COGNITIVE AND BEHAVIORAL PREDICTORS OF FALL RISK

IN PARKINSON DISEASE

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COGNITIVE AND BEHAVIORAL PREDICTORS OF FALL RISK IN PARKINSON DISEASE

by

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COGNITIVE AND BEHAVIORAL PREDICTORS OF FALL RISK

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ABSTRACT

Falls and their related injuries are a significant health issue for individuals with Parkinson disease (PD). Several factors have been identified that increase fall risk, including cognitive impairment, impulsiveness, and lower balance confidence, as well as PD-related characteristics. However, to date, no definitive predictor profile has been identified. As a result, there is a need

to develop a comprehensive model incorporating elements from each of the areas known to have a relationship with fall behaviors in PD. Such information could result in improved identification and treatment of PD patients at higher risk of falls. This study used stepwise logistic regression analyses to identify predictors of retrospectively reported falls from four domains, which included separate cognitive, impulsiveness/impulsive-compulsive disorder (ICD) related behaviors, disease characteristics, and balance confidence models. Each stepwise logistic regression yielded significant results ($p < .20$), and all of the significant predictor variables were included in a fifth combined model. The combined stepwise logistic regression was significant for postural instability (odds ratio = 8.66), verbal learning (California Verbal Learning Test-2 Total Learning T Score [CVLT-II]) (odds ratio = 0.95), and self-reported behavioral impulsiveness (Barratt Impulsiveness Scale-11 [BIS-11]) (odds ratio = 1.10). Model comparisons using net reclassification improvement (NRI) and the Hanley and McNeil (1983) method were conducted to determine if the combined model was significantly better at predicting fall risk than the domain-specific models. The combined model had the highest rate of accurately predicting fall risk (83%); however, the combined model was not significantly better at predicting fall risk than the impulsiveness/ICD or balance confidence models. These results showed that postural instability was the best predictor of fall risk; however, incorporating cognitive and impulsiveness measures improved prediction of fall risk. In light of these findings, screening for impulsiveness and, when possible, verbal learning, could be incorporated into routine clinical PD evaluations for better identification of patients at higher risk of falls.

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ABC	Activities-specific Balance Confidence Scale
AUC	Area Under the Curve
BD	Block Design
BIS-11	Barratt Impulsiveness Scale-11
CVLT-II	California Verbal Learning Test – Second Edition
DS	Digit Span
FOG	Freezing of Gait
HY	Hoehn and Yahr Staging Scale
ICD	Impulsive-Compulsive disorder
IRF	Impulsivity-Related Falls
L-dopa	L-dihydroxyphenylalanine
LDFR	Long Delay Free Recall
MCI	Mild Cognitive Impairment
MPTP	N-methyl-4 phenyl-1,2,3,6 tetrahydropyridine
NRI	Net Reclassification Improvement
PD	Parkinson Disease
PDFQ	Parkinson Disease Fall Questionnaire
PIGD	Postural Instability and Gait Difficulties
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale
ROC	Receiver Operating Characteristic
ROCF	Rey-Osterrieth Complex Figure

TMTB	Trail Making Test B
WAIS-IV	Wechsler Adult Intelligence Scale – Fourth Edition

CHAPTER ONE
Introduction

Parkinson disease (PD) is a degenerative disorder of the central nervous system that involves a combination of motor rigidity, resting tremor, bradykinesia, and gait difficulty. Cognitive and behavioral changes are also seen in a substantial proportion of individuals with PD. Common cognitive difficulties include deficits in executive functioning, memory, visuospatial processing, psychomotor speed, and attention, while language abilities remain relatively intact (Barone, Aarsland, Burn, Emre, Kulisevsky, & Weintraub, 2011). Observational studies suggest that a range of impulse control disorders (ICDs) also occur at a higher frequency in PD than in the general population (Weintraub et al., 2010). ICDs are characterized by a failure to resist an impulse, drive, or temptation to perform a pleasurable activity that is ultimately harmful because of its excessive nature. Impulse control-related disorders reported to occur in PD include pathological gambling, compulsive sexual behavior, impulsive buying, binge eating, punding (motor movements ranging between excessive "hobbyism" to highly stereotyped ritualistic behaviors), and excessive use of dopaminergic medication.

Among the more significant health issues in PD are falls, occurring in 40%-70% of individuals with PD, (Pickering et al., 2007), which can result in injuries (Johnell, Melton, Atkinson, O'Fallon, & Kurland, 1992), fear of falling (Adkin, Frank, & Jog, 2003), reduced mobility and a concomitant development of weakness (Sato, Kikuyama, & Oizumi, 1997; Taggart & Crawford, 1995), deterioration of fitness, loss of independence, increased risk of nursing home admission (Hely, Morris, Traficante, Reid, O'Sullivan, & Williamson, 2001), and reduced survival (Bloem & Bhatia, 2004). Several factors have been implicated as

causes of falls and injuries, including deficits in balance; however, to date, no definitive predictor profile has been identified (Currie, 2008). As a result, there is a need to identify risk factors for falls relevant to PD that may help with treatment planning.

Dementia is a known risk factor for falls (Buchner & Larson, 1987), but there is scant literature about the relationship between specific cognitive functions and fall risk. However, pilot data (Denney, Brown, Galusha, Lobue, Dewey, & Lacritz, 2014) have indicated that PD patients who reported one or more falls within the six months prior to neuropsychological evaluation performed worse on measures of attention, mental flexibility, and visuospatial abilities than PD patients who did not report falls. These results support the potential utility of examining cognitive profiles in PD to help identify those at increased risk for falls.

Impulsivity may also play a role in fall risk as impulsivity-related falls are a common subset of falls that occur in older adults and are associated with inattention and impaired cognitive function (Ferrari, Harrison, & Lewis, 2012). An editorial focusing on fall risk in PD provided some anecdotal evidence of the potential impact impulsiveness has on falls when Ahlskog (2010) stated that, "experience in the clinic reveals that some of the worst fallers are those who impulsively jump from their chair or turn without thinking." Despite the relatively high frequency of ICDs and falls within PD, the relationship between these two phenomena amongst individuals with PD has yet to be examined.

The following study aims to investigate the relationship between selected cognitive variables, impulsivity, and demographic features and recently reported falls among individuals with PD. This study hopes to add to the scientific knowledge about fall risk among individuals with PD and potentially improve awareness among clinicians treating this population, thereby enhancing clinical care.

CHAPTER TWO
Review of the Literature

PARKINSON DISEASE

Clinical Presentation

The syndrome now known as Parkinson Disease was originally described by James Parkinson (2002) in 1817 and characterized as "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace, the senses and intellect being uninjured" (p. 223). The term *paralysis agitans* was used to describe this collection of symptoms for many years, first appearing in Marshall Hall's 1841 textbook titled *On the Diseases and Derangements of the Nervous System*, but has since fallen out of favor for the more commonly used term, Parkinson Disease. Regardless of terminology, the syndrome now known as PD has been cogently labeled in the medical community for approaching 200 years and received considerable attention. In spite of a relatively well-understood and similar pathology, variations in course and overall clinical heterogeneity are well known and accepted features of PD (Zetusky, Jankovic, & Pirozzolo, 1985).

Clinical assessment using valid and reliable rating scales remains the gold standard in charting the course of the disease because of the lack of in vivo biomarkers in PD and limitations of neuroimaging methods to capture pathologic changes in dopaminergic brain structures (Goetz, 2005). Diagnosis made by neurologists specializing in movement disorders can be done with considerable accuracy (Hughes, Daniel, Ben-Shlomo, & Lees, 2002). Neurologists generally agree that the clinical diagnosis of PD requires identification of some combination of the key motor signs of bradykinesia, rigidity, tremor, and postural instability (Gelb, Oliver, & Gilman, 1999). These symptoms are evident as an expressionless face, poverty and slowness of voluntary

movement (global bradykinesia), “resting” tremor (typically 3-6 Hz), stooped posture, axial instability, rigidity, and festinating gait. Early symptoms often go overlooked by family members because of their slow evolution and attribution to naturally occurring changes due to age. The patient may also lack awareness of the changes early in the disease. Vague complaints of weakness or pain in the back, neck, shoulders or hips are often the first symptoms. Slowness of movement, stiffness, and reduction in the natural swing of one arm during walking may be overlooked until a physician recognizes that the patient has the general display of PD (Ropper & Samuels, 2009). Ioflupane iodine-123 injection (DaTSCAN) imaging has demonstrated efficacy in differentiating between parkinsonism and essential tremor but is limited in determining disease severity or monitoring progression (Benamer et al., 2000).

Tremor of a hand is often listed as the initial sign; however, family members commonly comment on the patient’s slowness of movement before the tremor appears. The characteristic “pill-rolling” tremor of the thumb and fingers is seen in roughly half of patients and typically manifests when the hand is at rest (i.e., when not being used in voluntary movement, thus use of the term “resting” tremor). Tremor and rigidity usually affect one side of the body before the other, with the tremor, in particular, remaining asymmetric as the illness advances. The tremor may fluctuate in severity, depending on the patient’s activity (e.g., being aggravated by walking and excitement), but frequency remains constant (Hunker & Abbs, 1990). Rigidity is less often an early finding but remains constant once it develops. The bradykinetic deficits cause the cardinal poverty of movement and are reflected by infrequency of swallowing, slowness of chewing, reduced capacity to make postural adjustments of the body, absence of arm swing, and other features of the parkinsonian visage. Strength is slightly diminished in small muscles while

larger muscles are capable of producing near normal power, despite a frequent complaint of muscle weakness among patients (Ropper & Samuels, 2009).

The disease becomes increasingly debilitating as it progresses. Handwriting becomes small (micrographia) and tremulous. Speech softens as the voice weakens to a whisper after first becoming monotonous. Gait reduces to a shuffle and often festinates with a series of increasingly rapid short steps to compensate for impaired balance. Gait in PD patients is characterized by a reduction in step length and velocity, decreased angular displacement and velocity of lower and upper limbs, high variability of step timing, poor bilateral coordination and asymmetric leg function (Lewis, Dove, Robbins, Barker, & Owen, 2003). Falls are a common problem, occurring in 37% to 68% of PD patients, resulting in a number of physical and psychological sequelae (Ashburn, Stack, Pickering, & Ward, 2001a; Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001; Charlett, 1997; Gray & Hildebrand, 2000; Koller, 1989; Paulson, Schafer, & Hallum, 1986; Pickering et al., 2007). Some PD patients engage in impulsive-compulsive behaviors, such as pathological gambling, compulsive sexual behavior, binge eating, excessive shopping, and punding (i.e., compulsive fascination with repetitive complex stereotyped behavior), as much as 3.5 times more frequently than the general population (Weintraub et al., 2010), creating increased risk of additional psychosocial and financial burden. Cognitive impairment is also a common problem as it affects roughly 25% of newly diagnosed patients (Aarsland, Bronnick, & Fladby, 2011; Muslimovic, Post, Speelman, & Schmand, 2005) and may develop into dementia over time (Aarsland et al., 2001; Williams-Gray, Goris, et al., 2009).

Given the heterogeneous nature of PD, along with the numerous comorbidities that can occur, the overall course of the disease is quite variable. Several subtypes have been described, including ‘hypokinetic-rigid,’ tremor-dominant,’ and postural instability-gait disorder’ forms

(Zetusky, Jankovic, & Pirozzolo, 1985; Jankovic et al., 1990). However, other classifications have been suggested by Reijnders, Ehrt, Lousberg, et al. (2009), such as 'rapid disease progression subtype,' 'young-onset subtype,' 'non-tremor-dominant subtype with psychopathology,' and 'tremor-dominant subtype.' They additionally conclude that non-tremor dominant PD is associated with greater cognitive deterioration and psychopathology. Progression of motor dysfunction in PD has also been described at varying rates. Before the advent of pharmacological therapy with levodopa, it was reported that the majority of patients would deteriorate to a chair-bound state within 7.5 years of its inception, albeit with a wide range (Hoehn & Yahr, 1967). Progression of disability has become decidedly slower with treatment of motor symptoms through dopaminergic therapies, as studies from the post-levodopa era have found latencies to debilitation to be as late as 40 years (Lucking et al., 2000). Not all modern studies have such positive results. According to a 2010 longitudinal study that followed more than 200 PD patients (Forsaa, Larsen, Wentzel-Larsen, & Alves, 2010), median survival from motor onset is 16 years. After 20 years, 70% of patients had died; though, time to death ranged from 2 to 37 years. Other risk factors that contribute to a higher likelihood of earlier death include a history of psychotic symptoms, comorbid dementia, and male gender.

Parkinson disease is among the most prevalent neurodegenerative conditions. It is observed across countries, ethnic groups, and socioeconomic classes; though, the incidence in African Americans is one quarter of that in whites. It is a relatively frequent disease in North America, with approximately one million affected patients, which constitutes roughly 1 percent of the population over the age of 65 years. Meta-analysis of worldwide data reveals a higher frequency of PD among males than females and a rising prevalence with age. Overall, 315 individuals per 100,000 are diagnosed with PD (Pringsheim, Jette, Frolkis, & Steeves, 2014). A

review of epidemiology of PD by de Lau and Breteler (2006) concluded that PD onset rarely occurs before age 50 years, with incidence sharply increasing after age 60. They add that mortality rates are difficult to deduce but state that life expectancy is consistently reduced with PD diagnosis, especially when dementia is present. A study by Levy, Tang, Louis et al. (2002) examining relationship between dementia and mortality in PD found that mortality risk only moderately increased in those who do not develop dementia.

Pathology

There are a large number of disorders possessing some or all of the cardinal clinical features of PD, with the clinical syndrome referred to as "parkinsonism." PD is but one of many parkinsonian disorders, all of which involve a neurodegeneration of dopaminergic neurons of the substantia nigra that project to the putamen (i.e., dopaminergic nigrostriatal pathway). PD is characterized by neuronal inclusions composed of α-synuclein, which are referred to as Lewy bodies (Dickson, 2012). Macroscopically, brains of PD patients are often unremarkable, with mild frontal atrophy in some cases. Sections of the brainstem typically reveal loss of the normally dark black pigment in the substantia nigra and locus ceruleus. This loss of pigmentation correlates with neuronal loss of dopaminergic neurons in the substantia nigra and noradrenergic neurons in the locus ceruleus (Dickson, 2012). The number of pigmented neurons in PD is reduced to 30 percent or less of that in age-matched controls (Ropper & Samuels, 2009). As the disease progresses, pathology extends to the basal forebrain, amygdala, and medial temporal lobe structures (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004).

The etiology of PD is not fully understood. Several factors are thought to play a role, including genetic and environmental influences. N-methyl-4 phenyl-1,2,3,6 tetrahydropyridine (MPTP) is a neurotoxin that induces a parkinsonian syndrome, a finding that has supported the

notion that environmental toxins may be the underlying cause of PD (Snyder & D'Amato, 1986; Uhl, Javitch, & Snyder, 1985). MPTP has been used to create an animal model of PD, as it causes a significant loss of dopaminergic neurons in the substantia nigra and other midbrain nuclei (German et al., 1996). While PD is more frequent in industrialized countries where such toxins are more prevalent, the universal occurrence of PD appears to argue against the hypothesis that environmental influences are solely responsible for PD. To date, no chemical toxin, heavy metal, or infection has been incriminated in the causation of idiopathic PD. Plausible theories include that a toxin might be implicated in the context of a particular genetic predisposition to the disease. The MPTP-induced disease model in animals serves as a example for the physiological changes associated with PD because of the damage done to the substantia nigra; however, it does not reflect the naturally occurring disorder (German et al., 1996).

Treatment

Currently, there is no treatment that halts or reverses the neuronal degeneration underlying PD. However, a number of viable options exist for clinicians and patients, which can afford relief from symptoms. Treatment can be pharmacological or surgical; however, at present, L-dihydroxyphenylalanine (L-dopa), which is the precursor to dopamine, is the most effective agent for the treatment of PD. Once L-dopa crosses the blood-brain barrier, it is converted into dopamine, thereby serving as an exogenous dopamine supplement. Over time, however, the remaining number of nigral neurons capable of producing dopamine from the available L-dopa become inadequate, causing excessive receptivity to dopamine of the striatal neurons. This results in dopaminergic complications to and paradoxical side effects (dyskinesias) with each dose. Dopamine agonists are an alternative pharmacological intervention, providing fewer dyskinetic motor complications, albeit with other cognitive and psychiatric side effects (Ropper

& Samuels, 2009). Surgical intervention via deep brain stimulation with the use of implanted electrical stimulators is a form of treatment that was first applied to PD patients in 1993 for treatment of tremor and is typically designated for patients with advanced symptoms that cannot be completely controlled with dopamine agonist treatment (Laitinen, Bergenheim, & Hariz, 1992; Limousin et al., 1995). The implantation of electrodes involves the placement of a wire in the posterior and ventral part of the subthalamic nucleus or the internal segment of the globus pallidus. In the largest randomized double-blind controlled trial comparing the comparative efficacy of subthalamic to pallidal stimulation, PD patients were observed to have similar reduction of motor symptoms. (Follett et al., 2010). A review by Benabid, Charbardes, and Seigneuret (2005) determined that complications are rare and mild with mortality rates extremely low. Transient cognitive disturbance is reported; however, cognitive impairment is not a common side effect.

