the initiation/perseveration subscale of the DRS-2 ($b = .35, SE = .33, p < .001$), to be significant predictors of everyday functioning. The copy condition of the clock drawing approached significance ($b = -.15, SE = 0.21, p = .03$).

3.5 Partial correlations: MMSE, DRS-2 and ADCS-ADL

To examine the relationship between everyday functioning and commonly used clinical measures of global cognition (MMSE; DRS-2), partial correlations were run between the ADCS-ADL and the MMSE and DRS-2, respectively. These analyses were performed to confirm the clinical utility of brief cognitive assessment tools in relation to everyday functioning. We hypothesized that both measures of overall cognition would be significantly correlated with everyday functioning. Confirming our hypothesis, overall cognition as assessed by both the MMSE ($r = .25, p < .01$) and DRS-2 ($r = .27, p < .01$) were significantly correlated with the ADCS-ADL.

3.6 Partial correlations: DRS-2 subscales and ADCS-ADL

To further explore the utility of the DRS-2, which assesses more varied cognitive domains than the MMSE, partial correlations were performed between each DRS-2 subscale and the ADCS-ADL. It was hypothesized that the initiation/perseveration subscale of the DRS-2 would be most significantly correlated with everyday functioning (ADCS-ADL) compared to DRS-2 subscales measuring other cognitive domains (attention; construction; conceptualization;
In addition to age, education, gender, global cognition, duration of illness and motor disability, the four remaining subscales were controlled for in correlation analysis of each individual subscale to address multicollinearity. Table 6 reports partial correlation coefficients for analysis of each subscale of the DRS-2 and the ADCS-ADL.

Similar to our first analysis, our hypothesis was only partially supported, in that both the construction and initiation/perseveration subscales of the DRS-2 were both correlated with everyday functioning. Again utilizing an alpha level of .01 to determine significance, the construction subscale was significantly correlated with the ADCS-ADL (r = .20, p = .01), and initiation/perseveration approached significance. (r = .16, p = .05). Other subscales and the total score did not demonstrate significant correlations.

3.6.1 Secondary analysis: DRS-2 subscales and BADL/IADL subscales of the ADCS-ADL

In a secondary, exploratory analysis, partial correlations were utilized to explore the relationship between differential cognitive domains as measured by the DRS-2, and both basic (BADL) and instrumental (IADL) activities of daily living. The construction subscale was significantly correlated with the IADL subscale (r = .19, p = .01), but not the BADL subscale (r = .13, p = .10). The initiation/perseveration subscale approached significance with the IADL subscale (r = .15, p = .05) but not the BADL subscale (r = .11, p = .16).
Although an exploratory analysis, these results are inconsistent with previous findings reported in the literature. As such, this warranted further examination of the ADCS-ADL items. In a subsequent exploratory analysis, the ADCS-ADL items were reclassified by the investigators as everyday activities that required more of a physical (PADL) or cognitive (CADL) load.

3.6.2. Secondary analysis: DRS-2 subscales and new physical/cognitive item classification of the ADCS-ADL

The ADCS-ADL was designed to assess everyday functioning in patients with Alzheimer’s disease. The investigators reclassified the ADCS-ADL into new PADL and CADL subscales to further address motor deficits associated with PD, carefully considering whether each item required more of a physical or cognitive load.

Partial correlations were utilized to explore the relationship between cognitive domains as measured by the DRS-2, and the total score of the PADL and CADL subscales. The construction subscale was significantly correlated with the PADL subscale ($r = .20, p = .01$), and the CADL subscale ($r = .20, p < .01$). The initiation/perseveration subscale was significantly correlated with the CADL subscale ($r = .20, p = .10$), and approached significance with the PADL subscale ($r = .17, p = .03$).

