APATHY, NEUROCOGNITIVE FUNCTIONING, AND PARKINSON'S DISEASE

By

LINDSEY KIRSCH-DARROW

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TABLE OF CONTENTS

page

LIST OF TABLES

LIST OF FIGURES

Abstract of Dissertation Presented to the Graduate School
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By

Lindsey Kirsch-Darrow

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Apathy is a common neuropsychological feature of Parkinson's disease (PD). The aims of the present study were twofold: 1) to test the hypothesis that apathy and depression are separate syndromes in PD, and 2) to determine the effect of apathy on neurocognitive performance in PD patients after controlling for important comorbidities such as dementia, depression, and disease variables.

One-hundred sixty-one non-demented PD patients (age = 64.1, ± 8.4 yrs; UPDRS motor severity = 25.13 ± 8.6) were administered neuropsychological tests and completed the Apathy Scale and Beck Depression Inventory-II. Items were proposed to load onto four factors: 1) an apathy factor representing loss of motivation, 2) dysphoric mood factor representing sadness and negativity, 3) loss of interest and pleasure factor, and 4) somatic factor representing bodily complaints. CFA was used to examine the fit of the items to the factors. Hierarchical regression was used to quantify whether apathy uniquely explained variance in specific cognitive domains (e.g. Executive functioning, Processing speed, Verbal episodic memory, Working memory, and Language domains).

There was a good fit for the overall CFA model, $\chi 2$ (128, N = 146) = 194.9, p <.01. RMSEA was .060 (p = .16). The four factor model was significantly better than all alternative nested models at p <.001. Apathy explained incremental variance in Executive functioning, but did not explain significant variance in any other cognitive domain. Apathy was negatively related to Executive functioning, and this relationship was driven by a significant negative relationship with Stroop Interference performance (p <.01) and a trend for a negative relationship between apathy and semantic fluency (p = .06).

Results support the concept that apathy and depression are discrete factors. This finding argues for an alternative "subfactor" scoring of the Apathy Scale and Beck Depression Inventory-II. This will help disentangle symptoms related to apathy, depression, overlapping symptoms, and somatic complaints. Findings also support a relationship between apathy and Executive functioning. Apathy is related to certain aspects of Executive functioning, such as cognitive interference/inhibition and verbal fluency, whereas it is not related to other aspects of Executive functioning such as shifting mental set.

CHAPTER 1
STATEMENT OF THE PROBLEM

Parkinson disease (PD) is one of the most common neurodegenerative disorders of late life. Over one million Americans suffer from PD, and 50,000 new cases are diagnosed each year (McDonald, Richard, & DeLong, 2003; Nussbaum & Ellis, 2003). The incidence of Parkinson disease increases with age and as the aging population increases the incidence of PD is expected to triple by the year 2050 (Tanner et al., 2002). The disease is characterized neuropathologically by loss of neurons in the substantia nigra pars compacta, dopamine depletion in the basal ganglia, and the presence of Lewy bodies. Patients present with motor symptoms of tremor, bradykinesia (slowness of movement), rigidity, and postural instability. While these motor symptoms are the hallmark features of the disorder, neuropsychiatric symptoms are highly prevalent and can be some of the most disturbing, disabling, and complex aspects of PD.

One such neuropsychiatric symptom is apathy. Apathy refers to negative/deficit symptoms such as blunted emotions, loss of interest, and lack of productivity. Many aspects of apathy are unknown. For example, it is unknown whether apathy is a unique syndrome or a subcomponent of depression in PD. This has important implications both for understanding the neural substrates of mood disorders (e.g. Do separate neural systems underlie the two types of symptoms?) and for differential diagnosis and treatment (e.g. treatments for depression may not be effective for apathy, and vice versa). Studies to date have suggested that depression and apathy are separable (Isella et al., 2002; Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006; Pluck & Brown, 2002). However, these studies are limited methodologically by the use of total scores on clinical inventories used to assess their presence and severity. This is problematic because apathy and depression scales overlap in content. It is possible that a particular symptom endorsement on the Beck Depression Inventory (BDI) might better represent apathy and is being