COGNITION AND PARKINSON DISEASE

Cognitive impairment in PD can occur in the early stages of the disease and is often characterized by subtle changes in cognitive function that are not always apparent to the patients, their families, or clinicians (Aarsland et al., 2011; Foltynie, Brayne, Robbins, & Barker, 2004; Muslimovic et al., 2005). Cognitive impairment in nondemented PD is therefore under recognized in practice (Mamikonyan et al., 2009). Cognitive function in PD often declines over time, with many patients eventually developing dementia; however, not all PD patients develop a dementia despite exhibiting early cognitive deficits (Aarsland et al., 2001; Williams-Gray, Evans, et al., 2009). Cognitive impairment can have a major impact on the daily lives of patients and their caregivers, with even mild cognitive deficits leading to subtle functional impairments (Klepac, Trkulja, Relja, & Babic, 2008; Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006;

Weintraub, Moberg, Duda, Katz, & Stern, 2004). A review by Tröster and Fields (2008) of the neuropsychological literature on PD patients states that 19% of nondemented PD patients have some form of cognitive impairment. In a study with a large, multi-center PD population, 26% of subjects were classified as having MCI (Aarsland et al., 2010). Cognitive domains most commonly affected included executive function and memory; though, disturbances in visuospatial problem solving were also noteworthy.

Patients with more advanced PD have greater impairment in multiple neuropsychological functions (Green et al., 2002). Impairment of executive abilities (e.g., planning, organizing, and regulating goal-directed behavior) is considered a core feature of PD-related dementia (PDD) (Litvan, Mohr, Williams, Gomez, & Chase, 1991; Pillon, Dubois, Lhermitte, & Agid, 1986). These deficits include impairment in concept formation, problem solving, and set shifting (Pillon, Boller, Levy, & Dubois, 2001). These patients have more difficulty initiating or making use of internally cued behavior, which affects their ability to shift attention to novel stimuli (Owen et al., 1993). Deficits in attention and working memory are also commonly found in PDD, particularly on tasks of reaction time and vigilance (Litvan et al., 1991). Memory is also impaired in these individuals, but deficits are less severe than the amnesia observed in patients with Alzheimer's disease (Helkala, Laulumaa, Soininen, & Riekkinen, 1989; Pillon, Dubois, Ploska, & Agid, 1991; Stern, Richards, Sano, & Mayeux, 1993). Specifically, memory impairments in PDD include difficulty with free recall of information; however, they benefit substantially from semantic cueing, implying that new information is stored but not readily accessible (Helkala, Laulumaa, Soininen, & Riekkinen, 1988; Pillon, Deweer, Agid, & Dubois, 1993). Memory decline in PDD has been associated with declines on executive function test scores, suggesting that the retrieval deficit may be due in part to dysexecutive syndrome (Pillon

et al., 2001). Visuospatial abilities progressively decline in PD and have been observed to be more severely impaired than patients with Alzheimer's disease with similar dementia severity (Huber, Shuttleworth, & Freidenberg, 1989; Stern et al., 1993). Visuospatial impairment in PD is seen in all subcategories of visuospatial functioning without a specific pattern, except for spared visual sensory abilities and visual recognition (Cummings & Huber, 1992). Impairment is especially evident in tasks with greater complexity of planning and sequencing of responses or those requiring self-generated strategies (Stern, Mayeux, Rosen, & Ilson, 1983).

The pathophysiology of cognitive impairment in PD is not well understood but is thought to involve multiple neurotransmitter systems, diffuse neurodegeneration, and possibly a combination of PD and Alzheimer's disease neuropathological changes (Carbon, Edwards, & Eidelberg, 2003; De Leonibus et al., 2009; Meyer et al., 2009). Impairments in the neural circuitry connecting the basal ganglia and cortex, including the prefrontal cortex, may contribute to cognitive impairment in PD (Carbon et al., 2004). Executive and attentional impairment has been linked to disruptions of neuronal circuits involving the caudate and prefrontal cortex (due to loss of nigrostriatal dopaminergic projections) as well as loss of brain stem dopaminergic projections to cortical areas (Carbon et al., 2003). Exposure to MPTP, which is thought to result in a relatively "pure" dopaminergic lesion, has been shown to cause impairments in executive functions, visuospatial skills, and verbal fluency (Stern & Langston, 1985; Stern, Tetrud, Martin, Kutner, & Langston, 1990). Early positron emission tomography studies of cerebral blood flow in PD during frontal lobe tasks indicate that cognitive deficits can be explained by neuronal dysfunction in the basal ganglia (Dagher, Owen, Boecker, & Brooks, 2001). Atrophied grey matter in areas including the primary visual cortex, visual association cortex, and cholinergic structures such as pedunculopontine nucleus and substantia innominate have been associated

with visuospatial perception, attention, and memory deficits among PD patients (Lenka, Jhunjhunwala, Saini, & Pal, 2015). Nondopaminergic neurotransmitter systems are also likely involved in cognitive impairment as only weak correlations have been observed between motor disability and cognitive impairment in PD, suggesting that cognitive dysfunction is somewhat independent of the nigrostriatal dopamine deficiency underlying motor disability (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991). Further supporting the notion that nondopaminergic mechanisms play a significant role in PD-related cognitive impairment is the finding that more rapid cognitive decline is associated with motor symptoms that are thought to be mediated by cholinergic and noradrenergic neurotransmitter systems (De Leonibus et al., 2009; Meyer et al., 2009; Muslimovic et al., 2005).

Lewy body-related neurodegeneration in cortical and subcortical structures, which occurs in advanced stages of PD, are also believed to contribute to cognitive dysfunction and correlates with the degree of impairment (Mattila, Rinne, Helenius, Dickson, & Roytta, 2000). PD patients with visual hallucinations, a clinical sign of Lewy body disease, have increased rate of cognitive decline compared with patients with no visual hallucinations (Bronnick, Emre, Tekin, Haugen, & Aarsland, 2011; Santangelo et al., 2007). Transition from minor hallucinations to major visual hallucinations with insight retained is related to higher frontal-striatal dysfunction, whereas loss of insight correlates with greater impairment of cognitive functions related to posterior cortical areas (Llebaria et al., 2010).

Reported frequency of cognitive impairment without dementia in PD has ranged between 19% and 55% across studies because of a variety of definitions and methodologies (Aarsland, Bronnick, Larsen, Tysnes, & Alves, 2009; Caviness et al., 2007; Foltynie et al., 2004; Janvin, Aarsland, Larsen, & Hugdahl, 2003; Muslimovic et al., 2005). Meta-analysis of 1346 patients

with PD approximated that 26% were classified as having MCI (Aarsland et al., 2010). It is likely that the proportion of patients with cognitive impairment increases with duration of PD, which is supported by a study showing that rates of cognitive impairment in PD exceed 50% after 10 years of disease duration (Janvin et al., 2003). Known risk factors for cognitive impairment in PD include older age, presence of hallucinations, male sex, more severe motor symptoms, and depression (Aarsland et al., 2004; Kulisevsky, Pagonabarraga, Pascual-Sedano, Garcia-Sanchez, & Gironell, 2008; Nazem et al., 2009; Uc et al., 2009). Approximately 10% of PD patients convert to dementia every year, though rates of decline widely differ among patients (Aarsland et al., 2001). Among PD patients with MCI, approximately 60% develop dementia over a 4-year period (Janvin, Larsen, Aarsland, & Hugdahl, 2006). While cognitive impairment is common in PD, the presence of dementia before or within one year of diagnosis of PD is suggestive of an alternative diagnosis (e.g., dementia with Lewy bodies) (Gelb et al., 1999). However, determining the exact relative timing of onset of motor symptoms and dementia is often difficult in clinical practice and depends on the accuracy of history provided by the patient and caregivers (Aarsland & Kurz, 2010)

Despite the available research devoted to cognitive impairment in PD, it remains unclear whether cognitive dysfunction represents an opportunity for treatment intervention (Barone et al., 2011). Despite initial optimism, more recent reports have demonstrated that levodopa has a limited effect on cognitive impairment in PD (Emre, 2003). The limited positive effects that exist are likely due to non-specific actions on alertness, mood, and arousal, though improved dopaminergic transmission may benefit some elements of information processing, working memory, and internal control of attention (Pillon et al., 2001). Other evidence shows that cognitive functions worsen with some dopamine agonists but not others, suggesting that these

drugs differently affect cognition in PD patients according to their pharmacological characteristics (Brusa, et al., 2013). Another study examining the impact of rasagiline on cognitive functioning failed to find any changes among non-demented individuals with mild to moderate PD (Frakey & Friedman, 2014).

IMPULSIVITY AND PARKINSON DISEASE

Impulse control disorders (ICDs) have become increasingly recognized as a relatively common comorbidity in PD (Driver-Dunckley, Samanta, & Stacy, 2003a; Evans & Lees, 2004; Giovannoni, O'Sullivan, Turner, Manson, & Lees, 2000; Voon & Fox, 2007; Weintraub et al., 2010). The prevalence for ICDs in PD has ranged between 14% and 24% in treated patients (Hassan et al., 2011; Weintraub et al., 2010) with the most frequent impulsive-compulsive behaviors being pathological gambling, hypersexuality, compulsive shopping, punding or "hobbyism," and binge eating (Dodd et al., 2005; Driver-Dunckley, Samanta, & Stacy, 2003b; Ferrara & Stacy, 2008; Kurlan, 2004; Nirenberg & Waters, 2006; Pontone, Williams, Bassett, & Marsh, 2006; Uitti et al., 1989). Patients' use of anti-parkinsonian medication (i.e., dopamine agonists, most often levodopa) in excess of what is required to control motor symptoms is another described ICD-related phenomenon termed dopamine dysregulation syndrome (DDS) (Giovannoni et al., 2000; O'Sullivan, Evans, & Lees, 2009). The consequences of ICDs can be devastating, resulting in major financial loss, indebtedness, disrupted social relationships and employment, and legal problems (Pezzella et al., 2005; Weiss, 2010).

The true prevalence of ICDs remains a topic of debate due to the varying rates reported across studies. This is thought to be, at least in part, a function of methodological differences, including disparities in recruitment and selection procedures, as well as variability in operational definitions of ICDs. A study of more than 3,000 subjects across multiple centers [the

DOMINION study (Impulse Control Disorders in Parkinson's Patients Treated with Pramipexole and Other Agents)] assessed the frequency of these behaviors finding that at least one ICD was identified in 13.6% of patients, while 4.9% of patients had multiple behaviors. Diagnosis of ICD was made as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR;* American Psychiatric Association, 2000), using a semi-structured interview. The frequencies of individual ICDs were: compulsive buying (5.7%), compulsive gambling (5.0%), binge-eating disorder (4.3%), and compulsive sexual behavior (3.5%) (Weintraub et al., 2008). By comparison, there are few reports of ICDs among individuals with behavioral variant frontotemporal dementia, a disease with clinical core features that include perseverative, stereotyped, and/or compulsive and ritualistic behaviors (Pompanin, Jelcic, Cecchin, & Cagnin, 2014).

The etiology behind the increased incidence of ICDs and related behaviors among PD patients is thought to be, in part, related to the pharmacological treatment of the motor symptoms in PD. Evidence suggests an association exists between ICD prevalence and both dopamine agonists and levodopa (Ondo & Lai, 2008; Singh, Kandimala, Dewey, & O'Suilleabhain, 2007; Voon et al., 2007; Weintraub et al., 2006). Frequencies indicate that dopamine agonist treatment in PD is associated with a 2- to 3.5-fold increased likelihood of having an ICD compared to PD patients not treated with this class of medications (Weintraub et al., 2010). Further supporting the hypothesis for iatrogenically induced ICDs with these medications is the finding that de novo, untreated PD is not associated with symptoms of any impulse control or related behavior (Weintraub, Papay, & Siderowf, 2013). Therefore, PD itself, does not seem to lead to an increased risk for development of impulse control or related behavior symptoms. Furthermore,

case reporting suggests that ICDs may occur in other conditions treated with dopamine agonists, such as restless leg syndrome and fibromyalgia (Holman, 2009; Ondo & Lai, 2008).

A possible neurobiological explanation for the association between dopamine agonist treatment and ICD prevalence implicates dopamine and its receptor binding profiles. $Dopamine_2$ and $Dopamine_1$ receptors are abundant in the dorsal striatum and are believed to mediate the motor effects of dopamine replacement therapies. $Dopamine_3$ receptors, in contrast, are abundant in the ventral striatum/nucleus accumbens, which is a region of the brain that modulates non-motor circuits (Gurevich & Joyce, 1999). These non-motor circuits include: the dorsolateral prefrontal cortex, regulating executive function; the lateral orbitofrontal cortex, modulating socially appropriate behavior and mood; and the anterior cingulate cortex, initiating activity and maintaining interest (Potenza et al., 2003; Reuter et al., 2005). The ventral striatum/nucleus accumbens has also been associated with both behavioral addictions (Holden, 2001) and substance use disorders (Brewer & Potenza, 2008). Second generation nonergot dopamine agonists (e.g., pamipexole, ropinirole, and rotigotine) demonstrate relative selectivity for $Dopamine_3$ receptors (Gerlach, Double, Reichmann, & Riederer, 2003), which may account for the disruptive ICD-related behaviors associated with dopamine replacement therapy.

Levodopa has also been implicated with high prevalence of ICDs, albeit at a less robust rate than dopamine agonists (Weintraub et al., 2010). This is consistent with the dopamine-receptor binding profile hypothesis, as dopamine (the physiologically active metabolite of levodopa) demonstrates greater selectivity for $Dopamine_1$ and $Dopamine_2$ receptors than the $Dopamine_3$ receptor when compared to dopamine agonists (Gerlach, Double, Arzberger, et al., 2003). While dopamine replacement therapy is generally believed responsible for the relatively high prevalence of ICDs in PD, worth noting are a minority of reports that propose increased

ICD behaviors in PD are independent of dopamine replacement therapy and, instead, due to disease severity and progression (Bearn, Evans, Kelleher, Turner, & Lees, 2004; Evans, Lawrence, Potts, Appel, & Lees, 2005; Ferrara & Stacy, 2008; Stacy, 2008).

Psychosocial factors have also been identified to play a role in the presence of ICDs. In the general population, younger age, unmarried status, and tobacco smoking have been associated with ICDs (Cottler et al., 1998; Grucza, Przybeck, & Cloninger, 2007; Koran, Faber, Aboujaoude, Large, & Serpe, 2006; Petry, Stinson, & Grant, 2005). These reports, in conjunction with the association of family history of gambling problems, supports the notion of a biopsychosocial model of contributors to the development of ICDs (Comings et al., 1999; Lilenfeld, Ringham, Kalarchian, & Marcus, 2008; Slutske et al., 2000). It is likely that multiple factors contribute to ICD development in patients with PD (Weintraub et al., 2010).

Impulsivity is a recognized personality characteristic in the psychological literature, independent of a full-blown ICD. This personality trait has been operationalized as a tendency to enter into situations or rapidly respond to cues for potential reward without much planning or deliberation and without consideration of potential punishment or loss of reward (Zuckerman & Kuhlman, 2000). Studies have shown that impulsivity is a trait associated with ICDs among pathological gamblers, suggesting that higher premorbid impulsivity personality traits may moderate the development of ICDs among PD patients treated with dopamine agonists (Blanco, Myers, & Kendler, 2012; Fuentes, Tavares, Artes, & Gorenstein, 2006; Isaias, Siri, Cilia, Gaspari, Pezzoli, & Antonini, 2007; Michalczuk, Bowden-Jones, Verdejo-Garcia, & Clark, 2011).

As noted above, variable prevalence rates of ICDs in PD have been reported. Weiss (2010) highlights several barriers that impact recognition of ICDs among PD patients. Most

notably, it is pointed out that patients have differing opinions about what activities qualify for impulsive-compulsive behaviors (e.g., not regarding purchasing of lottery tickets as a type of gambling). Additionally, patients with ICDs frequently deny or minimize the extent of their behaviors or do not regard their actions as abnormal, and some may actively deceive others to hide their behaviors. Thus, despite concerted efforts to obtain accurate information regarding ICD-related behaviors, the presence and extent of these problems are likely underestimated (Weiss, 2010).

Relationship with Cognitive Impairment

The relationship between cognitive functioning and ICDs in PD patients is not well understood, as few studies have directly investigated the associations between these disease elements. Amongst those few are conflicting reports of cognitive abilities within this population. Poorer performance in executive functioning (e.g., set shifting and phonemic fluency), working memory, visual memory, and spatial planning have been associated with ICD in PD (Biundo et al., 2011; Djamshidian et al., 2010; Santangelo et al., 2009; Vitale et al., 2011; Voon et al., 2010). In contrast, Rossi et al. (2010) found no differences in neuropsychological performance among PD patients with and without an ICD. Similarly, Bentivoglio and colleagues (2013) found no significant cognitive differences between PD patients with and without ICDs (though, trends toward worse performance of the PD-ICD group were detected on tasks sensitive to frontal lobe dysfunction). Strikingly, Siri et al. (2010) reported better performances in episodic memory, verbal fluency, and attention among PD patients with pathological gambling compared to PD patients without pathological gambling, suggesting that this ICD may be associated with higher levels of some cognitive abilities in PD patients. Despite these inconsistent findings, researchers

seem to generally believe that the status of cognitive abilities, in particular that of executive function, play a role in the etiology of ICD development (Poletti & Bonuccelli, 2012).