4. Discussion

This study sought to examine neuropsychological correlates and predictors of everyday functioning in PD, as well as identify clinically useful
neuropsychological measures to detect cognitive deficits in PD that may impact
everyday functioning. Specific goals were the identification of measures that
demonstrate a relationship with everyday functioning, as well as identification of
executive functioning measures, primarily assessing initiation/perseveration, and
working memory, that may predict everyday functioning deficits in PD. Clinical
utility is important across the spectrum of PD, as patients normally see a primary
care physician or neurologist for diagnosis and treatment. Taking this into
consideration, some patients may not receive a comprehensive neuropsychological
battery that is useful in the examination of cognitive decline, and assessment of its
potential influence on everyday functioning. PD patients are often only referred for
a comprehensive neuropsychological assessment if significant cognitive decline is
exhibited, or dementia is suspected (Troster & Woods, 2005). Neurologists are
therefore most often given the task of assessing and devising a treatment plan that
addresses a complex array of motor, cognitive, behavioral, and functional deficits.
This study supports the clinical utility of several neuropsychological measures of
both overall and domain-specific cognition that may simultaneously inform
clinicians of both cognitive and functional decline. The current results support
measures of global cognition, visuo-spatial perception, and executive tasks of
initiation/perseveration and working memory as most useful in the determination
of deficits in everyday functioning. This may have implications for integrative
treatment in multiple realms, such as medication therapy, physical therapy, and
cognitive remediation.
Participants exhibiting a spectrum of cognitive deficits were included in the sample. Also included were participants with psychiatric and behavioral disturbances, such as depression and compulsive/impulsive behaviors, as these symptoms have been commonly reported in PD (Grigsby et al., 2005; Levy & Chelune, 2007). Reijnders and colleagues (2008) performed a systematic review of studies assessing prevalence of depression in PD, and found that severe depression was present and substantial across studies, however normal to mild depressive symptomology described the majority of PD patients. This is consistent with the distribution of depression in the present sample. In sum, a wide range of PD participants were included to enhance generalizability.

The current state of the literature was supported in that representative measures of sub-domains of executive functioning (initiation/perseveration; working memory) were correlated with and predicted everyday functioning across the PD spectrum (Taylor & Saint-Cyr, 1995; Troster & Woods, 2005). The findings of this study support the notion that multiple sub-domains of executive functioning are predictive of everyday functioning in PD (Muslimovic, Post, Speelman & Schmand, 2005; Siegert et al., 2008; de Frias et al., 2007). As a cognitive construct, executive functioning is an umbrella term covering numerous specific cognitive abilities. The representative executive measures utilized in this study were limited in the range of sub-domains of executive functioning examined; future research may examine more varied sub-domains to obtain a more comprehensive account of the role of executive functioning in everyday functioning in PD.
Although representative measures of sub-domains of executive functioning demonstrated predictive value in everyday functioning, specific hypotheses concerning the expectation that executive measures alone would be most related were not supported. Our findings indicated that both visuo-spatial perception and executive tasks of initiation/perseveration and working memory are significant predictors to everyday functioning in PD. The literature on visuo-spatial and visuo-perceptual functioning initially received mixed results in which some studies found normal visuo-spatial abilities in PD (Hsieh et al., 1996; 1997), and other studies reported varying levels of impairment, from mild to severe (Doyon, Bourgeois, & Bedard, 1996; Kemps, Szmalec, Vandierandonck, & Crevits, 2005). Most recent studies, including a meta-analysis examining cognitive deficits in PD, agree upon the presence of visuo-spatial and visuo-perceptual deficits (Lyros, Messinis, & Papathanasopoulos, 2008; Siegert et al., 2008). The findings of the present study are also consistent with findings by Nieoullon and Coquerel (2003), in which executive tasks involving visual information were impaired in PD.

Although the aim of the present study was to isolate the cognitive contribution of everyday functioning deficits in PD, it is important to consider the difficulty in separating the two components, particularly in a progressive neurodegenerative disease such as PD. The two visuo-spatial/visuo-perceptual tasks utilized in this study were not correlated with one another. This suggests that each measures different aspects of visuo-spatial/visuo-perceptual functioning. These measures differ in both motor and cognitive demands. The DRS-2
construction subscale requires primarily motor output, and visuo-spatial reproduction. In contrast, the JOLO is free of motor demands and assesses visuo-perception. The differential motor and cognitive demands of visuo-spatial/visuo-perceptual tasks are important considerations in developing future research protocols.