counted towards depression and vice versa. The primary aim of the present study is to address whether apathy and depression are separable in a way that disentangles the total score confound of overlapping symptomatology. To overcome the limitation of overlapping symptoms being counted toward the "wrong" total score, confirmatory factory analysis will be used to examine individual items of the Beck Depression Inventory-II (BDI-II) and the Apathy Scale (AS). Based on preliminary observations, discrete factors were proposed to be: 1) an apathy factor representing loss of motivation, 2) a dysphoric mood factor representing sad mood/negativity, 3) a loss of interest and pleasure factor, representing the overlap between apathy and depression, and 4) a somatic factor representing bodily complaints. In this way, an a priori factor structure is hypothesized and can determine how well the items conform to these factors. This will be a strong test of whether apathy and depression are indeed dissociable in PD.

Another unknown factor regarding apathy is its relationship to cognitive functioning. Is apathy related to a particular pattern of cognitive impairment? Several studies have examined this question, but most have confounds (Isella et al., 2002; Pluck & Brown, 2002; Starkstein, Mayberg, Preziosi et al., 1992; Zgaljardic et al., 2007). Some studies did not screen out patients with dementia. This is problematic because groups of apathetic and nonapathetic patients appear to have an unequal distribution of dementia cases (Isella et al., 2002; Starkstein, Mayberg, Preziosi et al., 1992). With more demented individuals in the high apathy group, lower cognitive scores could be attributed to dementia and not to apathy per se. Second, studies did not control for depression or demographic variables that have been shown to effect cognitive functioning in PD. For example, although Zgaljardic et al. (2007) and Pedersen et al. (2009) screened out dementia patients, they did not control for depression (significantly higher in their apathetic group) or disease severity. The apathetic patients' Hoehn & Yahr staging was higher in the

apathetic group at trend for both Zgaljardic et al. (2007) and Pedersen et al. (2009). Further, the Pedersen (2009) study reported significantly higher UPDRS motor severity in their apathetic group versus their non-apathetic group. This makes it difficult to attribute cognitive differences between groups specifically to apathy. The second aim of the present study is to determine whether apathy influences cognitive functioning in a nondemented group of PD patients after controlling for depression, and demographic factors (i.e. age, gender, education), and disease factors (i.e. duration of PD, severity of PD).

CHAPTER 2
BACKGROUND

Motor Symptoms in Parkinson Disease

The hallmark motor symptoms of Parkinson disease are a resting tremor, bradykinesia, muscular rigidity, and a gait disturbance. Resting tremor is the most recognizable symptom of PD; however, some patients experience a tremor during activity (postural or action tremor) as well as during rest, and approximately 15% of patients never show tremor during the course of the disease (Martin et al., 1983). Bradykinesia is slowness in execution of movement, while muscular rigidity is tightness and stiffness of the muscles. Tremor, rigidity, and bradykinesia begin unilaterally, but become bilateral as the disorder progresses. Gait is characterized by stooped posture, shuffling steps, festination (short steps that become quicker and quicker as if the patient were about to run) and propulsion (forward inclination of the body as if the patient were about to fall forward) (Lieberman, 1995; Tyler, 1992). Patients may experience motoric "freezing," where they halt mid-gait and are unable to take any steps forward.

Given all of these motor symptoms, PD was once considered solely as a motor disorder. Now, we know that PD is a complex disorder that affects multiple domains of functioning. For example, PD causes disturbances of mood and motivation including depression, anxiety, and apathy. Of these, apathy is the least understood. As such, the purpose of the present study is further knowledge about this important non-motor symptom of PD. Before turning to specific aims and hypotheses of the present study, relevant background will be presented as follows: 1) an overview of depression in PD, 2) definition of apathy, 3) an overview of apathy in PD and differential diagnostic questions between apathy and depression, and 4) a review of the relationship between mood symptoms and cognitive symptoms in PD.