The reasoning behind this belief appears to follow this line of thinking: non-PD pathological gamblers have demonstrated deficits in inhibitory control, which plays a role in ICD development and maintenance, and also predicts relapse (Forbush et al., 2008; Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2008; Kertzman et al., 2008). PD patients present with cognitive difficulties independent of ICDs, particularly with executive dysfunction and inhibitory control. Therefore, poor inhibitory control could also be involved in the etiology of ICDs in PD patients. However, conclusive evidence about the relationship between cognition and ICDs in PD is lacking (Poletti & Bonuccelli, 2012; Weintraub et al., 2010). While impaired decision making has been reported in pathological gambling and can reasonably be thought to generalize to other ICDs, it remains unclear if executive dysfunction, at least as detected by standard neuropsychological testing, is a risk factor for the development of ICDs in PD (Shotbolt et al., 2012).

FALLS

Unintentional falls are the most common cause of injuries for people older than 65 years, and fall-related injuries are the most common cause of accidental death in this age group, resulting in roughly 41 deaths per 100,000 people each year (Currie, 2008). Physical injury and death are not the only consequences of falls (Adkin, Frank, & Jog, 2003; Schrag, Jahanshahi, & Quinn, 2000). Those who fall also experience fear of future falls and consequentially reduce mobility, develop concomitant weakness, and lose fitness and independence (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001; Johnell, Melton, Atkinson, O'Fallon, & Kurland, 1992; Melton, et al., 2006; Stolze et al., 2004). The consequences of falls are also

costly. Data from 2000 estimates that annual costs for nonfatal, fall-related injuries were as much as $19 billion across care settings in the community (Stevens, Corso, Finkelstein, & Miller, 2006). To date, no definitive predictor profile of the causes of falls among PD patients or the general population has been identified. As such, falls are a serious public health problem that warrants closer inspection to better understand how and why they occur.

By nature, identification of fall history is typically dependent upon an individual's self-report, potentially creating a discrepancy between subjective recall and objective reality. Mackenzie, Byles, and D'Este (2006) examined the validity of self-reported fall events by comparing self-reported falls over a six-month period with a prospective calendar-reported method. They found that the 84% of self-reported falls were in agreement with the prospective calendar method. Four percent of subjects self-reported false positive falls, and 13% gave false negative self-reports of falls, indicating that fallers are more likely to under-report falls. However, the majority of subjects accurately recalled their fall events within a six-month period, providing support for the validity using self-report as a means of accounting for fall history.

Relationships with Parkinson Disease

Individuals with PD fall at a much higher rate than the general public, as up to 70% of these patients fall at least once within a 12-month period (Pickering et al., 2007). Furthermore, 87% of patients that survive 20 years with PD experience at least one fall (Hely, Reid, Adena, Halliday, & Morris, 2008). The Centers for Disease Control and Prevention ("Risk Factors For Falls," 2014) recognizes numerous risk factors for falls, including advanced age, previous falls, muscle weakness, gait and balance problems, postural hypotension, and chronic medical conditions. Given these recognized risk factors and the constellation of symptoms of PD, it is not surprising that these patients fall so frequently.

Among PD patients, a number of disease-related factors have been identified to differ between fallers and non-fallers, including disease duration, disease severity, poorer postural stability and balance recovery, poor standing balance, freezing of gait (FOG), and presence of orthostatic hypotension (Ashburn et al., 2001a; Koller, Glatt, Vetere-Overfield, & Hassanein, 1989; Landers et al., 2008; Morris, Iansek, Smithson, & Huxham, 2000; Robinson et al., 2005; Valkovic, Brozova, Botzel, Ruzicka, & Benetin, 2008). Ashburn et al. (2001b) concluded that a reported history of two or more falls in the previous year was the best predictor of future falls, and prediction was not improved by the addition of disease severity measures.

Apart from physical factors, psychological factors such as self-perceived balance confidence and fear of future falls have also been identified as having a role in discriminating between fallers and non-fallers among PD patients (Mak & Pang, 2009a, 2009b; Pickering et al., 2007). PD non-fallers have significantly better scores on the Activities-specific Balance Confidence Scale (ABC), a self-report measure of balance confidence, than patients who fall. Even after adjusting for fall history and Unified Parkinson Disease Rating Scale (an assessment of disease severity), an ABC score of <69 (measure range = 0-100, 0 indicates no confidence and 100 indicates full confidence) remains a significant predictor of recurrent falls. This finding highlights the importance of considering psychological factors when assessing fall risk in PD.

Relationships with Cognition

Cognitive impairment and dementia are known risk factors for falls, as nursing home residents with dementia are almost twice as likely to fall as those without dementia (Buchner & Larson, 1987; Rubenstein, Josephson, & Robbins, 1994; van Doorn et al., 2003). Buchner and Larson (1987) reasoned that dementia patients are at higher risk of falls because of their impaired judgment, visuospatial perception, and ability to recognize and avoid hazard. However, the

relationship that specific cognitive functions have with falling is less clear, particularly among active adults without frank dementia.

Freezing of gait, a sudden and episodic inability to generate effective stepping, is a frequent symptom among patients with advanced PD and contributes to the development of major disability and frequent falls (Bloem, Hausdorff, Visser, & Giladi, 2004; Giladi & Nieuwboer, 2008). The disruption of frontostriatal pathways are thought to play a key role in FOG through executive control of action, including the capability to inhibit unwanted response tendencies (Bloem et al., 2004; Giladi & Nieuwboer, 2008). PD patients with FOG have demonstrated impairments with set-shifting and conflict resolution when compared to those without FOG; however, neuropsychological assessment of other aspects of executive dysfunction (e.g., abstract problem solving, mental flexibility, and verbal fluency) do not appear to reliably discriminate between patients with and without FOG (Amboni, Cozzolino, Longo, Picillo, & Barone, 2008; Naismith, Shine, & Lewis, 2010; Vandenbossche et al., 2011). Therefore, an association between aspects of executive dysfunction and fall risk seems likely in PD.

Data on the relationships between other aspects of cognitive function and falls are limited. Among older adults, impaired attention, processing speed, and visuospatial abilities have been linked with increased risk of falls (Anstey, von Sanden, & Luszcz, 2006; Liu-Ambrose, Ashe, Graf, Beattie, & Khan, 2008; Martin et al., 2009; Springer et al., 2006). This profile of cognitive impairment mirrors that commonly seen among PD patients. However, cognitive differences between fallers and non-fallers among PD patients have gone relatively unexamined. Pilot data have supported these findings, as PD patients who were candidates for deep brain stimulation surgery that reported at least one fall within 6 months prior to neuropsychological evaluation (N = 131) performed worse on measures of attention [e.g., Wechsler Adult

Intelligence Scale-IV (WAIS-IV) Digit Span (DS)], set-shifting [e.g., Trail Making Test B (TMTB)], and visuospatial abilities [e.g., WAIS-IV Block Design (BD) and Rey-Osterrieth Complex Figure Copy (ROCF Copy)] than non-fallers (Denney et al., 2014). Measures of memory, language, and other aspects of executive function did not significantly differ between fallers and non-fallers. These findings, along with the relative dearth of information about the relationship between cognitive functioning and falls, warrant further investigation of cognitive ability and fall risk among PD patients.

Relationships with Impulsivity

The relationship between fall risk and cognitive impulsivity or ICDs has not been directly examined. However, an interdisciplinary pilot study in 2007 determined that 28% of falls in older adult patients were due in part to impaired judgment about the consequences of a choice and lack of safety awareness; and were, therefore, termed "impulsivity-related falls" (Harrison, Ferrari, Campbell, Maddens, & Whall, 2010). Poor judgment about personal safety measures has been linked to impulsivity and may increase fall risk regardless of impairment on other dimensions such as visuospatial functioning (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001; Rapport et al., 1993). Among falls identified as impulsivity-related falls, Ferrari et al. (2010) found that inattention to be a more significant contributor than other known risk factors for falls. Wylie and colleagues (2012) recognized that patients with PD present a population of particular interest when examining the role that motor impulsivity has on fall risk. They found that PD patients with predominant postural instability and gait difficulties (PIGD), a subset of PD patients known to be at high risk for falling, demonstrated more motor impulsivity than tremor predominant subtype. That is, PIGD patients had reactions more often captured by strong, incorrect motor impulses than tremor predominant patients. While they did not directly assess the

relationship between motor impulsivity and falls, they identified motor impulsivity as a potential vulnerability of the PIGD subset of PD patients, which may play a role in their increased rates of falling. Furthermore, they found that general cognitive functioning or depression could not explain these patients' increased levels of impulsivity.

While these studies have identified impulsivity as a risk factor for falls, their methods of operationalizing the construct is either inconsistent or unclear. The role that impulsive personality traits have on fall risk has not been examined, nor has the relationship between ICDs and falls. Given the relatively high frequency of these phenomena in PD, further investigation of their relationship is warranted.

SUMMARY

Parkinson disease is a neurodegenerative disorder with numerous physical and psychological sequelae, including cognitive impairment and higher incidence and prevalence of ICDs. Among the more devastating health issues in PD are falls, which can result in various means of loss of independence and even death. While numerous risk factors for falls have been identified among PD patients, no predictor profile currently exists. Among the known risk factors for falls in PD is cognitive impairment; though, the relationships between specific cognitive abilities, especially among non-demented patients, and falls have not been examined. Low levels of balance confidence and fear of falling, common among PD patients, are also known to have predictive value when assessing fall risk. PD patients have high ICD prevalence, an issue thought to be a side effect of certain medications used to treat the motor symptoms of PD. The relationship between ICDs and falls has not been examined; however, other forms of impulsivity (e.g., motor impulsivity and poor judgment about personal safety) have an identified relationship with greater fall risk.

The current study was designed to investigate the relationship between fall risk and selected cognitive variables, measures of impulsivity, and disease characteristics among individuals with PD. The relative impact that cognitive, behavioral, and disease-related characteristics have on fall behaviors was discerned by sampling from multiple domains of functioning. It is hoped that the present study will add to the scientific knowledge about fall risk among individuals with PD and potentially increase awareness among clinicians treating this population, thereby improving identification of patients at risk of falls and enhancing clinical care.

CHAPTER THREE
Hypotheses

Overall Aim: To investigate cognitive and behavioral predictors of fall risk in Parkinson Disease.

Aim 1: To identify cognitive vulnerabilities in PD subjects with a recent history of falls.

Hypothesis 1: Performance on measures of visuospatial ability, attention, and mental flexibility will be significantly lower among PD subjects reporting a recent history of falls than those not reporting a recent history of falls. Performance on measures of learning and memory will not significantly differ between PD fallers and non-fallers.

Hypothesis 2: Performance on measures of visuospatial ability, attention, and mental flexibility will predict falls among PD subjects, while performance on measures of learning and memory will not.

Aim 2: To better understand the relationship between impulsivity and recent fall history in PD.

Hypothesis 3: PD subjects with a recent history of falls will report higher levels of behavioral impulsivity and ICD-related behaviors than PD subjects without a recent history of falls.

Hypothesis 4: Self-report measures of behavioral impulsivity and ICD-related behaviors will predict falls among PD subjects.

Aim 3: To better understand the relationship between disease characteristics and recent fall history in PD

Hypothesis 5: PD subjects with a recent history of falls will be older, have longer disease duration, and be more likely to have postural instability than PD subjects without a recent history of falls.

Hypothesis 6: Longer disease duration, older age, and presence of postural instability will predict falls among PD subjects.

Aim 4: To assess the relationship between balance confidence and recent fall history in PD.

Hypothesis 7: a) PD subjects with a recent history of falls will report lower levels of balance confidence than PD subjects without a recent history of falls. **b)** Lower levels of balance confidence will predict falls.

Aim 5: To determine the most significant predictor(s) of fall history in PD among cognitive, impulsivity/ICD, and disease characteristics variables.

Hypothesis 8: Combining cognitive, impulsivity, disease characteristics, and balance confidence variables will better predict fall group inclusion than any of the variables in isolation.

Exploratory Aim: To determine if PD subjects with a recent history of falls differ with respect to cognition, impulsivity, and disease characteristics based on their reported reasons for falling.

CHAPTER FOUR
Method

Participants

This study used data from 64 patients with Parkinson disease who were seen through the UT Southwestern Medical Center Neuropsychology Service as part of their standard clinical care. Diagnosis of PD was made by a movement disorders specialist. Patients were referred for neuropsychological evaluation to assist with treatment planning. For inclusion in this study, each patient consented to the use of their clinical data for research purposes. Patients were ambulatory and able to complete a core battery of neuropsychological tests, including additional measures of interest for this study. Exclusion criteria included PD patients who were not ambulatory.

Procedures

Patients were administered a neuropsychological battery by trained psychometrists or clinical psychology interns. Order of test administration varied to obtain optimal performance, and breaks were provided as needed. Patients were instructed to take their medications as usual. Chart review was performed to gather relevant data on patients' disease characteristics (e.g., disease duration and Hoehn and Yahr Staging Scale [HY]) and medication type (i.e., whether subjects were prescribed a nonergot 2nd generation dopamine agonist [e.g., pramipexole, ropinirole, and/or rotigotine] for PD symptoms).

Measures

Measure characteristics and psychometric properties are described in detail in Appendix A.

Cognitive Measures

The following tests were chosen for analysis from a larger battery of tests administered as part of their clinical evaluation.

Trail Making Test Part B (TMTB; Partington & Leiter, 1949)

Trail Making Test Part B is a timed test in which the goal of the task is to connect 25 alternating encircled numbers and letters in sequential order. Overall, this test is considered to examine speeded attention, sequencing, and flexibility for sequential processing. Scores are based on time of completion and the number of errors made. This study utilized time to complete TMTB as a measure of mental flexibility.

Wechsler Adult Intelligence Scale-IV Digit Span (WAIS-IV DS; Wechsler, 2008)

Digit Span is a subtest of the WAIS-IV. It is composed of three tasks: DS Forward, DS Backward, and DS Sequencing. It is thought to measure simple attention and working memory. This study employed DS age-adjusted scaled score as a measure of attention.

Wechsler Adult Intelligence Scale-IV Block Design (BD; Wechsler, 2008)

Block Design is a subtest of the WAIS-IV. It is a timed test in which examinees use three-dimensional red/white blocks to reproduce a model or a picture presented to them. It measures the ability to analyze and synthesize abstract visual stimuli and involves nonverbal concept formation and reasoning, broad visual intelligence, and visual perception and organization (Wechsler, 2008). This study utilized BD age-adjusted scaled score as a measure of visuospatial ability.

Rey-Osterrieth Complex Figure (ROCF; Osterrieth, 1944; Rey, 1941)

The ROCF is a measure of visuospatial constructional ability and visual memory. Factor analysis supports the validity of the ROCF as a measure of visual-constructional ability (copy) and memory (recall and recognition) (Chervinsky,

Mitrushina, & Statz, 1992). The present study employed the ROCF Copy raw score as a measure of visuospatial ability.

California Verbal Learning Test Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000)

The CVLT-II is a measure of verbal learning and memory in which a list of 16 words is presented for five learning trials, followed by a 16-item distractor list. Short and long delayed free and cued recall trials are then administered, as is delayed recognition testing. The CVLT-II has been shown to be sensitive to learning and memory dysfunction across neuromedical and psychiatric populations. Variables of interest for the present study included demographically-adjusted Total Learning and Long Delayed Free Recall (LDFR) T-Scores.

Behavioral Measures

Barratt Impulsiveness Scale-11 (BIS-11; Patton, Stanford, & Barratt, 1995)

The BIS-11 is designed to assess the personality/behavioral construct of impulsiveness. It is the 11th iteration of the original BIS (Barratt, 1959) and is arguably the most commonly administered self-report measure specifically designed for the assessment of impulsiveness (Stanford et al., 2009). Raw scores range between 30 and 120 with scores from 52 to 71 identified as being within "normal limits of impulsiveness." Scores at 72 or above are suggested to be used to classify individuals as "highly impulsive," while scores below 52 are indicative of "over controlled" individuals or those not answering the questionnaire honestly (Stanford et al., 2009). This study utilized the total raw score of the BIS-11 as a measure of personality/behavioral impulsiveness. See Appendix B for a copy of the measure.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS; Weintraub et al., 2012)

The QUIP-RS is a self-report measure of impulsive-compulsive disorders (ICD) in PD that assesses the severity of ICD behaviors and has four primary questions (pertaining to commonly reported thoughts, urges/desires, and behaviors associated with ICDs), each applied to the four ICDs (compulsive gambling, buying, eating, and sexual behavior) and three related disorders (medication use, punding, and hobbyism). Raw scores for each of the four ICDs and related disorders can range from 0 to 16. The Total ICD score ranges from 0 to 64, and the Total QUIP-RS Score ranges from 0 to 112. Cutoff scores for significant ICD behaviors have been identified: gambling = 6; buying = 8; eating = 7; sexual behavior = 8; Total ICD = 10. A cutoff for the Total QUIP-RS Score has not been identified. This study examined the QUIP-RS ICD raw score and QUIP-RS Total raw score as screening measures for ICD-related behavior in PD patients. See Appendix C for a copy of the measure.

Hoehn and Yahr Staging Scale (HY; Hoehn and Yahr, 1967)

The HY was designed to be a simple descriptive staging scale that provided an estimate of clinical function in PD. It combines functional deficits (disability) and objective signs (impairment) into the rating. It utilizes a seven-point Likert scale (1, 1.5, 2, 2.5, 3, 4, and 5) to identify disease severity. By definition, the patients in Stages I, II, and III are minimally disabled, whereas patients in IV and V are severely disabled. This study utilized HY ratings determined through chart review with the assistance of a movement disorders specialist as a measure of disease severity and presence of postural instability. Postural instability was determined by examining HY

staging for each subject via chart review. Subjects with a HY score of 2.5 (i.e., mild bilateral disease with recovery on pull test) or above were deemed to demonstrate some indication of postural instability.