Initiation/perseveration, working memory and visuo-spatial functioning demonstrated a relationship to everyday functioning deficits in PD. However, it is important to note that results of two exploratory analyses utilizing two differential item classifications of the ADCS-ADL (BADL/IADL, and PADL/CADL subscales) yielded differing results. Utilizing the traditional BADL and IADL subscales, the BADL subscale was significantly related to visuo-spatial functioning, but not initiation/perseveration. Initiation/perserveration and working memory were not related to either BADLs or IADLs. However, reclassification of the items of the ADCS-ADL into new subscales emphasizing ADLs requiring more of a physical (PADL) or cognitive (CADL) load relevant to motor deficits encountered by PD patients, yielded significant associations with both visuo-spatial functioning and initiation/perseveration. Initiation/perseveration was related to cognitive activities of daily living (CADLs), and marginally related to PADLs. The results of this second exploratory analysis support findings of a similar study by Cahn and colleagues (1998), in which executive functioning was related to cognitive ADLs but not physical ADLs. In contrast, visuo-spatial functioning was related to both PADLs and CADLs. This suggests that while both of these cognitive domains may be related to
everyday functioning in PD, initiation/perseveration and working memory may better inform the relationship between cognition and everyday functioning, while visuo-spatial functioning may be more informative concerning the interplay between motor and cognitive decline in everyday functioning deficits. These results support existing research demonstrating that overall disability and presentation of parkinsonian signs is associated with both BADLs and IADLs (Fleischman, Wilson, & Schneider, 2007). The results further support the need for the development of a questionnaire exploring everyday functioning in PD. Key aspects of PD may not be captured by the ADCS-ADL, which was developed specifically for Alzheimer’s disease. Integration of the extant literature concerning motor, cognitive, and everyday functioning deficits will aid the development of a PD-specific questionnaire.

This study also examined the association between two of the most commonly used clinical measures of global cognition (MMSE, DRS-2) and everyday performance. Results indicated that both of these clinical tools are significantly related to everyday functioning. However, considering the findings that neuropsychological assessment of visuo-spatial perception and executive functioning were associated with everyday functioning while assessment of other cognitive domains were not, it can be argued that the DRS-2 provides more detailed information than the MMSE and may be more clinically relevant and meaningful for PD patients as it covers more varied cognitive domains. The DRS-2 may provide more varied information than the MMSE, in that it measures five domains of
cognition; attention, executive functioning (initiation/perseveration), visuospatial
abilities (construction), abstract concept formation skills (conceptualization), and
memory. Similar to results of other analyses in the current study, executive
functioning and visuospatial perception as measured by the respective DRS-2
subscales were significantly correlated to functional performance, while other
cognitive domains were not.

This is consistent with the broader literature in that the MMSE, although
sensitive to cognitive dysfunction, may not be as specific as the DRS-2 regarding the
nature of cognitive dysfunction (Brown et al., 1999; Athey & Walker, 2006; Song et
al., 2008). It is important to note that the MMSE is more commonly used in the clinic
than the DRS-2 (Song et al., 2008). The DRS-2 takes 15-20 minutes to administer on
average, and while that is generally longer than MMSE administration time, it is
more practical for use in neurology clinics than a comprehensive
neuropsychological assessment.

The results of each correlation analysis yielded small to medium effect sizes,
consistent with previous literature and common in psychological research.
However, interpretation should be weighed against the small percentage of the
variance of everyday functioning explained by these neuropsychological variables.
Measures of global cognition demonstrated medium effect sizes and the highest
percentage of variance in everyday functioning explained. This suggests a stronger
association of between everyday functioning and global cognition compared to
cognitive domains, again highlighting the clinical utility of the MMSE and DRS-2.
There are several limitations to the current study. Due to the retrospective nature of this study, a full battery of the neuropsychological measures analyzed was not available for every participant. However, each analysis still met the requirements of the proposed power analysis. Participants who received the MIB, exhibiting significant motor, cognitive and everyday functioning deficits were included in the analysis to maximize generalizability. Although a small subset (n=9), considering our large sample, it is important to note that the severity of impairment in each of these areas may have influenced our results.

Although reliable and well validated, the scoring system used for the clockdraw test (Cosentino et al., 2004) is the only measure that did not have available normative data. Therefore, raw scores were used in the present analysis. The representative executive measures utilized in this study were limited to sub-domains of initiation/perseveration, working memory, and planning/execution. Using tests measuring more varied sub-domains of executive functioning with normative data would strengthen future studies. Another important limitation to address is the motor demand of several of the neuropsychological measures examined. Each executive measure required some form of motor involvement at varying levels. The clockdraw and DRS-2 initiation/perseveration subscale require drawing and reproduction. Although less of a motor demand, verbal fluency requires buccofacial movement and output. It is important to carefully choose measures and consider the impact of motor demands on performance in PD. Finally, in the current study, only one test was used to operationalize the cognitive domain.
being examined (aside from executive tasks). The tests used in this study may not necessarily be the most representative of a particular cognitive domain.