Depression in PD

Depression is a common occurrence in PD and has been studied extensively. There have been over 100 published English language studies specifically examining depression in PD. Distinction should be drawn between depression symptoms based on clinical scales versus the diagnosis of Major depressive disorder (MDD) using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria. Rates found in studies vary, with number of patients meeting DSM criteria being less frequent than those endorsing levels of depression above a particular cut-off point on clinical scales (Slaughter, Slaughter, Nichols, Holmes, & Martens, 2001). Even if patients do not meet full diagnostic criteria, they may still have significant disability from their mood symptoms and benefit from treatment (Judd, Paulus, Wells, & Rapaport, 1996; Lyness et al., 1996). A recent meta-analysis by Reijnders et al. (2009) reviewed 36 studies of depression in PD and found the overall prevalence of MDD to be 19%. This prevalence is much higher than the 2-9% prevalence of MDD found in the general population (Diagnostic and Statistical Manual of Mental Disorders IV, DSM-IV). The prevalence of clinically significant depression in PD, whether or not there was a presence of a DSM diagnosis, was 35% (Reijnders, Ehrt, Lousberg, Aarsland, & Leentjens, 2009). Moreover, depressive symptoms are a primary factor impacting quality of life (McDonald et al., 2003; Phillips, 1999). In a randomized, multi-center study of patients with PD, caregivers, and clinicians, depressive symptoms were cited as the *most important factor* in patient quality of life ratings—more important than medications and disease severity ("Factors impacting on quality of life in Parkinson's disease: results from an international survey," 2002).

Unfortunately, depression is difficult to assess in PD. Many of the symptoms of Parkinson disease itself overlap with those of depression. Patients often have insomnia, psychomotor slowing, fatigue, and concentration difficulties. Also, the symptom of reduced facial

expressivity (e.g. "masked facies") can appear to represent sadness in nondepressed individuals with PD. Misdiagnosis of depression can go either way— by assigning symptoms to depression that actually represent PD symptoms or by assigning symptoms to PD that actually represent depression. Accurate recognition and diagnosis is critical for appropriate and effective treatment. Failing to treat depression symptoms may cause increased disability whereas inappropriate treatment may lead to unnecessary side effects. Selective serotonin reuptake inhibitors (SSRIs) are the typical first-line choice for depression in PD. In addition, a recent clinical trial of antidepressant treatment in 52 PD patients reported that nortriptyline, a dual reuptake inhibitor of serotonin and norepinephrine, was more efficacious than both placebo and the SSRI paroxetine for remitting depressive symptoms (Menza et al., 2009). Selective serotonin reuptake inhibitors (SSRIs) can cause side effects of insomnia, nausea, agitation, and sexual dysfunction. Similarly, the norepinephrine side effect profile includes orthostatic hypotension, constipation, dry mouth, insomnia, and dizziness (Menza et al., 2009). Apathy may not respond to antidepressant agents and thus patients may experience negative side effects without receiving benefit from their mood symptoms.

Defining Apathy

The word "apathy" derives its roots from the Greek 'a' 'pathos,' meaning lack of passions. The term first appeared in medical use in the writings of Hughlings Jackson (Hughlings Jackson, 1931). He distinguished the florid/positive symptoms from the deficit/negative symptoms in schizophrenia. Positive symptoms were seen as an excess of normal function (e.g. hallucinations), whereas negative symptoms (e.g. alogia, apathy, and poverty of speech) were seen as a loss of normal function. Yet, this loss of normal function is seen in disorders beyond schizophrenia. Robert Marin highlighted this fact in the early 1990s. He proposed that apathy could manifest in neurological disorders as both a symptom and a syndrome. His key paper in