Activity-specific Balance Confidence Scale (ABC; Powell & Myers, 1995)

The ABC is a 16-item self-report measure of confidence in performing various ambulatory activities without falling or experiencing a sense of unsteadiness. Each activity is stemmed with: "How confident are you that you will not lose your balance or become unsteady when you…" Items are rated on a scale that ranges from 0 – 100 where a score of zero represents no confidence while a score 100 represents complete confidence. Overall score is calculated by adding item scores and then dividing by the total number of items (16). This study utilized the ABC as a measure of balance confidence. See Appendix D for a copy of the measure.

Parkinson Disease Fall Questionnaire (PDFQ)

The PDFQ was created for the purposes of this study. It is an unpublished self-report measure that was designed to assess the presence, number, and cause(s) of falls for a PD population over a six month period. Number of falls (e.g., groups defined as $\leq$1[Low Fall Risk] vs. $\geq$2 [High Fall Risk]) as reported on this measure served as the primary dependent variable for this study. Two or more falls were operationalized as "high risk" due to Ashburn's et al. (2001b) conclusion that reported history of two or more falls was the best predictor of future falls. See Appendix E for a copy of the measure.

Data Analysis

Subjects were categorized into one of two groups (fallers or non-fallers) based on their report of falls on the PDFQ. Subjects that reported zero or one fall were included in the "Low Fall Risk" group, while subjects reporting more than one fall were included in the "High Fall Risk" group.

Aim 1

To determine cognitive vulnerabilities in PD subjects with a recent history of falls, mean performances on each cognitive measure were compared between groups with independent *t* tests to determine fall risk group differences. A stepwise logistic regression, with all cognitive variables entered (TMTB, DS, BD, ROCF Copy, and CVLT-II Total Learning and Long Delay Free Recall) was then performed to determine the utility of combining cognitive measures to predict fall risk. A reduced model was then run, which only included significant predictor(s) of High Fall Risk group membership from the stepwise logistic regression. Regression models were presumed significant at $p = .20$ or below, per Hosmer and Lemeshow (1989).

Aim 2

To better understand the relationship between impulsiveness/ICD-related behaviors and fall risk, mean performances on each impulsiveness/ICD measure were compared between groups with independent *t* tests to determine fall group differences. Chi Square was performed to determine group differences related to being prescribed a 2^{nd} generation dopamine agonist medication. A stepwise logistic regression, with all impulsiveness/ICD variables entered (BIS-11, QUIP-RS Total, (+) 2^{nd} generation dopamine agonist) was then performed to determine the utility of combining impulsiveness/ICD variables to predict fall risk. Medication type was included in this analysis to account for the theoretical assumption that dopamine agonist therapy increases incidence of ICDs in PD. A reduced model was then run, which only included

significant predictor(s) of High Fall Risk group membership from the stepwise logistic regression. Regression models were presumed significant at $p = .20$ or below, per Hosmer & Lemeshow.

Aim 3

To better understand the relationship between disease characteristics and recent fall risk in PD, mean age and disease duration were compared between groups with independent *t* tests to determine fall risk group differences. Due to the limited sample size in the study, results from the Hoehn and Yahr staging scale (HY) were dichotomized into subjects without any signs of postural instability (HY = 1 – 2) and those demonstrating some indication of postural instability (HY = 2.5 – 5). Chi Square was performed to determine group differences related to disease severity/postural instability. A stepwise logistic regression, with all disease characteristics variables entered (age, disease duration, and (+) postural instability) was then performed to determine the utility of combining disease characteristics to predict fall risk. A reduced model was then run, which only included significant predictor(s) of High Fall Risk group membership from the stepwise logistic regression. Regression models were presumed significant at $p = .20$ or below, per Hosmer and Lemeshow (1989).

Aim 4

To assess the relationship between balance confidence and fall risk in PD, mean ABCs scores were compared between groups with an independent *t* test to determine fall risk group differences. A logistic regression was performed to determine the ABCs' ability to predict fall risk. The regression model was presumed significant at $p = .20$ or below, per Hosmer and Lemeshow (1989).

Aim 5

In order to determine the most significant predictor(s) of fall risk in PD among cognitive variables, impulsivity variables, and disease characteristics and better understand their shared relationship with recent fall risk in PD, a stepwise logistic regression was performed utilizing the significant variable(s) from each domain of interest, based on results from logistic regression analyses in Aims 1, 2, 3, and 4. The regression model was presumed significant at $p = .20$, per Hosmer and Lemeshow (1989). In order to determine the combined model's ability to better predict fall risk than prior models, Receiver Operating Characteristic (ROC) analyses were conducted, using the predictions from logistic regression from each reduced model in Aims 1, 2, 3, and 4 as well as for the combined model to examine their accuracy in distinguishing the High Fall Risk group from the Low Fall Risk group. For comparison between the balance confidence model (Aim 4) and the reduced combined model, *ROC* curves for each were compared using the method described by Hanley and McNeil (1983). The ability of the reduced models in Aims 1 (cognitive), 2 (impulsiveness/ICD), and 3 (disease characteristics) to accurately detect High Fall Risk group membership were compared to the reduced combined model's ability to detect High Fall Risk group membership using *Net Reclassification Improvement* (*NRI*) analyses (Pencina, D'Agostino, D'Agostino, & Vasan, 2008), as a means of quantifying differences in classification rates between two models with overlapping predictors. This method was used to determine if the inclusion of combining predictors of interest (i.e., cognitive, impulsiveness/ICD, disease characteristics, balance confidence) in the final model would significantly improve fall risk group discriminative value, as compared to any of the predictor domains in isolation.

Exploratory Aim

Additional analyses were performed to determine if PD subjects with and without a recent history of falls differ with respect to certain cognition, impulsivity, balance confidence,

and disease characteristics variables based on their reported reasons for falling on the PDFQ. Subjects were grouped based on their reported reasons for falling (with non-fallers as the comparison group), and differences in cognitive, impulsive, balance confidence, and disease characteristics variables were determined via independent *t* tests. Subjects can indicate more than one reason for their fall(s) on the PDFQ. Therefore, the various fall samples included overlapping subjects when multiple reasons were endorsed.

CHAPTER FIVE
Results

SAMPLE CHARACTERISTICS

Study Sample and Excluded Participants

A total of 64 consecutive patients with Parkinson disease were recruited from the UTSW Neuropsychology Clinic for inclusion into this study. Only subjects with all requisite data were included in the respective logistic regression analyses, leaving 59 subjects in the cognitive regressions, 62 subjects in the disease characteristic regressions, 61 subjects in the impulsivity/ICD regressions, 60 subjects in the balance confidence regression, and 55 subjects in the combined stepwise logistic regressions. For the exploratory analyses related to reasons for falling, two subjects were excluded due to missing data on the outcome measure (PDFQ).

Demographic Characteristics

Demographic characteristics of the study sample are described in Table 1. Age ranged from 40 to 86, with a mean of 66.6 (*SD* = 9.7; median = 69) years. Education ranged from 9 to 20, with a mean of 15.4 (*SD* = 2.2; median = 16) years. The sample was primarily Caucasian (88%) and right handed (88%).

Descriptive Statistics of Predictor Variables

Descriptive statistics for all study variables are presented in Table 2. Overall mean performance on BD, DS, and CVLT-II Learning and LDFR was within the average range. Mean TMT B time of completion in seconds was 145.0 (*SD* = 82; median = 120.0; range = 26 to 300). Mean ROCF Copy raw score was 29.7 (*SD* = 5.6). Overall impulsiveness, as measured by the BIS-11, was within the normal limits on this measure (mean = 61.2; *SD* = 10.0). Mean QUIP-RS ICD score was 10.8 (*SD* = 8.8; *median* = 9.0), which is considered elevated for combined ICDs, while mean QUIP-RS Total score was 20.9 (*SD* = 16.0; *median* = 18), which is similar to the

mean previously reported by Weintraub, Mamikonyan, Papay et al. (2012) (19.3; SD = 18.5) for a PD sample. Mean ABCs was 73.9 (*SD* = 19.8), very similar to the previously reported mean total score among PD patients (73.6, SD = 19.3; Mak, Pang, & Mok, 2012). Disease duration ranged from 1 to 30 years, with a mean of 8.6 (*SD* = 5.6; median = 8). Twenty nine (47%) of subjects demonstrated some sign of postural instability (HY score $\geq$ 2.5), and 27 (42%) were prescribed a 2nd generation dopamine agonist. Number of reported falls within 6 months prior to neuropsychological evaluation ranged from 0 to 200, with a mean of 6.9 (*SD* = 25.5; *median* = 1.5). The most commonly reported reasons for falling were problems with balance (while standing in one spot = 31%; while turning = 27%).

GROUP COMPARISONS

Subjects were divided into groups based on report of falls on the PDFQ. Forty (63%) subjects reported having at least one fall within the six months prior to their neuropsychological evaluation. Thirty two (50%) subjects reported two or more falls within the 6 months prior to their neuropsychological evaluation (High Fall Risk group), and 32 subjects reported zero or one fall within the 6 months prior to their neuropsychological evaluation (Low Fall Risk group) for an equal number of subjects in each group.

Demographics

Summary of demographic characteristics for the Low Fall Risk and High Fall Risk groups can be found in Table 3. No significant differences were noted between the groups in terms of age [$t(62) = 1.205$, $p = .233$) or education [$t(62) = .961$, $p = .340$). Groups were also similar across sex [$X^2(1, N = 64) = 0.00$, $p = >.999$], race [$X^2(1, N = 64) = 0.571$, $p = .450$], and handedness [$X^2(1, N = 64) = .571$, $p = .450$].

Cognition

Summary statistics of the cognitive tests for the Low Fall Risk and High Fall Risk groups can be found in Table 4. Contrary to what was hypothesized, no significant differences were noted between the groups for any of the cognitive variables [Block Design $t(58) = .413$, $p = .681$; Digit Span $t(61) = .146$, $p = .884$; Trail Making Test B $t(60) = .479$, $p = .634$; Rey-Osterrieth Copy $t(58) = .951$, $p = .345$; CVLT-II Learning $t(61) = 1.493$, $p = .141$; CVLT-II Long Delay Free Recall $t(61) = .992$, $p = .325$].

Impulsiveness/ICD

Impulsiveness/ICD results for the Low Fall Risk and High Fall Risk groups can be found in Table 4. As predicted, the High Fall Risk group had significantly higher levels of impulsiveness ratings as measured by the BIS-11 [Low Fall Risk group $M = 58.0$, $SD = 9.8$; High Fall Risk Group $M = 64.2$, $SD = 9.4$; $t(60) = 2.565$, $p = .013$; Cohen's $d = 0.646$] and higher levels of ICD-related behaviors as measured by the QUIP-RS ICD Score [Low Fall Risk group $M = 8.3$, $SD = 7.2$; High Fall Risk group $M = 13.2$, $SD = 9.7$; $t(57.216) = 2.259$, $p = .028$; Cohen's $d = 0.574$] and QUIP-RS Total Score [Low Fall Risk group $M = 15.9$, $SD = 13.1$; Low Fall Risk group $M = 25.7$, $SD = 17.2$; $t(61) = 2.537$, $p = .014$; Cohen's $d = 0.641$] than the Low Fall Risk group. However, both groups had similar frequencies of subjects who were taking a second generation dopamine agonist [$X^2(1, N = 63) = 0.762$, $p = .383$].

Balance Confidence

Balance confidence results for the Low Fall Risk and High Fall Risk groups can be found in Table 4. As predicted, the High Fall Risk group had significantly lower balance confidence than the Low Fall Risk group [Low Fall Risk group $M = 82.7$, $SD = 15.7$; High Fall Risk group $M = 65.6$, $SD = 19.9$; $t(58) = 3.687$, $p = .001$; Cohen's $d = 0.954$].

Disease Characteristics

Disease characteristics of the Low Fall Risk and High Fall Risk groups can be found in Table 4. As predicted, the High Fall Risk group had significantly longer disease duration [Low Fall Risk group M = 6.8, SD = 4.1; High Fall Risk group M = 10.4, SD = 6.3; $t(62) = 2.653$, p = .01; Cohen's d = 0.677] and higher frequency of postural instability than the Low Fall Risk group. Postural instability was determined by examining HY staging for each subject via chart review. Subjects with a HY score of 2.5 or above were deemed to demonstrate some indication of postural instability. This method resulted in six (19%) subjects in the Low Fall Risk group with postural instability, and 24 (74%) subjects in the High Fall Risk group with postural instability ($X^2[1, N = 62] = 18.723$, $p < .001$; $r = 0.550$).

LOGISTIC REGRESSIONS

Logistic regression models were used to determine the ability of cognitive, impulsiveness/ICD, disease characteristics, and balance confidence variables to predict fall risk in domain-specific and combined models. The cognitive, impulsiveness/ICD, disease characteristics, and combined models were analyzed for examination of fall risk predictability when all variables of interest are included, as well as a forward Wald stepwise method with alpha to enter = .20 and alpha to leave = .25. A final logistic regression model included the measures from the last step of the stepwise procedure; this model included all non-missing cases for the measures included in the logistic regression model. Therefore, only the reduced models are reported. As the balanced confidence model contained one variable, it was analyzed with only the forced entry method.

Cognition

It was hypothesized that measures of visuospatial ability, attention, and mental flexibility would predict fall risk among PD subjects, while measures of learning and memory would not.

Logistic regression was used to examine falls with BD, DS, TMT B, ROCF Copy, and CVLT-II Learning and Long Delay Free Recall (LDFR) predicting membership in the High Fall Risk group (see Table 5). For the entry model, no cognitive measures were significant predictors of High Fall Risk group membership. Counter to expectation, measures of visuospatial ability, attention, and mental flexibility were not predictive of High Fall Risk group membership, while higher CVLT-II Learning T scores lowered the likelihood of being in the High Fall Risk group in the stepwise model (Reduced Model $p = .14$).

Impulsiveness/ICD

It was hypothesized that taking a 2nd generation dopamine agonist medication and higher scores on self-report measures of behavioral impulsivity and ICD-related behaviors would predict fall risk among PD subjects. Logistic regression was used to examine fall risk with the BIS-11, QUIP-RS Total score, and (+/-) presence of a 2nd generation dopamine agonist predicting membership in the High Fall Risk group (see Table 6). For the entry model, higher QUIP-RS Total scores were predictive of membership in the High Fall Risk group ($p = .18$), while higher BIS-11 scores were predictive of High Fall Risk group membership in the stepwise model (Reduced Model $p = .02$). Being prescribed a 2nd generation dopamine agonist was not predictive of High Fall Risk group membership. Additional ROC analyses were conducted to determine a cutoff score for the QUIP-RS that differentiated between fall risk groups. Results indicate that when screening for ICDs with the QUIP-RS, a Total Score of 13 (AUC = .67, $p = .02$; sensitivity = .72, specificity = .48) may be helpful in identifying which patients are more likely to fall

Disease Characteristics

It was hypothesized that disease characteristics (i.e., disease duration and postural instability) would predict fall risk among PD subjects. Logistic regression was used to examine fall risk with disease duration, age, and (+) postural instability predicting membership in the High Fall Risk group. For the entry model, presence of postural instability was most predictive of membership in the High Fall Risk group (p = .001). Presence of postural instability (p = .001) and longer disease duration (p = .179) were kept in the stepwise model to predict membership in the High Fall Risk group (see Table 7).

Balance Confidence

It was hypothesized that balance confidence would predict fall risk among PD subjects. Logistic regression was used to examine fall risk with the ABCs predicting membership in the High Fall Risk group. As predicted, higher ABCs scores lowered the likelihood of being in the High Fall Risk group (Odds Ratio = 0.947; Wald's p = .002). Additional ROC analyses were conducted to determine a cutoff score for the ABC that differentiated between fall risk groups in the current population. With the current sample, a raw score of 79 was the best cutoff score (AUC = 0.77, p < .001; sensitivity = .72%, specificity = .68%) for discriminating between fall groups.

Combined Models

It was hypothesized that combining cognitive, impulsivity, disease characteristics, and balance confidence variables would better predict fall risk than the prior models using these predictors in isolation. Variables from each domain were selected based upon their inclusion in the previous reduced models derived from the stepwise regression results. Logistic regression was used to examine fall risk with (+) postural instability, ABC, BIS-11, disease duration, and CVLT-II Learning predicting membership in the High Fall Risk group (see Table 8). For the

entry model, presence of postural instability (odds ratio = 3.63, p = .172) was the most predictive of membership in the High Fall Risk group, followed by the BIS-11 (odds ratio = 1.05, p = .159), and CVLT-II Learning (odds ratio = 0.96, p = .165) (higher T scores lowered the odds of being in the High Fall Risk group). Similar to the entry model, the reduced stepwise model included the presence of postural instability (odds ratio = 8.66, p = .001), the BIS-11 (odds ratio = 1.06, p = .112), and CVLT-II Learning (odds ratio = 0.95, p = .117) to predict membership in the High Fall Risk group. When combined with the other variables, disease duration and the ABC were no longer significantly (> .20) predictive of fall risk group membership.

MODEL COMPARISONS

ROC analyses for each of the models were conducted with the predicted values derived from each of the reduced models. This procedure was required to compare the balance confidence and combined logistic regression models' predictive ability, as this method examines area under the curve for models with dissimilar predictor variables per Hanley and McNeil (1983). ROC analyses were also applied to the cognitive, impulsiveness/ICD, and disease characteristics models to examine their accuracy in distinguishing the High Fall Risk group from the Low Fall Risk group. For models with overlapping predictors (e.g., combined model with the cognitive, impulsiveness/ICD, and disease characteristics models), NRI analyses were conducted as a means of quantifying differences in classification rates (Pencina et al., 2008).