Despite these limitations, the overarching strength of this study is the use of a large sample in the identification of several useful clinical tools in determining the nature and contribution of specific cognitive domain deficits related to everyday functioning in PD. Brief assessment of initiation/perseveration, working memory and visuo-spatial perception may be used in the clinic to obtain more detailed information than measures of global cognition concerning the nature of potential impairments in functional performance. The identification of executive functioning measures that predict functional performance deficits in PD provides additional support for this conclusion. Considering significant correlational evidence in the present results, further research is needed concerning the predictive value of measures of visuo-spatial perception. In the present study a regression analysis was run examining multiple measures of executive functioning, but a regression with visuo-spatial measures was not performed. Considering strong correlation evidence uncovered by the present results, future studies may examine other measures of visuospatial abilities to expand upon correlation support, and examine its predictive value in everyday functioning through regression analyses, in either cross-sectional or longitudinal designs.

Further research on useful clinical measures that may examine the impact of cognition on everyday functioning PD should be conducted. This would further inform the cognitive rehabilitation literature as to the development of specific
domain-targeting treatment plans. Another important avenue of further research is the development of PD-specific global cognitive measures, and everyday functioning measures. Although some PD-specific measures of global cognition have been developed (Mathuranath et al., 2000; Marinus et al., 2003; Reyes et al., 2009), the developers of these scales have stressed that further understanding of cognitive domains most affected in PD are needed to improve and validate such measures. Considering the often-limited time that neurologists have in the clinic to assess multiple domains of functioning in PD patients, future research in which relationships between multiple domains of functioning are examined (e.g., motor disability, cognitive deficits, functional decline, psychiatric/behavioral disturbances) may better inform integrative treatment plans for patients with PD.
List of References


Table 1. Neuropsychological Test Descriptions

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Overall Cognitive Severity</strong></td>
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<tr>
<td>Mini Mental State Examination (MMSE)</td>
<td>Participants asked to answer questions of temporal orientation, attention, immediate and short-term recall, language, etc. The Total Score ranges from 0-30, with lower scores reflecting greater overall impairment/dementia severity.</td>
<td>Folstein et al., 1975</td>
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<tr>
<td>Dementia Rating Scale-2 (DRS-2)</td>
<td>Yields a total score summed from performance on five subscales. Subscales: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory.</td>
<td>Mattis, 1988</td>
</tr>
<tr>
<td><strong>Executive Functioning</strong></td>
<td></td>
<td></td>
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<tr>
<td>DRS-2 Initiation/Perseveration Subscale</td>
<td>Tasks include generation of a list of grocery store items, drawing alternating shapes, and meaningless syllable pronunciation (e.g., bee-key-gee said 4 times in a row).</td>
<td>Mattis, 1988</td>
</tr>
<tr>
<td>Phonemic Verbal Fluency (FAS)</td>
<td>The total number of words produced in 3 60-second trials beginning with F, A, and S, excluding proper nouns.</td>
<td>Spreen &amp; Strauss, 1991</td>
</tr>
<tr>
<td>Clock Drawing Test - Copy Condition</td>
<td>Copy a drawing of a clock in which the hands are set at 10 after 11.</td>
<td>Libon et al., 1996; Cosentino et al., 2004</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test - Revised (HVLT-R)</td>
<td>Participants were asked to remember a 12 word list over three learning trials, and again asked to recall the list after a delay with intervening, nonverbal tasks.</td>
<td>Brandt, 1991</td>
</tr>
<tr>
<td>DRS-2 Memory Subscale</td>
<td>Includes questions of orientation to time, date, and place, and tests of immediate and short-delay recall.</td>
<td>Mattis, 1988</td>
</tr>
<tr>
<td><strong>Visuospatial/Visuoperceptual Abilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benton Judgment of Line Orientation (JOLO)</td>
<td>Participants must match the position and direction of two lines from an array of 11 lines.</td>
<td>Benton et al., 1978</td>
</tr>
<tr>
<td>DRS-2 Construction Subscale</td>
<td>Copying of figures of increasing complexity.</td>
<td>Mattis, 1988</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRS-2 Attention Subscale</td>
<td>Repetition of numbers forward and backward, successive commands given by examiner (e.g., &quot;Open your mouth and close your eyes.&quot;)</td>
<td>Mattis, 1988</td>
</tr>
</tbody>
</table>
Table 2. Sample Motor Disability as measured by Hoehn & Yahr

<table>
<thead>
<tr>
<th>Hoehn and Yahr</th>
<th>Description</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>No signs of disease.</td>
<td>0</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Unilateral symptoms only.</td>
<td>2.3%(7)</td>
</tr>
<tr>
<td>Stage 1.5</td>
<td>Unilateral and axial involvement.</td>
<td>1.9%(6)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Bilateral symptoms. No impairment in balance.</td>
<td>28.2%(88)</td>
</tr>
<tr>
<td>Stage 2.5</td>
<td>Mild bilateral disease with recovery on pull test.</td>
<td>8.8%(27)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Balance impairment. Mild to moderate disease. Physically independent.</td>
<td>12.0%(37)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Severe disability, but still able to walk or stand unassisted.</td>
<td>4.2%(13)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Needing a wheelchair or bedridden unless assisted.</td>
<td>1.0%(3)</td>
</tr>
</tbody>
</table>
Table 3. Cognitive/Behavior Questionnaire
*Coded if currently occurring, or if symptoms are currently treated with medication.