1991 proposed diagnostic criteria for a syndrome of apathy (Marin, 1991) (see Table 2-1 for Marin's criteria). According to his view, a syndrome of apathy includes a *primary lack of motivation*. Marin defined motivation as a higher-order construct that refers to "the direction, intensity and persistence of goal-directed behavior" (Marin, 1991). He operationalized this definition by positing that apathy manifests itself in behavioral, cognitive, and emotional domains. At least one symptom from each domain is required for a diagnosis of apathy. The behavioral domain includes symptoms such as of lack of effort, lack of productivity, and dependence on others to structure one's activities. The cognitive domain includes symptoms such as loss of interest in new experience and lack of concern about one's personal problems. The affective domain includes symptoms of flattened affect and lack of response to positive or negative events. The lack of motivation in a syndrome of apathy is primary, and not purely accounted for by intellectual impairment such as dementia, emotional distress, or impaired consciousness (e.g. delirium). Marin emphasized that if apathy did occur in these states (e.g. such as emotional distress such as depression) then apathy would be considered a symptom and not a full syndrome.

Levy and Dubois (2006) refined Marin's concept of apathy and lack of motivation. The authors defined apathy as an "observable behavioral syndrome consisting of a quantitative reduction of voluntary [or goal-directed] behaviors." They distinguished their definition as being more quantifiable (i.e. observable behavior change) than the psychological term 'motivation.' They, like Marin, pointed out that the reduction in voluntary behavior must be below the patient's previous levels of functioning. They recommend examining the patient's environment to make sure it is unchanged (i.e. not related to changes in reward contingencies in the

environment) and disability status in order to ensure the behavior is not related to the physical inability to perform previous social roles, work, and recreation (R. Levy & Dubois, 2006).

Lack of Accepted Diagnostic Criteria for Apathy

Although Marin proposed the criteria for a syndrome of apathy, these criteria have never been formally accepted into the Diagnostic and Statistical Manual of Mental Disorders (DSM). The DSM-IV uses the term apathy only as one of a list of possible symptoms of personality change due to a general medical condition (DSM-IV-TR). The ICD-10 does not include apathy at all (ICD-10, World Health Organization). The lack of formally accepted diagnostic criteria is problematic because researchers and clinicians do not have a set of standardized instructions to diagnose patients in a uniform manner. This leads to variability in patient classification and hampers comparisons across studies. It is also difficult for treatment-oriented clinical trials to appropriate select patients and evaluate outcome (e.g. full remission, partial remission, etc) without clearly accepted criteria.

Towards the goal of creating consensus criteria, Starkstein and colleagues modified Marin's original criteria (Starkstein, 2000; Starkstein & Leentjens, 2008). Starkstein and Leentjens (2008) added a duration requirement that apathy symptoms must occur during most of the day for at least four weeks. They removed the exclusion criteria of 1) intellectual impairment and 2) emotional distress. Importantly, the authors pointed out that a patient could have ***both*** a syndrome of apathy and dementia. Patients can also have both a syndrome of apathy and a major depressive disorder (Starkstein, 2000; Starkstein & Leentjens, 2008). Marin's original criteria overlooked these dual diagnosis situations. Recent work from this research group confirmed the common overlap between apathy and dementia and depression (Starkstein et al., 2009). Out of 164 PD patients assessed, 52 (32%) were diagnosed with apathy based on the Apathy Scale. Further, a full 83% of this apathetic group had DSM-IV based depression diagnoses of major

depression, minor depression, or dysthymia. Fifty-six percent of the apathetic group had dementia based on DSM-IV assessment (Starkstein et al., 2009).