In *ROC* analyses, the reduced combined model showed the greatest *area under the curve* (*AUC* = .83, p < .001) when distinguishing between the Low Fall Risk and High Fall Risk groups, followed closely by the reduced disease characteristics model (i.e., postural instability and disease duration) (*AUC* = .81, p < .001). The balance confidence model *AUC* = .74 (p = .002), and the reduced impulsiveness/ICD model *AUC* = .70 (p = .009) were also significant. The

ROC analysis of the cognitive model was not significant (*AUC* = .64, *p* = .073). *ROC* curves for each model predicting High Fall Risk group membership can be found in Figure 1. A summary of *AUC*, cutscores, and accuracy of models predicting High Fall Risk group membership using predicted values derived from each respective final logistic regression is displayed in Table 9. Best cutscores were determined for each reduced model by examining the best accuracy in predicting group memebership and greatest distance from the diagonal in the ROC plot. With these cutscores, the accuracy of each model predicting High Fall Risk group membership was as follows: cognitive model = 66.1%, impulsiveness model = 72.9%, disease characteristics model = 76.3%, balance confidence model = 72.2%, combined model = 83.1%.

The difference detected between *ROC* curves of the reduced combined model and the balance confidence model when distinguishing between fall risk group membership, per Hanley and McNeil (1983), was not significant (*z* = 1.27, *p* = .203). *NRI* analyses revealed that the reduced combined model significantly improved fall risk group membership accuracy when compared to the reduced cognitive model (*NRI* = .34, *z* = 2.14, *p* = .032) and the reduced disease characteristics model (*NRI* = .13, *z* = 2.00, *p* = .046) but was not significantly better than the reduced impulsiveness/ICD model (*NRI* = .21, *z* = 1.55, *p* = .122). See Table 10 for a summary of model comparisons using *NRI*.

EXPLORATORY ANALYSES

Differences with respect to cognition, impulsiveness/ICD, disease characteristics, and balance confidence were explored based on subjects' reported reasons for falling. Descriptive data across the reported reason(s) of falling on the PDFQ can be found in Table 11. Subjects among each reported reason for falling were compared to subjects who reported zero falls.

Regarding cognitive measures, CVLT-II LDFR was significantly lower in the (+) Trip/Slip group than the No Fall group [$t(35) = 2.257$, $p = .03$], CVLT-II Learning was significantly lower in the (+) Standing Balance group than the No Fall group [$t(39) = 2.066$, $p = .046$], and TMT B was significantly faster in the (+) "Other" group than the No fall Group [$t(28.057) = 3.331$, $p = .002$]. Other differences on cognitive variables were not significant between groups.

Regarding impulsiveness/ICD variables, the BIS-11 was significantly higher in the (+) Freezing group [$t(33) = 2.643$, $p = .012$], (+) Festination group [$t(32) = 2.718$, $p = .011$], (+) Turn Balance group [$t(40) = 2.477$, $p = .018$], and (+) Stand Balance group [$t(37) = 2.664$, $p = .011$] than in the No Fall group. The QUIP-RS ICD score was significantly higher in the (+) Freezing group [$t(34) = 2.320$, $p = .026$], (+) Festination group [$t(17.591) = 2.077$, $p = .053$], and the (+) Stand Balance group [$t(38) = 2.178$, $p = .036$]. The QUIP-RS Total score was significantly higher in the (+) Freezing group [$t(34) = 2.939$, $p = .006$], (+) Turn Balance group [$t(41) = 2.235$, $p = .031$], and the (+) Stand Balance group [$t(38) = 2.610$, $p = .013$]. Subjects were more likely to be taking a 2nd generation dopamine agonist in the (+) Other group than the No Fall group [$X^2(1, N = 32) = 7.446$, $p = .006$].

Regarding balance confidence, all fall groups (except [+] Other) were significantly lower on the ABC than the No Falls group [(+) Freezing $t(33) = 2.643$, $p = .012$; (+) Festination $t(32) = 4.229$, $p = <.001$; (+) Orthostatic Hypotension $t(35) = 3.514$, $p = .001$; (+) Trip/Slip $t(33) = 2.176$, $p = .037$; (+) Turn Balance $t(40) = 4.442$, $p = <.001$; (+) Stand Balance $t(37) = 4.035$, $p = <.001$].

Regarding disease characteristics variables, disease duration was significantly longer among those in the (+) Freezing group than the No Falls group [$t(35) = 2.959$, $p = .006$]. For

postural instability, all fall groups (except [+] Other) were significantly different than the No Falls group [(+) Freezing $X^2(1, N = 35) = 17.764$, $p = <.001$; (+) Festination $X^2(1, N = 35) = 14.287$, $p = <.001$; (+) Orthostatic Hypotension $X^2(1, N = 37) = 8.397$, $p = .004$; (+) Trip/Slip $X^2(1, N = 36) = 5.202$, $p = .023$; (+) Turn Balance $X^2(1, N = 42) = 18.624$, $p = <.001$; (+) Stand Balance $X^2(1, N = 39) = 15.649$, $p = <.001$]. Age was not significantly different between groups.

CHAPTER SIX
Discussion

FINDINGS

Cognition and Falls

Overall performance on cognitive measures of interest was mostly within the average range. Demographically adjusted performance on BD, DS, CVLT-II Learning, and CVLT-II LDFR were similar to the general population. Raw scores were used for TMTB and ROCF Copy, making assertions about relative performance on these measures more challenging; however, demographically adjusted norms provided by Heaton, Miller, Taylor, and Grant (2004) were used to examine TMTB performance. According to these norms, the current sample performed one standard deviation below the mean overall, (*Mean* T score = 40.0; *SD* = 14.8), which is on the cusp of mild impairment according to Heaton's et al. (2004) criteria. This implies that the current sample as a whole demonstrated a relative weakness in mental flexibility, which has been shown to be an area regularly impaired in PD patients (Pillon et al., 2001). However, the sample as a whole was mostly non-impaired on the cognitive measures in this study.

Contrary to prediction, no significant differences ($p \leq .05$) were detected between fall risk groups for any of the cognitive measures. The variable that most closely approached a significant difference between groups was CVLT-II Learning ($p = .14$); however, learning in each group was within the average range and group differences were neither statistically nor clinically meaningful. The results of the regression analyses echoed those of the group comparisons, as only the CVLT-II Learning was kept in the stepwise logistic model ($p = .14$). Findings from both the group comparison and logistic regression analyses do not support Hypotheses One and Two, which predicted the utility of measures of visuospatial ability (BD and ROCF Copy), mental flexibility (TMTB), and attention (DS) in discriminating the High Fall Risk group from the Low

Fall Risk group. Furthermore, it was hypothesized that measures of learning and memory (CVLT-II Learning and CVLT-II LDFR) would not differ between groups or predict fall risk.

These findings are inconsistent with those from previous studies examining relationships between cognition and falls. General cognitive impairment and dementia are known risk factors for falls, and impaired attention and visuospatial abilities have been linked with increased fall risk among older adults (Anstey et al., 2006; Buchner & Larson, 1987; Liu-Ambrose et al., 2008; Rubenstein et al., 1994; Springer et al., 2006; van Doorn et al., 2003). In addition, executive dysfunction has been implicated as having a relationship with freezing of gait among PD patients (Amboni et al., 2008; Naismith et al., 2011; Vandenbossche et al., 2011). Furthermore, pilot data examining falls among PD subjects who were candidates for deep brain stimulation surgery showed that fallers performed significantly worse on the measures used in this study than non-fallers (Denney et al., 2014).

One potential explanation for this unexpected finding could relate to the current sample's high education level (mean = 15.4). None of the cognitive variables were adjusted for education, and individuals with higher intelligence are known to do better in school and complete more years of education (Brody, 1997; Gustafsson & Undheim, 1996). With the current sample likely having a higher than average level of intelligence, a phenomenon known as cognitive reserve may be clouding the impact that disease is having on cognitive changes. Put simply, the theory of cognitive reserve posits that individuals with higher reserve capacities, due to higher intelligence and education attainment levels, are more able to sustain greater brain damage before demonstrating functional deficits. Previous work has identified education levels below 12 years to be highly predictive of dementia in PD (Odds Ratio = 21), with higher levels of education modifying the risk of cognitive decline (Glatt et al., 1996). Therefore, the current sample's high

education level may preclude broadly generalizable conclusions related to cognitive vulnerabilities in PD and how they relate to falls.

Results from the current sample indicate that individuals with PD who fall do not have a distinct cognitive profile from those who do not fall. Learning most closely approached a significant difference between fall groups and was kept in the logistic regression because of the higher level of accepted significance ($p < .20$) within the model. While the significance level was not robust, this finding implies that better learning could offer a protective factor against fall risk. As High Fall Risk group inclusion was operationalized by report of multiple falls, it stands to reason that those individuals who are falling may fail to adapt to their circumstances (i.e., learn) to reduce future falls. PD patients with higher learning capabilities may be more able to accommodate to physical changes they are experiencing from the progression of their disease. Subtle adjustments in their behaviors, incorporated from their ability to learn from their ongoing physical changes, could make them more able to adapt to their disease course and less likely to fall.

Impulsiveness/ICDs and Falls

Presence of a 2nd generation dopamine agonist was included in the analyses because of the presumed involvement these agents have in the high ICD incidence rates among PD patients. As impulsivity has been identified as a possible fall risk factor and been shown to moderate the development of ICDs, 2nd generation dopamine agonists were incorporated to account for their possible role in exacerbating impulsiveness/ICD behaviors. Overall, 42% of subjects were prescribed a 2nd generation dopamine agonist at the time of their neuropsychological evaluation, though there was no significant difference between fall groups. Additional analyses comparing

QUIP-RS and BIS-11 scores between subjects who were on a 2nd generation dopamine agonist revealed no significant differences.

The overall level of impulsiveness, as self-reported on the BIS-11, was within the range of normal (i.e., total score of 52 – 71) (Stanford et al., 2009). Stanford et al. (2009) stated that raw scores on the BIS-11 exceeding 71 are reflective of individuals considered "highly impulsive," while scores less than 52 reflect those that are "over-controlled" or not honest in their responding. Group comparisons for impulsiveness revealed that the High Fall Risk group reported significantly higher levels of impulsiveness than the Low Fall Risk group; however, the *mean* scores for both groups were well within the range of normal limits. This indicates that while being "highly impulsive" is not a requisite for increased likelihood of falling, there appears to be a relationship such that higher levels of self-reported impulsiveness are associated with a history of repeated falls among individuals with PD. It is possible that PD patients who have greater levels of self-control, or those that are more cautious, are less likely to react carelessly and/or to put themselves into risky or compromised circumstances that increase chances of falling. These findings support Hypothesis 3 and are in keeping with a study showing a positive association between trait impulsivity and fall risk in PD (Smulders, Esselink, Cools, Bloem, 2014). It also further supports previous studies identifying associations between general fall risk and various forms of impulsivity (Harrison et al., 2010; Moeller et al., 2001; Rapport et al., 1993; Wylie et al., 2012).

Overall levels of ICD-related behaviors (including punding/hobbyism and dopamine dysregulation syndrome behaviors), as reported on the QUIP-RS Total Score, were consistent with previously described normative data (Weintraub et al., 2012). However, overall reported ICD behaviors, which includes only compulsive gambling, buying, sex, and eating, was equal to

the optimal cutoff score for combined ICD (i.e., $\geq$ 10). The combined ICD score sums the scores from each of the established ICDs (gambling, buying, sex, eating) and does not necessarily suggest that a formal ICD is present; however, higher scores are indicative of ICD-related behaviors across multiple activities. When examined for group differences, the High Fall Risk group reported significantly higher levels of ICD-related behaviors on both the ICD Total Score and the QUIP-RS Total score (which combines the ICD Total score with punding/hobbyism and dopamine dysregulation syndrome behaviors). These findings also support Hypothesis 3 and reveal ICD-related behavior to be more common among PD subjects with a recent history of repeated falls. To our knowledge, the relationship between ICD-related behaviors and falls has not yet been examined, making this study the first to do so. Given the higher prevalence of ICDs among patients with PD, the identification of a relationship between ICD-related behaviors and falls could represent a valuable reference for clinicians treating patients with PD. Additional ROC analyses indicate that when screening for ICDs with the QUIP-RS, a Total Score of 13 may be helpful in identifying which patients are more likely to fall.

For the logistic regression analysis, only the BIS-11 was kept in the model among the impulsiveness/ICD variables as being significantly associated with fall risk. This indicates that trait impulsiveness is more significantly predictive of falling than ICD-related behaviors. Previous studies have identified premorbid impulsivity traits to moderate the development of ICDs, and the current results could be reflective of this phenomenon (Blanco et al., 2012; Fuentes et al., 2006; Michalczuk et al., 2011). While screening for ICD-related behaviors may be more clinically relevant for PD patients given the high prevalence of these destructive behaviors among this population, assessing for trait impulsiveness could be more informative when identifying PD patients at higher risk of falls.

Parkinson Disease Characteristics and Falls

Overall, 47% of the sample showed some indication of postural instability (i.e., HY stage $\geq$ 2.5), the majority of which were in the Fall group (83%). The overall sample *mean* disease duration was 8.6 years and was significantly higher among the subjects in the High Fall Risk group. Meanwhile, age did not significantly differ between fall groups. These results partially support Hypothesis 5, which predicted each variable would be higher in the High Fall Risk group. Increased risk of falling with disease progression, particularly disease duration and postural instability, is a well-established axiom in PD (Ashburn et al., 2001a; Koller et al., 1989; Landers et al., 2008; Robinson et al., 2005). Current results are consistent with this, indicating that progression of disease-specific characteristics, irrespective of age, are associated with fall risk. Stepwise logistic regression analyses mirrored the group comparison findings, supporting Hypothesis 6. Unsurprisingly, presence of postural instability was the most significant variable to predict fall risk, followed by disease duration, while age did not predict fall risk.

Balance Confidence and Falls

Overall *mean* balance confidence (73.9) was virtually identical to previously reported levels for PD patients (Mak, Pang, & Mok, 2012). As expected, balance confidence was significantly lower among PD subjects with a recent history of falls and significantly predicted High Fall Risk group membership in logistic regression analysis. These findings support Hypothesis 7 and are consistent with outcomes from previous studies regarding balance confidence in PD (Mak & Pang, 2009a, 2009b; Mak et al., 2012; Pickering et al., 2007). Previously, a raw score of 69 (AUC = 0.82, sensitivity = 93%, specificity = 69% has been implicated as a good cutoff for identifying PD fallers from non-fallers (Mak, Pang, & Mok, 2012). ROC analysis of the ABC discriminating between the High Fall Risk and Low Fall Risk

groups in the current study indicates that a raw score of 69 yielded similar sensitivity (79%) but lower specificity (55%). With the current sample, a raw score of 79 was a better cutoff score (AUC = 0.77, $p < .001$; sensitivity = .72%, specificity = .68%) for discriminating between fall groups. This finding suggests that while the ABC is consistently good at discriminating between fallers and non-fallers in PD, optimal cutoff scores are likely to vary between populations and should be used cautiously.

Combined Model and Model Comparisons

All variables that significantly predicted falls from the previous stepwise logistic regression models (cognitive, impulsiveness/ICD, disease characteristics, and balance confidence) were entered into a combined stepwise logistic regression model. This included the CVLT-II Learning, BIS-11, (+/-) postural instability, disease duration, and ABC score variables. Perhaps unsurprisingly, results of the logistic regression revealed presence of postural instability to be the most significant predictor among these variables. However, in the presence of the other noted variables, disease duration and the ABC score were not kept in the model, while the BIS-11 ($p = .11$) and CVLT-II Learning ($p = .12$) were retained in the model. This indicates that fall risk is better predicted when combining variables from these various areas than when using them in isolation. However, balance confidence and disease duration appear to lose their predictive ability when combined with impulsiveness and learning. There likely is a significant association between postural instability and lower balance confidence, eliminating the utility of assessing balance confidence when postural instability is already identified for a given patient.

The degree to which the combined model added predictive ability compared to the domain-specific models was examined using two different methods. Because the ABC was not retained in the combined model, the Hanley and McNeil (1983) method was used to compare

ROC curves using predicted scores derived from the models. The combined model was compared to the cognitive, impulsiveness/ICDs, and disease characteristics models using *net reclassification improvement* (*NRI*) analyses (Pencina et al., 2008). Results revealed that the combined model better predicted fall risk than any of the other models, as measured by both *ROC area under the curve* (*AUC*) and predictive accuracy; however, differences reached significance only in comparison with the disease characteristics and cognitive models when using the NRI analyses. The combined model was not significantly better at predicting fall risk than the balance confidence or the impulsiveness/ICD models with the respective Hanley and McNeil and *NRI* analyses.

Examination of the *NRI* results between the impulsiveness/ICD and combined models showed that the lack of a significant difference in fall risk prediction was due to five subjects being incorrectly moved (down) into the Low Fall Risk group (i.e., false negatives), whereas only two subjects correctly moved (up) to the High Fall Risk group (i.e., true positives) when the learning and postural instability variables were added to the impulsiveness variable for comparison. However, nine subjects correctly moved (down) into the Low Fall Risk group (i.e., true negative) while no subjects were incorrectly moved (up) into the High Fall Risk group (i.e., false positive) when learning and postural instability variables were added to the impulsiveness variable. The number of subjects that correctly moved into their respective fall risk group when learning and postural instability predictors were added to the impulsiveness predictor equaled six subjects. This demonstrates a more accurate rate of fall risk prediction for the combined model; however, the higher rate of false negatives for the combined model make it less than ideal in clinical practice when failure to identify those at higher risk of falling portends more damaging consequences than conservatively entering patients with lower fall risk into a fall treatment plan.