<table>
<thead>
<tr>
<th>Symptom/Behavior</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive fluctuations</td>
<td>33.1%(59)</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>24.9%(45)</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>9.9%(18)</td>
</tr>
<tr>
<td>Illusions</td>
<td>5%(9)</td>
</tr>
<tr>
<td>Delusions</td>
<td>5.5%(10)</td>
</tr>
<tr>
<td>Mood fluctuations</td>
<td>24.9%(45)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.3%(15)</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>17.7%(32)</td>
</tr>
<tr>
<td>Apathy</td>
<td>17.7%(32)</td>
</tr>
<tr>
<td>Aggression</td>
<td>6.6%(12)</td>
</tr>
<tr>
<td>Dopamine agonist abuse</td>
<td>2.2%(4)</td>
</tr>
<tr>
<td>Compulsive/Impulsive behaviors (gambling, hypersexual behavior, compulsions, over-eating, spending)</td>
<td>21.6%(39)</td>
</tr>
</tbody>
</table>
Table 4. Mean Neuropsychological Test Scores and Everyday Functioning Scores

<table>
<thead>
<tr>
<th>Neuropsychological Variables</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE Total (n=179)</td>
<td>26.39</td>
<td>3.82</td>
</tr>
<tr>
<td>DRS-2 Total Age-Scaled Score (n=181)</td>
<td>8.41</td>
<td>3.65</td>
</tr>
<tr>
<td>FAS T-score (n=131)</td>
<td>46.05</td>
<td>14.62</td>
</tr>
<tr>
<td>Clock Draw Copy Condition raw score (n=165)</td>
<td>6.46</td>
<td>4.23</td>
</tr>
<tr>
<td>HVLT-R Delayed recall T-score</td>
<td>37.68</td>
<td>14.30</td>
</tr>
<tr>
<td>JOLO T-score (n=135)</td>
<td>37.79</td>
<td>14.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DRS-2 Subtest Scaled Scores (n=181)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>9.94</td>
<td>2.79</td>
</tr>
<tr>
<td>Initiation/Perseveration</td>
<td>8.62</td>
<td>3.35</td>
</tr>
<tr>
<td>Construction</td>
<td>9.04</td>
<td>3.03</td>
</tr>
<tr>
<td>Conceptualization</td>
<td>9.66</td>
<td>2.75</td>
</tr>
<tr>
<td>Memory</td>
<td>7.72</td>
<td>3.50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Everyday Functioning Variables (n=181)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCS-ADL Total Score (0-78)</td>
<td>64.74</td>
<td>15.58</td>
</tr>
<tr>
<td>BADL Score (0-28)</td>
<td>19.45</td>
<td>4.44</td>
</tr>
<tr>
<td>IADL Score (0-50)</td>
<td>45.29</td>
<td>12.18</td>
</tr>
</tbody>
</table>
Table 5. Partial Correlation Coefficients (r) – Representative Neuropsychological Tests and ADCS-ADL

<table>
<thead>
<tr>
<th>Overall Cognitive Severity</th>
<th>Attention</th>
<th>Executive Functioning</th>
<th>Episodic Memory</th>
<th>Visuospatial Perception</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>DRS-2 Total</td>
<td>DRS-2 Attention Subscale</td>
<td>Verbal Fluency (FAS)</td>
<td>HVLT-R Delayed Recall</td>
</tr>
<tr>
<td>0.25**</td>
<td>0.27**</td>
<td>0.06</td>
<td>0.18*</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

**p<.01, *p<.05

Table 6. Partial Correlation Coefficients (r) – DRS-2 Subscales and ADCS-ADL

<table>
<thead>
<tr>
<th>Attention</th>
<th>Initiation/ Perseveration</th>
<th>Construction</th>
<th>Conceptualization</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>0.16*</td>
<td>0.20**</td>
<td>-0.03</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**p<.01, *p<.05