Very recently, a task force of experts from Europe, Australia, and North America convened in France and developed and published consensus diagnostic criteria for apathy in neuropsychiatric and neurological disorders (Robert et al., 2009). Sergio Starkstein was a member of this task force and the proposed criteria are similar to his criteria described above (Starkstein & Leentjens, 2008). The European diagnostic consensus criteria require: loss of, or diminished motivation accompanied by loss of goal-directed behavior, cognitive activity, or diminished emotion. See Table 2-2. The duration criteria is that apathy occurs most of the day, every-day for at least four weeks. A difference between the European criteria and Starkstein's criteria are the requirement of one symptom in at least two of the three domains: behavior, cognition, and emotion (Robert et al., 2009). Previous criteria required at least one symptoms in all three domains (Starkstein, 2000; Starkstein & Leentjens, 2008). Further, the European criteria structure each domain with two symptoms each—one representing self-initiated or 'internal' actions, cognitions and emotions, and the second symptom referring to the patient's responsiveness to 'external' stimuli. See Table 2-2.

Apathy Rating Scales in PD

Researchers are currently working towards the goal of uniformly accepted gold standard diagnostic criteria for a syndrome of apathy. In the meanwhile, a number of assessment scales that measure symptoms are used to quantify apathy. These include the Apathy Evaluation Scale (AES), an abbreviated version of the AES known as the Apathy Scale (AS), the Apathy Inventory (AI), the Lille Apathy Rating Scale (LARS), and the Frontal Systems of Behavior Scale (FrSBe). Single items are also used from the Unified Parkinson's Rating Scale (item 4) and the Neuropsychiatric Inventory (item 7).

Apathy Evaluation Scale (AES) and Apathy Scale (AS). The AES is an 18 item Likert scale measuring the behavioral, cognitive, and emotional symptoms of apathy. There are self, clinician, and informant versions. It was developed by Robert Marin (Marin, Biedrzycki, & Firinciogullari, 1991). Marin validated the original scale on approximately 90 subjects aged 55-85 years with a diagnosis of either stroke, Alzheimer's disease, or major depressive disorder and compared their scores to those of normal elderly controls. Convergent and divergent validity with other scales (e.g. anxiety and depression scales) was established with the multitrait-multimatrix method (Marin et al., 1991). Predictive and external validity were investigated by observing participants in various scenarios such as persistence at video game play and time spent examining novelty gadgets. Self-reported apathy scores were negatively correlated with total scores on video games and the difficulty level at which participants chose to play. Thus, there was a behavioral correlate to the self-reported symptoms.

The Apathy Scale (AS) is a modified version of the AES. The AES was shortened to 14 items from 18 items and wording was simplified by Starkstein and colleagues (Starkstein et al., 1992). It was validated specifically in PD patients and showed good internal consistency reliability and test-retest reliability (Starkstein et al., 1992). The AS has been used frequently in PD studies since its validation (Isella et al., 2002; Czernecki et al., 2002; Kirsch-Darrow et al., 2006; Zahodne et al., 2009; Starkstein et al, 2009). A recent study from our laboratory demonstrated evidence for construct validity of the AS. Twenty-eight nondemented PD patients and 19 age-matched controls were administered a modified version of Marin's novelty toy task. They also completed the AS, Lille Apathy Rating Scale (LARS), BDI, and UPDRS-motor section. Participants were videotaped while they sat alone with six novel toys/gadgets on a table in front of them. The amount of time spent engaging with the gadgets was the dependent

variable. The apathetic group (classified based on both the AS and LARS) spent significantly less time interacting with the gadgets than the nonapathetic group. Depression, motor severity, and levodopa equivalent dosage were not related to the amount of time spent engaged with the gadgets. Results indicated a strong correlation between 'real life' apathetic behaviors and the AS, demonstrating evidence for the construct validity of the AS (Ferencz et al., 2009; submitted to the American Academy of Neurology).

Apathy Inventory (AI). The AI is a 3 item 0-12 point Likert scale assessment of apathy. Adequate internal consistency and test-retest reliability were established with 60 patients with Alzheimer's disease (AD) and 12 patients with PD. However, no subsequent studies have used it besides the original authors and it needs to be further validated in a larger population of PD patients (Robert et al., 2002; (Leentjens et al., 2008).