Despite being among the most significant predictors of fall risk in isolation used in the present study, the ABC was not retained in the combined logistic regression. This is likely due to having an objective measure of postural instability in the model, which better or more accurately captured balance difficulty than subjective balance confidence. *ROC AUC*s between the balance confidence model (.74) and the combined model (.83) were compared using the Hanley and McNeil (1983) approach, revealing an insignificant difference ($p = .20$). This indicates that while the ABC was not kept in the combined model, and therefore not among the best predictors when combined with the other present measures of seemingly disparate constructs, it is able to hold up relatively well in comparison to the more complex model involving cognitive, impulsiveness, and postural instability variables. This finding further supports previous studies that have identified balance confidence, as measured by the ABC, a substantial factor when assessing for fall risk among individuals with PD (Adkin et al., 2003; Mak & Pang, 2009a, 2009b). When formal assessment of postural instability or other detailed assessment is not feasible, the ABC could be used as a good screening measure for identifying PD patients at greater risk for falling.

Overall, the results of the model comparisons appear to support Hypothesis 8, which predicted an improvement in fall risk prediction when combining noted variables of interest, as compared to their predictive ability in isolation. However, not all improvements were significant ($p < .05$) with the respective comparison methods, making the findings somewhat complicated. When comparing the models from an absolute perspective, the combined model was "better" than all others by every metric (*ROC AUC*, group prediction accuracy, net improvement of group reclassification). However, *NRI* comparisons were nonsignificant for the impulsiveness/ICD model due to a higher number of false negatives for the combined model, and the Hanley and McNeil (1983) method showed a nonsignificant difference in *ROC AUC* between the combined

model and the balance confidence model. Differences in fall risk group prediction ability between the combined and the cognitive models as well as between the combined and the disease characteristics models were significant with *NRI* analyses (see Table 10). These findings partially support the notion that combining cognitive, impulsiveness/ICD, and disease characteristics variables significantly improves identification of high fall risk PD patients from low fall risk PD patients than any of the variables in isolation.

Reported Causes of Falls

In an attempt to identify patterns in the predictor variables of interest as they pertained to causes of falls, subjects who reported at least one fall were grouped based on the endorsed reason of their fall(s) (as reported on the PDFQ). Subjects who reported multiple falls were able to endorse more than one reason for falling, causing overlapping subjects in the fall groups. All fall groups were compared to the subjects who reported zero falls on the PDFQ. This method resulted in small and uneven *n*s for each group, therefore making these findings very preliminary and exploratory in nature.

There are scant obvious patterns in cognitive performances across the reported reasons for falling. There were only three comparisons identified as significantly different from the No Falls group (lower CVLT-II LDFR in the Tripping/Slipping group; lower CVLT-II Learning in the Standing Balance group; and *faster* TMTB time in the Other group). However, each of these differences are isolated within their respective groups, likely making them an artifact of chance given the high number of uncorrected comparisons made. Perhaps it is worth noting that, while only the TMTB difference was significant, performance was better on all cognitive measures in the Other group than in the No Falls group. It is unclear what implications this finding poses; however, these “Other” fallers could represent a subset of PD patients who are not experiencing

typical gait disturbance seen in PD. Their falls may not be due to any disease-related factors, and, therefore, their data may be distorting the presently observed impact of cognitive factors on falls among individuals with PD. Further study is needed for clarification; however, future studies aiming to examine causes of falling in PD could consider excluding data from subjects who fall due to non PD-related factors.

Impulsiveness/ICD results across reasons for falling revealed a clearer depiction than the cognitive results. The Freezing and difficulty with Standing Balance groups reported higher levels of impulsiveness and ICD-related behaviors than the No Falls group for all three variables (BIS-11, QUIP-RS ICD Total, and Total QUIP-RS Score). Meanwhile, the Festination (BIS-11 and QUIP-RS ICD) and difficulty with Turning Balance (BIS-11 and Total QUIP-RS Score) groups reported higher levels of impulsiveness on two of the measures. All four of these groups represent common reasons for falling in PD. The remaining groups of reported reasons for falling, Orthostatic Hypotension, Tripping/Slipping, and Other, had no significant differences from the No Falls group on measures of impulsiveness/ICD-related behaviors. Orthostatic hypotension is also a known PD-related event; however, falls that occur in the context of orthostatic hypotension are less likely to ensue because of judgment errors or risk-taking behaviors. All of the groups with elevated impulsiveness/ICD scores are gait-related disturbances that are known sequelae of PD and seemingly require consistent monitoring by the individual to ensure compromised situations do not occur. These results imply that impulsiveness/ICD related behaviors may be a particular risk factor for PD patients who fall because of gait disturbances that include freezing, festination, and standing and turning balance problems.

Significant differences were observed between all fall groups (except the Other group) and the No Falls group in terms of balance confidence as measured by the ABC. This finding

further supports the notion that the Other group consists of a subset of PD patients who fall because of uncommon and typically innocent factors, given the repeated observation that balance confidence is lower among individuals who fall (Adkin et al., 2003; Mak & Pang, 2009a, 2009b; Pickering et al., 2007).

Aspects of disease characteristics were different among the falling groups when compared to the No Falls group. Age was not different for any of the comparisons. Disease duration was significantly longer for the Freezing group. This is unsurprising given that freezing of gait is more common among patients with advanced PD (Giladi et al., 2001). Postural instability was significantly more common for all of the falling groups than the No Falls group, except for the Other falls group. Once again, there is an implication that those PD patients who fall for a reason not pre-designated on the PDFQ are different from the patients who report falls due to disease factors known to increase fall risk. With this finding, there is the added power of having an objectively assessed risk factor of for falls (postural instability as determined by HY score made by movement disorders neurologists) to support the notion that the Other group fallers may need to be excluded or studied separately in order to better understand how risk factors relate to falling in PD.

Overall, the results at least partially support all but one of the hypotheses for this study. Impulsiveness/ICD-related behaviors, disease characteristics, and balance confidence were more problematic for the High Fall Risk group than the Low Fall Risk group, while cognitive performance was not different between groups. All of the examined domains contributed at least one variable that was predictive of High Fall Risk group membership. The combined model was significantly better at predicting fall risk than the cognitive and disease characteristics models, while there was not a significant improvement in fall risk prediction by the combined model over

the balance confidence and impulsiveness models. Results from exploratory analyses on the PDFQ revealed that some differences in impulsiveness/ICD-related behaviors, balance confidence, and disease characteristics may exist between individuals who endorse falls that are related to Parkinson disease-state factors and those who fall for other reasons.

IMPLICATIONS

The present findings confirm that individuals with PD who fall are measurably different across a number of disease-related and behavioral factors from those who do not fall. Cognitive factors appear to play a more limited role. The findings reflect an incomplete understanding of the contribution of cognition to falls in PD, evidenced by current results that are inconsistent with previous findings. As discussed above, these discrepant findings could be partially attributable to the uniquely high education level of the current sample, potentially invoking a higher cognitive reserve effect known to occur among more intelligent and highly educated individuals, such that they are able to sustain greater brain dysfunction before demonstrating deficits (Stern, 2002). Unsurprisingly, disease characteristics, particularly postural instability, were most predictive of fall risk; however, higher trait impulsiveness and ICD-related behaviors demonstrated discriminability between high fall risk and low fall risk in PD. Likewise, lower rates of balance confidence was a good predictor of fall risk in PD. However, when combined with other cognitive, impulsiveness, and disease characteristics variables, balance confidence loses its predictive ability. When other means of assessing fall risk are not available, screening with the ABC appears to be an efficient and valid method of identifying individuals with PD at a higher risk of falling with a recommended cutoff of 79 (Mak, Pang, and Mok [2012] reports an optimal cutoff of 69). Results were mixed when comparing the combined model to the smaller models, as fall risk prediction was significantly improved over the cognitive and disease

characteristics models but not over the balance confidence and impulsiveness models. Overall, findings indicate that falls in PD are a multi-determined behavior involving both disease-specific state and personality/behavioral trait components.

Treatment

The first step in treating or preventing falls among individuals with Parkinson disease is identifying those with Parkinson disease. This will typically involve a thorough workup with a neurologist and include an examination of cardinal motor sequelae, including whether a patient demonstrates signs of postural instability. In the current study, postural instability was the variable most predictive of fall risk. Therefore, fall risk is already largely accounted for in standard clinical care. However, with the knowledge that one can better predict fallers from non-fallers with measures of impulsiveness and learning, clinicians may consider enhancing their clinical routine by adding such measures as a means of preventative screening.

The question becomes, however, whether the improvement in fall risk prediction, as demonstrated from these results, is significant enough to warrant a change in clinical practice. The CVLT-II is a sophisticated measure of learning and memory and requires training in psychometric testing to properly administer. In addition, administration of the measure can be lengthy, adding to an already full set of responsibilities for clinicians. These considerations make adding the CVLT-II to a routine PD assessment rather implausible. While the CVLT-II may be a typical measure included in neuropsychological assessment in PD, not all PD patients warrant a referral for formal testing. Further examination of the relationship between cognition and falls in PD is necessary in order to determine a feasible method of incorporating cognitive testing into a fall risk assessment.

While the CVLT-II can be time consuming, the BIS-11 can be completed relatively quickly (~5 minutes) and without a specially trained examiner. Patients would be able to take the questionnaire while in a clinic waiting room without interfering with an established routine. An online version may also be useful to help identify patients at higher risk before they even arrive to their appointment. Scores at or above 60 on the BIS-11 may be a reasonable cutoff for identifying those at higher risk of falls (ROC AUC = 0.70, $p < .01$; Sensitivity = 78%; Specificity = 63%). Patients identified for being at greater fall risk may then be entered into a fall risk clinical program earlier than they might otherwise as a preventative measure.

Much more stands to be investigated in order to identify means of incorporating assessment of cognitive and behavioral risk factors into fall risk treatment plans. The current study provides evidence that these are contributing areas of influence for fall behaviors; however, a practical set of recommendations for physicians that routinely treat individuals with PD remains elusive. Nevertheless, there appears to be utility in supplementing standard clinical care with brief measures of impulsiveness and/or ICD-related behaviors to identify PD patients at greater risk of falling. Clinicians are encouraged to consider adding the BIS-11 or the QUIP-RS to their practice when needing to determine a given PD patient's fall risk.

Future Directions

As with all scientific research, study replication is necessary for helping to confirm the validity of any set of findings. This is particularly true with this study, given the relatively small sample size, exploratory nature of the analyses, and inclusion of a newly developed measure. With the PDFQ, this study used a newly developed measure, which retrospectively identified fallers from non-fallers in a sample of PD patients. A previous study examining the accuracy of self-reported falls revealed an 84% agreement between retrospective self-report and a

prospective calendar report of falls over a six month period among elderly adults aged 70 and older (Mackenzie, Byles, D'Este, 2006). This suggests that clinicians can rely on patients' self-report of falls with relative confidence in most cases within a six-month period, supporting the use of the PDFQ as a measure of fall history. The PDFQ additionally included a set of items intended to identify the reasons behind falls that occurred, and the reliability to which patients can properly identify reasons for falls has not been examined. Therefore, there is merit in investigating the accuracy to which PD patients can correctly identify the reasons for their falls, as reported on the PDFQ. Future studies with larger samples will also be useful in replicating the methods of the current study for the sake of investigating the role that cognitive and behavioral factors play in PD-related falls (freezing of gait, festination of gait, impaired balance, and orthostatic hypotension). Future investigation could also replicate the current method but with a longitudinal approach, using a prospective calendar report of falls rather than a retrospective report utilized in the current study.

Investigating subsamples among those who report falls may also reveal fruitful advances. The current study operationally defined fallers as those who endorsed at least two falls in the previous six months. While there is support for this method of identifying those at higher risk of falls (Ashburn et al., 2001b), there may also be utility in examining differences between absolute non-fallers versus those who fall in terms of their cognitive and behavioral characteristics. Another interesting sub sample includes those subjects who have postural instability but do not report falls. There were six individuals in the current study who demonstrated postural instability but did not report a recent fall. With a larger sample size, there may be utility in investigating the characteristics of these individuals to determine the veracity of their reported fall history and identify any unique qualities they possess that keep them from falling despite having the highest

risk factor. With a larger sample size, there may also be utility in replicating the current study with a more robust measure of PD severity, such as the Unified Parkinson's Disease Rating Scale.

Another area of future study could include investigating the role that anosognosia has on factors examined in the present study. Anosognosia is the "complete or partial lack of awareness of different neurological . . . and/or cognitive dysfunctions" (Bottini, Paulesu, Gandola, et al., 2010, p. 17). This phenomenon is known to occur with a number of illnesses or injuries that affect both hemispheres in the brain (Prigatano, Maier, & Burns, 2010). Reports of frank anosognosia in PD are relatively uncommon (McGlynn & Kaszniak, 1991). However, patients often appear to have diminished awareness of their motor disorders and their psychosocial consequences. A study conducted by Maier, Prigatano, Kalbe, et al. (2012) determined that 61% of a PD sample demonstrated signs of impaired self-awareness. Furthermore, they concluded that higher severity of impaired self-awareness significantly correlated with higher postural instability and gait difficulties. As this study was heavily reliant on measures of self-report across several areas susceptible to differences in self-awareness, incorporating a method of accounting for reduced insight into a replicated version of the present study appears to be a valuable step in better understanding the relationships between cognitive and behavioral factors and PD-related falls.

LIMITATIONS

Several considerations should be taken into account when interpreting the findings of this project. The current study used a relatively small sample size ($N = 64$), leading to a higher threshold for accepted significance (p-value = .20) on logistic regression analyses. While this method has support for model building, Hosmer and Lemeshow (1989) caution that this

approach has the disadvantage of including variables of questionable importance, thereby increasing the risk of Type I error, in which some significant results may have occurred by chance. Furthermore, findings concerning the differences in variables of interest among the reasons for falling as endorsed on the PDFQ are very preliminary, as small sample sizes precluded more detailed exploration of the data.

Another issue to note in the current study is the heavy reliance on self-report for several of the variables used in the prediction of falls. Of foremost consideration is the use of subjects' recollection of falls experienced as the dependent variable in the study. While there is support for the accuracy of self-reported falls (Mackenzie et al., 2006), caution must be used when making conclusions about each predictive variable and their respective contribution to fall risk. Similarly, tests of impulsiveness, ICD-related behavior, and balance confidence were self-report measures and subject to the same caution used when interpreting subjective claims. This may be particularly true for a neurological sample that is more likely to demonstrate insight impairments. Insight was not accounted for in the current study and could have affected the findings on self-report measures.

Finally, the current sample was highly educated (M = 15.4 years), which may affect the generalizability of aspects of the results, as education has been shown to modify cognitive impairment in PD (Glatt et al., 1996). Education did not differ between the fall groups and was therefore not included in the logistic regression analyses with other variables to predict fall risk. Overall, the current sample was cognitively non-impaired, which may affect the generalizability of the findings regarding cognition.

CONCLUSION

The current study indicates that fall risk among PD patients can be predicted with cognitive, impulsivity, and disease characteristics variables with good accuracy. Adding formal cognitive testing to routine clinical care may not be feasible; however, clinicians are encouraged to consider incorporating brief measures of impulsiveness/ICD-related behaviors into their clinical practice for better identifying PD patients at greater risk of falling. Future investigation is needed to identify ways to integrate cognitive assessment into routine fall risk assessment. This was the first study to combine cognitive and impulsiveness/ICD variables with disease-related characteristics for investigation of their isolated and collective contribution to falls in PD. Results support a model of fall risk prediction that includes presence of postural instability, impulsiveness, and learning, as combining these elements significantly improved the identification of individuals with PD who are at greater risk of falls. Investigation of sub samples of fallers (e.g., those due to freezing, festination, orthostatic hypotension, and balance difficulties) is warranted to better understand cognitive and behavioral factors on PD-related falls.