Lille Apathy Rating Scale (LARS). The LARS is a 33 item semistructured interview for apathy based on Marin's original conceptualization. It yields a global score and four composite subscores that reflect different dimensions of apathy (i.e. intellectual curiosity, action initiation, emotion, and self awareness). The total score ranges from -36 to +36, with more positive scores indicating more severe apathy. The LARS was especially designed for PD patients, and validated in 159 French PD patients with and without dementia (Sockeel et al., 2006). It has good internal consistency, test-retest, interrater reliability, and acceptable item-total correlation. The authors validated it against clinical judgment of apathy. A recent study from our laboratory validated the English version of this scale in an American population. It used receiver operating characteristic (ROC) analysis to compare the LARS to the AS (Zahodne et al., 2009). A cut-off score was identified of -22 (sensitivity = 64%, specificity = 92%, PPV = 88%, NPV = 75%), which was slightly higher than the -16 cut-off score in the French population. Recently, the

authors have validated a caregiver version as well, the LARS-i (Dujardin, Sockeel, Delliaux, Destee, & Defebvre, 2008).

Frontal Systems of Behavior Scale (FrSBe). The FrSBe is a 46 item rating scale with self-report and family-report versions. It measures behavioral traits associated with damage to frontal-subcortical circuits. The FrSBe has three subscales, the Apathy Scale (14 items), the Disinhibition Scale (15 items), and the Executive Dysfunction Scale (17 items). Patients are asked to rate their pre-PD status and their current status on each of the items. The FrSBe has been validated in frontal lobe brain injury and neurodegenerative disorders, including PD (Grace & Malloy, 2001).

Single item assessments: Unified Parkinson's Disease Rating Scale (UPDRS) item 4 and Neuropsychiatric Inventory (NPI) item 7. The UPDRS is the most widely used assessment instrument in PD and has four sections. Part I includes mood, mentation, and behavior. A single item, item 4, assesses motivation/initiative on a 5 point Likert scale. It focuses on withdrawl from behavioral activities and does not capture the emotional dimension of apathy. Mixed results have been found with regard to the sensitivity and specificity of the UPDRS item 4. Two studies report that a cut-off of 2 has adequate sensitivity/specificity when compared to a shortened version of the AS (Starkstein & Merello, 2007); Pederson et al., 2007). A study from our laboratory used the full AS for validation purposes and found that a cut-off of 2 had poor sensitivity (52%), while higher cut-offs unacceptably lowered the specificity. Consequently, caution was recommended for using item 4 as a screening instrument for apathy (Kirsch-Darrow et al., 2009).

The Neuropsychiatric Inventory (NPI) also has a single item that assesses apathy. The NPI is a structured interview given by the clinician to an informant regarding 10 forms of behavioral

disorder that occur with dementia (Cummings, Mega, Gray et al., 1987). These include delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior. All items assess frequency and severity of the behavior being evaluated. In a small sample (n = 12) of PD patients, the NPI item 7 had good inter-rater agreement, otherwise the specific item still needs to be validated in PD patients.

Task Force Recommendations for Apathy Scales in PD. To evaluate these apathy scales and their use in PD, a task force was commissioned by the Movement Disorders Society in 2008 (Leentjens et al., 2008). The task force divided their findings into three levels: Recommended, Suggested, and Listed. They recommended the AS. They suggested further study for the AES, LARS, and NPI. The task force recommended using the UPDRS item 4, but only for screening purposes because it is a single item. They did not recommend the AI (i.e. they listed it as a scale that was available). They did not evaluate the FrSBe. The authors deemed it outside the scope of the assignment because the FrSBe also evaluates the neuropsychological features of disinhibition and executive dysfunction (Leentjens et al., 2008). The current study used the recommended AS.