TABLES

Table 1. *Demographic Characteristics*

	(N = 64)	
	M (SD)	*Range*
Age	66.6 (9.7)	40-87
Education	15.4 (2.2)	9-20
Race n (%)		
African American	2 (3%)	
Asian	4 (6%)	
Hispanic	2 (3%)	
Caucasian	56 (88%)	
Sex *n* (% Male)	52 (81%)	
Handedness *n* (% Right)	56 (88%)	

Table 2. *Descriptive Statistics for Cognitive, Impulsivity/ICD, Balance Confidence, Disease Characteristic, and Fall Variables*

Variable	*M*	*SD*	*Median*	*Range*
Cognitive				
Block Design T (*N* = 60)	48.2	9.4	47.0	30-73
Digit Span T (*N* = 63)	48.2	9.2	50.0	27-67
TMT B seconds (*N* = 62)	145.0	82.0	120.0	26-300
TMT B T (*N* = 62)	40.1	14.8	37.5	13-79
ROCF Copy raw (*N* = 60)	29.7	5.6	32.0	14-36
CVLT-II Learning T (*N* = 63)	49.1	11.5	50.0	23-73
CVLT-II LDFR T (*N* = 63)	48.7	11.0	50.0	25-70
Impulsivity/ICD				
BIS-11 (N = 62)	61.2	10.0	61.5	41-82
QUIP-RS ICD Score (*N* = 63)	10.8	8.8	9.0	0-37
QUIP-RS Total Score (*N* = 63)	20.9	16.0	18.0	0-63
(+) 2nd Gen. DA Agonist (*n*, %)			27 (42)	
Balance Confidence				
ABCs (*N* = 60)	73.9	19.8	79.5	23-99
Disease Characteristics				
Disease Duration (years)	8.6	5.6	8.0	1-30
(+) Postural Instability[a] (*n*, %); (*N* = 62)			29 (47)	
Falls				
Number of Falls (*median, range)*	1.5			0-200
(+) Fall (*n*, %)			40 (63)	
(+) > 1 Fall (*n*, %)			32 (50)	
Falls due to (N = 62):				
Freezing (*n*, %)			13 (21)	
Festination (*n*, %)			12 (19)	
Orthostatic Hypotension (*n*, %)			15 (24)	
Tripping/Slipping (*n*, %)			13 (21)	
Turning Balance Difficulty (*n*, %)			20 (32)	
Standing Balance Difficulty (*n*, %)			17 (27)	
Other (*n*, %)			8 (13)	

Notes: N = 64 unless otherwise specified; Data are raw scores unless otherwise specified; TMT B = Trail Making Test B; ROCF = Rey-Osterrieth Complex Figure Copy; CVLT-II = California Verbal Learning Test-2; BIS-11 = Barratt Impulsiveness Scale-11; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale;ICD Total = Impulsive-Compulsive Disorders summed total score; (+) 2nd Gen. DA Agonist = percentage of Ss on a 2nd generation dopamine agonist; ABCs = Activity-specific Balance Confidence Scale

[a.] Determined via Hoehn and Yahr staging scale $\geq$ 2.5.

Table 3. *Demographic Characteristics for Each Fall Risk Group*

	0-1 Fall (n = 32)		*>1 Fall (n = 32)*	
	M (SD)	*Range*	*M (SD)*	*Range*
Age	65.1 (10.3)	40-80	68.0 (9.0)	50-87
Education	15.7 (2.4)	12-20	15.2 (2.0)	9-20
Race n (%)				
African American	1 (3)		1 (3)	
Asian	2 (6)		2 (6)	
Hispanic	2 (6)		0 (0)	
White	27 (84)		29 (91)	
Sex (*n*, % Male)	26 (81)		26 (81)	
Handedness (*n*, % Right)	27 (84)		29 (91)	

Note. No significant differences were observed between groups

Table 4. *Descriptive Statistics of Predictor Variables for Each Fall Risk Group*

	0-1 Fall		*>1 Fall*		*p*	*Effect Size (d)*
	M	*(SD)*	*M*	*(SD)*		
Cognitive						
Block Design T	47.7	(9.8)	48.7	(9.2)	0.68	
Digit Span T	48.4	(8.8)	48.0	(9.8)	0.88	
TMT B seconds	140.0	(86.1)	150.0	(78.7)	0.63	
TMT B T	40.5	(16.2)	39.7	(13.5)	0.83	
ROCF Copy raw	30.4	(5.6)	29.1	(5.7)	0.35	
CVLT-II Learning T	51.3	(11.6)	47.0	(11.1)	0.14	
CVLT-II LDFR T	50.0	(10.5)	47.3	(11.5)	0.33	
Impulsivity/ICD						
BIS-11	58.0	(9.8)	64.2	(9.4)	0.01	0.65
QUIP-RS ICD Total	8.3	(7.2)	13.2	(9.7)	0.03	0.57
QUIP-RS Total Score	15.9	(13.1)	25.7	(17.2)	0.01	0.64
(+) 2nd Gen. DA Agonist (%)	38		48		0.38	
Balance Confidence						
ABCs	82.7	(15.7)	65.6	(19.9)	0.001	0.95
Disease Characteristics						
Disease Duration (years)	6.8	(4.1)	10.4	(6.3)	0.01	0.68
(+) Postural Instability (%)	19		74		<.001	0.55[a]

Notes: Data are raw scores unless otherwise noted. TMT B = Trail Making Test B time in seconds; ROCF = Rey-Osterrieth Complex Figure Copy; CVLT-II California Verbal Learning Test-2; LDFR = Long Delay Free Recall scores; BIS-11 = Barratt Impulsiveness Scale-11; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; ICD Total = Impulsive-Compulsive Disorder summed total score; (+) 2nd Gen. DA Agonist = percentage of Ss on a 2nd generation dopamine agonist; ABCs = Activity-specific Balance Confidence Scale

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Table 5. *Logistic Regression Predicting Fall Risk with Cognitive Measures*

Model	*Measure*	*B*	*S.E.*	*Wald's p*	*Odds Ratio*	*95% C.I.*		*Hosmer & Lemeshow*
						Lower	*Upper*	
Entry (N = 59)	Block Design	0.026	0.039	.496	1.027	0.952	1.108	.411[a]
	Digit Span	-0.003	0.040	.934	0.997	0.921	1.079	
	TMT B	-0.002	0.005	.688	0.998	0.989	1.007	
	ROCF Copy	-0.050	0.056	.370	0.951	0.852	1.061	
	CVLT-II Learning	-0.057	0.047	.229	0.945	0.861	1.036	
	CVLT-II LDFR	0.013	0.047	.776	1.014	0.924	1.112	
Reduced Stepwise (N = 63)	CVLT-II Learning	-0.034	0.023	.142	0.967	0.924	1.011	.843[a]

Notes: df = 1 for all variables in each model. TMT B = Trail Making Test B time in seconds; ROCF = Rey-Osterrieth Complex Figure Copy; CVLT-II California Verbal Learning Test-2; LDFR = Long Delay Free Recall

a. The data are an excellent fit for the model.

Table 6. *Logistic Regression Predicting Fall Risk with Measures of Impulsiveness, ICD-related Behaviors, and (+/-) 2nd Generation Dopamine Agonist Medication*

Model	*Variable*	*B*	*S.E.*	*Wald's p*	*Odds Ratio*	*95% C.I.*		*Hosmer & Lemeshow*
						Lower	*Upper*	
Entry (N = 61)	(+) 2nd DA Agonist	0.651	0.569	.253	1.917	0.628	5.853	.723[a]
	QUIP-RS Total	0.028	0.021	.184	1.028	0.987	1.072	
	BIS-11	0.042	0.033	.207	1.043	0.977	1.112	
Reduced Stepwise (N = 62)	BIS-11	0.069	0.029	.017	1.071	1.012	1.133	.034[b]

Notes: df = 1 for all variables in each model. BIS-11 = Barratt Impulsiveness Scale-11; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale.

a. The data are an excellent fit for the model.

b. The data are not a good fit for the model.

Table 7. *Logistic Regression Predicting Fall Risk with Disease Characteristics*

Model	*Variable*	*B*	*S.E.*	*Wald's p*	*Odds Ratio*	*95% C.I.*		*Hosmer & Lemeshow*
						Lower	*Upper*	
Entry	(+) Postural Instability	2.156	0.656	.001	8.633	2.386	31.231	.716[a]
	Age	0.009	0.033	.784	1.009	0.947	1.076	
	Disease Duration	0.095	0.070	.174	1.100	0.959	1.262	
Reduced Stepwise	(+) Postural Instability	2.204	0.635	.001	9.059	2.608	31.463	.536[a]
	Disease Duration	0.093	0.069	.179	1.098	0.958	1.258	

Notes: $N = 62$. $df = 1$ for all variables in each model.
a. The data are a good fit for the model.

Table 8. *Logistic Regression Predicting Fall Risk with Combined Models*

Model	*Variables*	*B*	*S.E.*	*Wald's p*	*Odds Ratio*	*95% C.I.*		*Hosmer & Lemeshow*
						Lower	*Upper*	
Entry (N = 55)	(+) Postural Instability	1.288	0.943	.172	3.627	0.571	23.024	.302[c]
	Disease Duration	0.106	0.083	.201	1.112	0.945	1.309	
	ABCs	-0.016	0.027	.546	0.984	0.934	1.037	
	BIS-11	0.051	0.036	.159	1.052	0.980	1.129	
	CVLT-II Learning	-0.042	0.031	.165	0.958	0.903	1.018	
Reduced Stepwise (N = 59)	(+) Postural Instability	2.158	0.650	.001	8.656	2.422	30.930	.013[b]
	BIS-11	0.053	0.034	.112	1.055	0.988	1.127	
	CVLT-II Learning	-0.045	0.028	.117	0.956	0.905	1.011	

Notes: df = 1 for all variables in each model. ABCs = Activity-specific Balance Confidence Scale; BIS-11 = Barratt Impulsiveness Scale-11; CVLT-II California Verbal Learning Test-2.

c. The data are an acceptable but not ideal fit for the model.

b. The data are not a good fit for the model.

Table 9. *Area Under the Curve, Cutscores, and Accuracy of Models Predicting Fall Risk Group Membership*

	ROC						
				95% C.I.			
Reduced Models	*AUC*	*S.E.*	*p*[a]	*Lower Bound*	*Upper Bound*	*Best Cutscore*[b]	*Accuracy*
Cognitive	.636	.073	.072	.493	.779	0.49318	66.1%
Impulsiveness/ICD	.699	.071	.009	.561	.838	0.42139	72.9%
Disease Characteristics	.805	.056	<.001	.695	.916	0.69610	76.3%
Balance Confidence	.739	.068	.002	.606	.871	0.37773	72.2%
Combined	.831	.056	<.001	.721	.941	0.55824	83.1%

Notes: Cognitive model includes the California Verbal Learning Test-2 Learning T score; Impulsiveness/ICD model includes the Barratt Impulsiveness Scale-11; Disease Characteristics model includes postural instability and disease duration; Balance Confidence model includes the Activities-specific Balance Confidence Scale; The Combined model includes the California Verbal Learning Test-2 Learning T score, Barratt Impulsiveness Scale-11, and postural instability.

a. Asymptotic significance, under the nonparametric assumption

b. Cutscores are from the predicted values derived from each respective final logistic regression

Table 10. *Results of Net Reclassification Improvement Model Comparisons*

Reduced Cognitive Model vs. Reduced Combined Model

Cases that Changed Groups					*NRI*			
Group	*LR to HR (Up)*	*HR to LR (Down)*	*Group z*	*Group p*	*Total*	*S.E.*	*z*	*p*
Fall	9	4	1.387	0.166	0.339	0.159	2.138	0.032
No Fall	2	7	1.667	0.096				

Reduced Impulsiveness/ICD Model vs. Reduced Combined Model

Cases that Changed Groups					*NRI*			
Group	*LR to HR (Up)*	*HR to LR (Down)*	*Group z*	*Group p*	*Total*	*S.E.*	*z*	*p*
Fall	2	5	-1.133	0.257	0.210	0.136	1.547	0.122
No Fall	0	9	3.000	0.003				

Reduced Disease Characteristics Model vs. Reduced Combined Model

Cases that Changed Groups					*NRI*			
Group	*LR to HR (Up)*	*HR to LR (Down)*	*Group z*	*Group p*	*Total*	*S.E.*	*z*	*p*
Fall	3	0	1.732	0.083	0.134	0.067	2.000	0.046
No Fall	0	1	1.000	0.317				

Notes: High Fall Risk group $n = 30$; Low Fall Risk group $n = 29$. LR = Low Fall Risk group; HR = High Fall Risk group

Table 11. *Descriptive Statistics of Cognitive, Impulsiveness/ICD, Disease Characteristics, and Balance Confidence Variables across Reported Reasons for Falling on the Parkinson Disease Fall Questionnaire*

	Zero Falls	*(+) Freezing*	*(+) Festination*	*(+) Orthostatic Hypotension*	*(+) Trip/Slip*	*(+) Turn Balance*	*(+) Stand Balance*	*(+) Other*
	n = 24	*n = 13*	*n = 12*	*n = 15*	*n = 13*	*n = 20*	*n = 17*	*n = 8*
Cognitive								
Block Design T	47.7 (9.9)	47.4 (7.2)	50.6 (7.9)	45.5 (10.1)	47.3 (8.9)	47.5 (9.4)	49.4 (7.5)	53.8 (11.7)
Digit Span T	48.4 (8.5)	47.8 (8.7)	47.3 (11.1)	49.1 (10.2)	44.1 (9.9)	46.2 (9.2)	46.9 (8.7)	51.9 (8.9)
TMT B seconds	147.4 (91.4)	120.7 (59.6)	159.7 (91.1)	127.9 (45.2)	158.1 (79.2)	152.9 (76.1)	143.8 (75.6)	70.6 (38.3)**
ROCF raw	30.0 (6.0)	30.0 (4.3)	28.1 (6.2)	27.5 (5.7)	30.6 (3.5)	29.3 (4.3)	29.9 (3.9)	31.7 (4.7)
CVLT-II Learning T	50.8 (10.2)	46.9 (11.5)	44.6 (12.5)	48.6 (12.9)	44.3 (11.6)	46.0 (11.7)	44.0 (10.5)*	53.4 (10.7)
CVLT-II LDFR T	51.0 (9.8)	47.7 (10.5)	44.1 (11.1)	48.3 (11.8)	43.1 (11.1)*	46.3 (12.0)	45.9 (10.9)	52.5 (8.0)
Impulsivity/ICD								
BIS-11	57.4 (9.3)	65.7 (8.3)**	66.2 (8.3)**	62.7 (10.4)	63.6 (10.0)	64.4 (8.8)*	65.9 (10.7)**	64.9 (11.1)
QUIP-RS ICD Total	8.6 (7.1)	14.4 (7.4)*	15.1 (9.6)*	11.9 (8.3)	11.6 (12.1)	13.7 (9.5)	14.4 (9.7)*	14.0 (13.7)
QUIP-RS Total Score	17.0 (13.4)	30.4 (12.6)**	27.5 (17.4)	24.8 (16.5)	23.0 (22.1)	27.5 (17.2)*	29.4 (16.5)**	24.4 (22.0)
(+) 2nd Gen. DA Agonist (%)	41.7	38.5	41.7	20.0	25.0	40.0	43.8	100.0**
Balance Confidence								
ABCs	83.9 (14.7)	59.9 (14.6)**	60.9 (15.9)**	63.7 (20.3)**	71.1 (20.0)*	59.9 (20.2)**	61.8 (19.5)**	82.4 (7.3)
Disease Characteristics								
Age	65.3 (9.3)	64.1 (10.6)	64.2 (12.1)	69.8 (10.4)	67.2 (10.9)	67.8 (9.3)	68.1 (9.8)	61.5 (7.2)
Disease Duration (years)	6.9 (4.5)	12.9 (7.8)**	10.8 (7.9)	10.2 (8.0)	7.3 (2.9)	9.4 (6.5)	9.7 (6.3)	8.9 (3.3)
(+) Postural Instability (%)	17.4	91.7**	83.3**	64.2**	53.8*	84.2**	81.3**	50.0

Notes: Data are compared to the No Falls group. All comparisons are *t* tests except (+) 2nd Gen. DA Agonist and (+) Postural Instability, which are X^2. There are overlapping subjects in the fall groups, as subjects can endorse more than one reason for falls on the PDFQ. TMT B = Trail Making Test B; ROCF = Rey-Osterrieth Complex Figure Copy; CVLT-II = California Verbal Learning Test-2; LDFR = Long Delay Free Recall; BIS-11 = Barratt Impulsiveness Scale-11; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; ICD Total = Impulsive-Compulsive Disorders summed total score; (+) 2nd Gen. DA Agonist = percentage of Ss on a 2nd generation dopamine agonist; ABCs = Activity-specific Balance Confidence Scale

*$p \leq .05$

**$p \leq .01$

FIGURES

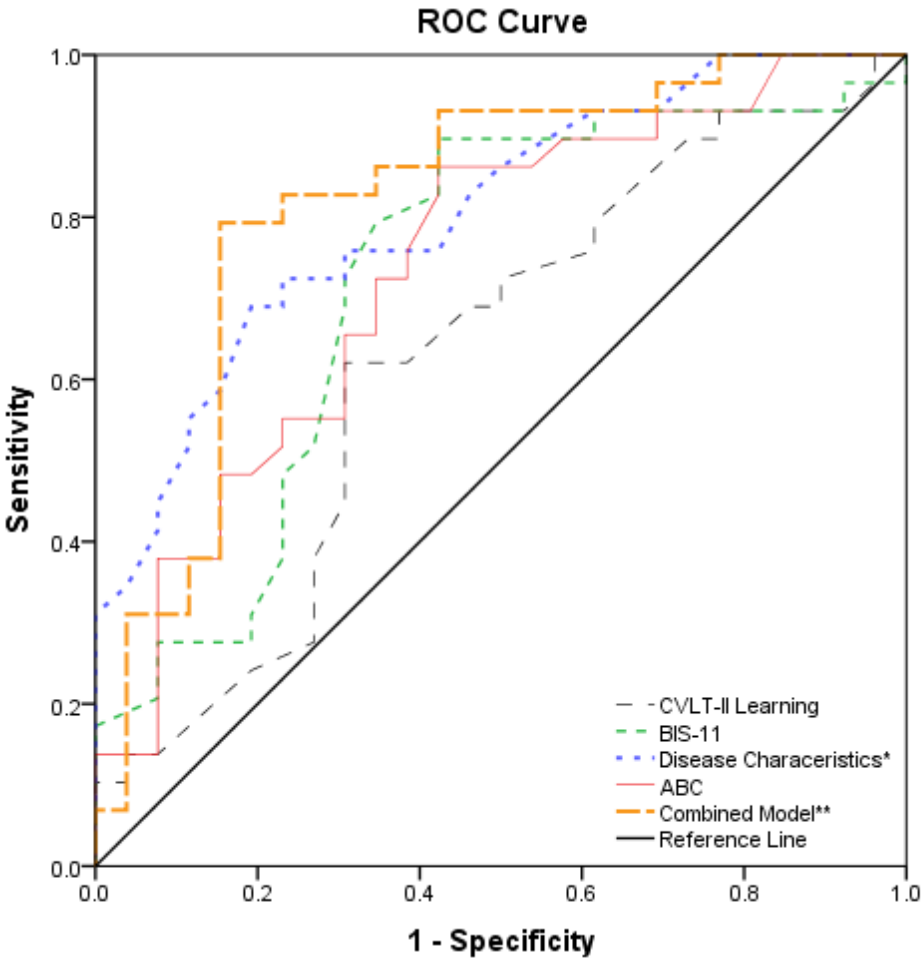

Figure 1. Area Under the Curve Receiver Operating Characteristics for the Reduced Logistic Regression Models, Discriminating between High Fall Risk and Low Fall Risk Groups using Predicted Values

Notes: CVLT-II = California Verbal Learning Test-2; BIS-11 = Barratt Impulsiveness Scale-11; ABC = Activities-specific Balance Confidence Scale.
* Includes Postural Instability and Disease Duration Variables.
** Includes Postural Instability, Barratt Impulsiveness Scale-11, and California Verbal Learning Test-2 Learning variables.