Phenomenology of Apathy: Clinical Correlates and Course

Relationship to demographics and disease variables. Progress has been made in identifying the clinical correlates of apathy in terms of its association with demographics and disease variables. Multiple studies have found no relationship between apathy and age or years of education (Starkstein et al., 1992; Pluck & Brown, 2002; Isella et al., 2002; Zgalardic et al., 2007; Dujardin et al., 2007; Pedersen, Alves et al., 2009). One exception is a recent population based study in Norway. Authors reported that their apathetic group of patients with PD was older and had fewer years of education than their non-apathetic patients with PD (Pedersen,

Larsen, Alves, & Aarsland, 2009). Approximately one quarter of their total patients with PD had a dementia diagnosis, and their apathetic-nonapathetic groups differed with respect to the number of patients with dementia (50% of patients with apathy had dementia and 12% of patients without apathy had dementia). Due to this, it is hard to know whether age and educational differences might have been similar in their non-demented apathetic and nonapathetic patients.

The majority of studies that examined apathy and gender found no relationship between them (Starkstein et al., 1992; Pluck & Brown, 2002; Isella et al., 2002; Zgaljardic et al., 2007; Dujardin et al., 2007; Pedersen, Larsen et al., 2009). However, another population-based study in Norway of early drug-naive nondemented patients with PD found that apathy was significantly associated with male gender. Seventy-five percent of patients were male in their apathetic group (30 out of 40 patients), and 53% were male in their non-apathetic group (72 out of 135 patients (Pedersen, Alves et al., 2009). Gender also significantly predicted apathy in the regression models. The authors reported that this finding was unexpected and hypothesized that low testosterone levels may be related to apathy in their male PD patients—but testosterone was not measured in the study. Alternately, they also speculated that female caregivers were more likely to report negative symptoms than male caregivers (Pedersen, Alves et al., 2009). This explanation implies that apathy levels are actually similar between genders, but there is a bias of more frequent reporting of apathy by female caregivers. It also assumes female caregivers of male patients.

There are mixed findings with regard to the relationship between apathy and the severity of Parkinson's disease. Several studies do not find a relationship between apathy and disease severity based on the UPDRS-III motor subscale (Isella et al., 2002; Dujardin et al., 2007), the

Hoehn-Yahr staging of PD severity (Aarsland et al., 1999), or the tremor, akinesia, or rigidity items from the UPDRS-III (Starkstein et al., 1992; Aarsland et al., 1999). Two other studies report that higher apathy is associated with greater disease severity based on the UPDRS-III motor subscale (Pedersen, Alves et al., 2009); (Pedersen, Larsen et al., 2009). Another reports a trend towards higher apathy scores in patients with more severe Hoehn-Yahr stages (Zgaljardic et al., 2007).

In contrast to the mixed findings regarding disease severity, studies do not find a relationship between apathy and disease duration (e.g. length of PD) (Starkstein et al., 1992; Aarsland et al., 1999; Pluck & Brown, 2002; Isella et al., 2002; Dujardin et al., 2007; Pedersen, Alves et al., 2009). The fact that apathy is not related to disease duration, but is frequently related to disease severity may at first seem counterintuitive. However, it is reasonable given the variability of progression of the disease across patients. Some patients can stay relatively healthy with PD for 10-15 or more years, whereas others may decline more rapidly (Nutt, Hammerstad, & Gancher; Peretz & Cummings, 1988). Therefore, it seems that apathy symptoms may increase with disease severity (at least in some findings) but that duration of the illness is not associated with apathy.

Course of apathy. Apathy occurs in all stages of PD, including early drug-naive patients who are recently diagnosed (Pedersen, Alves et al., 2009). However, the longitudinal course of apathy in terms of factors such as fluctuations in severity across time, length of an episode, and remission information are relatively unknown. In a recently completed study from this laboratory, 139 idiopathic PD patients were assessed at two time points separated by 18 to 30 months (mean = 24 months, SD = 3.6 months). The AS, BDI, anxiety scores, quality of life scores, and motor scores were completed at these time points. Results indicated that AS and

motor scores significantly worsened, while depression scores showed no difference. Worsening apathy correlated with increased motor severity at trend. Worsening apathy was associated with lower baseline AS, worsening anxiety trait scores, motor scores, and quality of life. This study suggests that apathy and depression may have a separate course of presentation in moderately severe PD patients, with apathy worsening and depression remaining stable over two years (Zahodne et al., 2009; Submitted to the American Academy of Neurology). Other studies have focused on apathy following deep brain stimulation (DBS) surgery for PD. Some studies have found that apathy increases after surgery (Kirsch-Darrow et al., 2009, submitted). Other information about the longitudinal course in surgery-naive patients is unknown.