APPENDIX A
Measure Characteristics and Psychometric Properties

A. Cognitive Measures

Trail Making Test Part B (TMTB; Partington & Leiter, 1949)

TMTB is a timed test in which the goal of the task is to connect 25 alternating encircled numbers and letters in sequential/alphabetical order. TMTB is administered immediately after a similar, less complex task (Trail Making Test Part A), in which examinees connect 25 encircled consecutive numbers in sequential order. Overall, TMTB is considered to examine speeded attention, sequencing, and flexibility for sequential processing. Scores are based on time of completion and the number of errors made. Reliability coefficients have been found to range from .80-.90 in populations of neurological impairment, and as low as .60 for non-neurological aged populations (Spreen & Strauss, 1998). In a pilot study examining cognitive differences in fallers and non-fallers in PD, performance on TMTB was significantly worse among fallers than non-fallers [$t(123.63) = -2.37$, $p = .019$; Denney et al., 2014]. This study utilized time to complete TMTB as a measure of mental flexibility.

Wechsler Adult Intelligence Scale-IV Digit Span (DS; Wechsler, 2008)

Digit Span is a core Working Memory subtest of the WAIS-IV. It is composed of three tasks: DS Forward, DS Backward, and DS Sequencing. For DS forward, the examinee recalls a sequence of numbers in the same order stated to them. For DS backward, the examinee is read a sequence of numbers and recalls the numbers in reverse order. For DS Sequencing, the examinee is read a sequence of numbers and recalls the numbers in ascending order. Totals from each task are summed for a total raw score, which is converted into an age-adjusted scaled score. Poor performance on DS is diagnostically significant, particularly for suspected brain dysfunction or concern about mental deterioration across the life span (Lichtenberger & Kaufman, 2009). In a

pilot study examining cognitive differences in fallers and non-fallers in PD, performance on DS was significantly worse among fallers than non-fallers [$t(125) = 2.55$, $p = .012$; Denney et al., 2014]. This study utilized DS age-adjusted scaled score as a measure of attention.

Wechsler Adult Intelligence Scale-IV Block Design (BD; Wechsler, 2008)

Block Design is a core Perceptual Reasoning subtest of the WAIS-IV. It is a timed test in which examinees use three-dimensional red/white blocks to reproduce a model or a picture presented to them. It measures the ability to analyze and synthesize abstract visual stimuli and involves nonverbal concept formation and reasoning, broad visual intelligence, and visual perception and organization (Wechsler, 2008). Performance on this test is especially impacted by right parietal brain damage (Lichtenberger & Kaufman, 2009). Impaired performance on BD has been shown to differentiate freezers from non-freezers in PD (Nantel, McDonald, Tan, & Bronte-Stewart, 2012). In addition, pilot data examining cognitive differences in fallers and non-fallers in PD showed that fallers performed significantly worse on BD than non-fallers [$t(110) = 3.08$, $p = .003$; Denney et al., 2014]. This study utilized BD age-adjusted scaled score as a measure of visuospatial ability.

Rey-Osterrieth Complex Figure (ROCF; Osterrieth, 1944; Rey, 1941)

The ROCF is a measure of visuospatial constructional ability and visual memory. The ROCF is one of the most commonly used tests in the field (Camara, Nathan, & Puente, 2000) and ranks among the top 10 tests used by neuropsychologists (Rabin, Barr, & Burton, 2005). Administration involves a copy trial followed by an immediate and 15-minute delayed recall. After the 15-minute delayed recall, a recognition trial is administered in which the examinee is asked to choose the correct design from nine options. Drawings are scored by assessing accuracy of copy and recall trials through criteria provided by Loring, Lee, and Meador (1988). Factor

analysis supports the validity of the ROCF as a measure of visual-constructional ability (copy) and memory (recall and recognition) (Chervinsky, Mitrushina, & Statz, 1992). The test has been shown to have sensitivity to individuals with a history of PD (Cooper et al., 1991; Freeman et al., 2000; Ogden, Growdon, & Corkin, 1990). In a pilot study examining cognitive differences in fallers and non-fallers in PD, performance on ROCF Copy was significantly worse among fallers than non-fallers [$t(114) = 2.05$, $p = .04$; Denney et al., 2014]. Performance on ROCF recall trials did not differ between groups. The present study utilized the ROCF Copy raw score as a measure of visuospatial ability.

California Verbal Learning Test Second Edition (CVLT-II; Delis et al., 2000)

The CVLT-II is a measure of verbal learning and memory in which a list of 16 words is presented for five learning trials, followed by a 16-item distractor list. Short and delayed free and cued recall trials are then administered, as is delayed recognition testing. The examinee's responses are entered into a computer program, which provides raw and standardized scores that are controlled for age and gender. The CVLT-II has been shown to be sensitive to learning and memory dysfunction across neuromedical and psychiatric populations. In a pilot study examining cognitive differences in fallers and non-fallers in PD, performance on the CVLT-II did not significantly differ between groups (Denney et al., 2014). Variables of interest for the present study include demographically-adjusted Total Learning T-Score and Long Delayed Free Recall *z*-score.

B. Behavioral Measures

Barratt Impulsiveness Scale-11 (BIS-11; Patton, Stanford, & Barratt, 1995)

The BIS-11 is a 30-item self-report instrument, scored on a Likert scale from one to four, designed to assess the personality/behavioral construct of impulsiveness. It is the 11th iteration of

the original BIS (Barratt, 1959) and is arguably the most commonly administered self-report measure specifically designed for the assessment of impulsiveness (Stanford et al., 2009). Internal consistency of the BIS-11 is good (Chronbach's $\alpha = 0.83$), as is test-retest reliability at one month (Spearman's Rho = 0.83). The BIS-11 is highly correlated with similar self-report measures (convergent validity) but not significantly correlated with behavioral measures of impulsiveness. Raw scores range between 30 and 120 with scores from 52 to 71 identified as being within "normal limits of impulsiveness." Scores at 72 or above are suggested to be used to classify individuals as "highly impulsive," while scores below 52 are indicative of "over controlled" individuals or those not answering the questionnaire honestly (Stanford et al., 2009). The BIS-11 Total score is significantly elevated in a wide range of neuropsychiatric conditions thought to have an impulsivity component (Stanford et al., 2009). This study utilized the total raw score of the BIS-11 as a measure of personality/behavioral impulsiveness. See Appendix B for a copy of the measure.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS; Weintraub et al., 2012)

The QUIP-RS is a self-report measure of impulsive-compulsive disorders (ICD) in PD that assesses the severity of ICD behaviors and has four primary questions (pertaining to commonly reported thoughts, urges/desires, and behaviors associated with ICDs), each applied to the four ICDs (compulsive gambling, buying, eating, and sexual behavior) and three related disorders (medication use, punding, and hobbyism). It uses a five-point Likert scale (score 0-4 for each question) to gauge the frequency of behaviors, and instructs patients to answer questions based on behaviors that occurred in the preceding 4 weeks (or any 4-week period after PD diagnosis). Scores for each item within a particular ICD are summed. The individual ICD scores

are summed for a Total ICD score. The QUIP-RS was validated with 104 participants completing the self-report measure and undergoing a semi-structured diagnostic interview for each of the ICD behaviors. The optimal cutoff point [with both (1) sensitivity and specificity ≥80% and (2) highest combined sensitivity and specificity] for the Total ICD score is ≥10. Inter-rater and test-retest reliability are good (*r*s = 0.95 and 0.90, respectively) (Weintraub et al., 2012). Raw scores for each of the four ICDs and related disorders can range from 0 to 16. The Total ICD score ranges from 0 to 64, and the Total QUIP-RS Score ranges from 0 to 112. Cutoff scores for significant ICD behaviors have been identified: gambling = 6; buying = 8; eating = 7; sexual behavior = 8; Total ICD = 10. A cutoff for the Total QUIP-RS Score has not been identified. This study used the Total ICD raw score as a screening measure for ICDs in PD patients. See Appendix C for a copy of the measure.

Hoehn and Yahr Staging Scale (HY; Hoehn and Yahr, 1967)

The HY was designed to be a simple descriptive staging scale that provided an estimate of clinical function in PD. It combines functional deficits (disability) and objective signs (impairment) into the rating. It utilizes a seven-point Likert scale (1, 1.5, 2, 2.5, 3, 4, and 5) and is based on the concept that the severity of overall parkinsonian dysfunction relates to bilateral motor involvement and compromised balance/gait. Advances in parkinsonian motor impairment is chronicled from unilateral (Stage I) to bilateral disease (Stage II) without balance difficulties, to the presence of postural instability (Stage III), loss of physical independence (Stage IV), and being wheelchair- or bed-bound (Stage V). By definition, the patients in Stages I, II, and III are minimally disabled, whereas patients in IV and V are severely disabled. This study utilized HY ratings determined through chart review with the assistance of a movement disorders specialist as a measure of disease severity for identification of postural instability (2.5 or above). Subjects

in this study were in stages I, II, III, or IV. Any subject determined to be in stage V were excluded from the study, as subjects must be ambulatory for inclusion.

Activity-specific Balance Confidence Scale (ABC; Powell & Myers, 1995)

The ABC is a 16-item self-report measure of confidence in performing various ambulatory activities without falling or experiencing a sense of unsteadiness. Each activity is stemmed with: "How confident are you that you will not lose your balance or become unsteady when you…" Items are rated on a scale that ranges from 0 – 100 where a score of zero represents no confidence while a score 100 represents complete confidence. Overall score is calculated by adding item scores and then dividing by the total number of items (16). Mean total score among PD patients has been identified at 73.6 (SD = 19.3) while a cutoff score of 69 has been shown to have utility in predicting recurrent falls among individuals with idiopathic PD (AUC = 0.82, sensitivity = 93%, specificity = 69%; Mak, Pang, & Mok, 2012). Test-retest reliability among PD patients has repeatedly been good (ICC ranges from 0.79 to 0.96; Dal Bello-Hass, Klassen, Sheppard, & Metcalfe, 2011; Lohnes & Earhart, 2010; Steffen & Seney, 2008). This study utilized the ABC as a measure of balance confidence. See Appendix D for a copy of the measure.

Parkinson Disease Fall Questionnaire (PDFQ)

The PDFQ is an unpublished self-report measure that was designed to assess the presence, number, and cause(s) of falls for a PD population. It was developed with the assistance of two board certified neurologists who specialize in movement disorders. The measure was sent to 11 neurologists who specialize in movement disorders, 10 of which responded with ratings of each item, and a content validity ratio (CVR) was computed to determine the essentialness of each item on the measure for an assessment of content validity (Lawshe, 1975). All of the items met the threshold of .62, as suggested by Lawshe (1975) for 10 panelists, for inclusion in the

measure. A content validity index (CVI) of the measure, which is the mean of the CVR values of the retained items, was computed for the measure's overall content validity. The PDFQ has a CVI of .88. Number of reported falls (e.g., groups defined as $\leq$1 vs. $\geq$2), as reported on this measure, served as the primary dependent variable for this study. The reported causes of falls from this measure were used in exploratory analyses. See Appendix E for a copy of the measure.

APPENDIX B
The Barratt Impulsiveness Scale-11 (BIS-11)

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate number on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

1	2	3	4
Rarely/Never	Occasionally	Often	Almost Always/Always

1	I plan tasks carefully.	1	2	3	4
2	I do things without thinking.	1	2	3	4
3	I make-up my mind quickly.	1	2	3	4
4	I am happy-go-lucky.	1	2	3	4
5	I don't "pay attention."	1	2	3	4
6	I have "racing" thoughts.	1	2	3	4
7	I plan trips well ahead of time.	1	2	3	4
8	I am self controlled.	1	2	3	4
9	I concentrate easily.	1	2	3	4
10	I save regularly.	1	2	3	4
11	I "squirm" at plays or lectures.	1	2	3	4
12	I am a careful thinker.	1	2	3	4
13	I plan for job security.	1	2	3	4
14	I say things without thinking.	1	2	3	4
15	I like to think about complex problems.	1	2	3	4
16	I change jobs.	1	2	3	4
17	I act "on impulse."	1	2	3	4
18	I get easily bored when solving thought problems.	1	2	3	4
19	I act on the spur of the moment.	1	2	3	4
20	I am a steady thinker.	1	2	3	4
21	I change residences.	1	2	3	4
22	I buy things on impulse.	1	2	3	4
23	I can only think about one thing at a time.	1	2	3	4
24	I change hobbies.	1	2	3	4
25	I spend or charge more than I earn.	1	2	3	4
26	I often have extraneous thoughts when thinking.	1	2	3	4
27	I am more interested in the present than the future.	1	2	3	4
28	I am restless at the theater or lectures.	1	2	3	4
29	I like puzzles.	1	2	3	4
30	I am future oriented.	1	2	3	4

Patton, Stanford, & Barratt, 1995. *J Clin Psy*, vol 51, pp. 768-774

APPENDIX C
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS)

Reported by: _____ Patient _____ Informant _____ Patient and Informant

Patient / Subject: _____

Date: _____

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

Subject: _____

Date: _____

SCORING SHEET

A. Gambling	_____	**(0-16)**
B. Sex	_____	**(0-16)**
C. Buying	_____	**(0-16)**
D. Eating	_____	**(0-16)**
E. Hobbyism-Punding	_____	**(0-32)**
F. PD Medication Use	_____	**(0-16)**
Total ICD Score (A-D)	_____	**(0-64)**
Total QUIP-RS Score (A-F)	_____	**(0-112)**

APPENDIX D
The Activities-specific Balance Confidence Scale (ABC)

The Activities-specific Balance Confidence (ABC) Scale*

Instructions to Participants:
For each of the following, please indicate your level of confidence in doing the activity without losing your balance or becoming unsteady from choosing one of the percentage points on the scale from 0% to 100%. If you do not currently do the activity in question, try and imagine how confident you would be if you had to do the activity. If you normally use a walking aid to do the activity or hold onto someone, rate your confidence as if you were using these supports. If you have any questions about answering any of these items, please ask the administrator.

The Activities-specific Balance Confidence (ABC) Scale*

For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale:

0% 10 20 30 40 50 60 70 80 90 100%
no confidence completely confident

"How confident are you that you will not lose your balance or become unsteady when you…

1. …walk around the house? ____%
2. …walk up or down stairs? ____%
3. …bend over and pick up a slipper from the front of a closet floor ____%
4. …reach for a small can off a shelf at eye level ____%
5. …stand on your tiptoes and reach for something above your head? ____%
6. …stand on a chair and reach for something? ____%
7. …sweep the floor? ____%
8. …walk outside the house to a car parked in the driveway? ____%
9. …get into or out of a car? ____%
10. …walk across a parking lot to the mall? ____%
11. …walk up or down a ramp? ____%
12. …walk in a crowded mall where people rapidly walk past you? ____%
13. …are bumped into by people as you walk through the mall? ____%
14. …step onto or off an escalator while you are holding onto a railing? ____%
15. …step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? ____%
16. …walk outside on icy sidewalks? ____%

*Powell, LE & Meyers AM. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol Med Sci* 1995; 50(1): M28-34

APPENDIX E
The Parkinson Disease Fall Questionnaire (PDFQ)

Name/ID: _____

Date: _____

Research Consent: Y N N/A

PD Falls Questionnaire

Instructions:

Please answer each of the following to the best of your ability. If the answer to item **1** is **NO**, do NOT proceed to items **2** and **3.**

1. Have you fallen in the previous six months?

YES **NO**

2. How many times have you fallen within the past six months?

_____

3. I have fallen within the past six months because of the following reasons (check all that apply):

____ Freezing as if my feet were stuck to the floor or feeling that I cannot pick up my foot to start or continue walking

____ Shuffling with quick short steps that made it difficult to slow down (festination of gait)

____ Feeling dizzy, lightheaded, or faint or having "tunnel vision" after standing up (orthostatic hypotension or a drop in blood pressure after standing up)

____ Tripping over an obstacle or slipping on a slick surface

____ Losing my balance after turning

____ Losing my balance (falling forward or backward) while standing in one spot

____ Other (please specify): _____

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