Separating Apathy and Depression in PD

The majority of the literature points to the ability to separate apathy from depression. Specifically in PD, it has been argued that apathy can occur in the absence of depression and depression can occur in the absence of apathy. Starkstein and colleagues (1992) examined a consecutive series of 50 PD patients for apathy and depression symptoms and found that 12% were at or above the cut-off score for clinically significant apathy but did not meet criteria for depression (criteria based on DSM-III). They also found no difference in apathy levels between patients with and without depression. Many other studies have shown apathy without depression in patients with PD (Levy et al., 1998; Aarsland et al., 1999; Isella et al., 2002; Pluck & Brown, 2002; Kirsch-Darrow et al., 2006; Zgaljardic et al., 2007; Pedersen et al., 2009)

Pluck and Brown (2002) found apathy to be significantly higher in PD than in control osteoarthritis patients. They did not find a difference in depression levels between patients with high levels of apathy and those with low levels of apathy. A study from our laboratory compared apathy and depression in a PD group and a movement-disordered control group of dystonia patients (Kirsch-Darrow et al., 2006). It was hypothesized that PD patients would have

significantly more apathy than patients with dystonia and a large proportion of PD patients would experience apathy in the absence of depression. Eighty PD patients and 20 with dystonia completed mood questionnaires that included the Apathy Scale and the Beck Depression Inventory. Apathy was significantly more frequent in PD (freq=51%, 41/80) than in dystonia (freq=20%, 4/20, p = .012). Moreover, the frequency of apathy in the absence of depression was substantial in PD and nonexistent in dystonia (PD = 29%, dystonia = 0%, p <.01) (see Figure 2-1). These data provide support for the hypothesis that apathy may not be limited to co-occur within depression, but may be its own separate syndrome.

However, a weakness of current studies is the manner by which patients are classified as exhibiting 'apathy' or exhibiting 'depression.' To date, this classification has primarily involved using total scores from apathy and depression inventories (ex. Beck Depression Inventory [BDI] and Apathy Scale [AS]). This is problematic because apathy and depression have overlapping symptoms such that the scales overlap in content. The BDI includes item content that purportedly overlaps with apathy (ex. 'I am less interested in other people than I used to be'). It is possible that a particular symptom endorsement on the BDI might better represent apathy and is being counted toward depression total score and vice versa. One way to address this limitation is to use a more sophisticated methodological approach—that of confirmatory factor analysis. Factor analytic techniques can investigate whether items load onto discrete apathy and depression factors. Confirmatory factor analysis, in particular, will allow specific a priori hypotheses about the underlying structure of the data to be tested.

Confirmatory Factor Analysis: Rationale for Selection of Factors

The present study will take a confirmatory analytic approach to test the hypothesis that patients' scores on the Apathy Scale and Beck Depression Inventory-II will load onto 4 factors: 1) an apathy factor representing loss of motivation, 2) a dysphoric mood factor representing

sadness and negativity, 3) a loss of interest and loss of pleasure factor representing the overlap between apathy and depression, and 4) a somatic factor representing bodily complaints. See Table 4-2 for a detailed listing of hypothesized factors and the items that compose them. The rational for these hypothesized factors is based on several ideas about how apathy and depression can be parsed. Sad mood, dysphoria, and tearfulness are commonly found in depressive syndromes. However, literature suggests that apathy does not include sad mood, and apathy has instead been described as a "blunted" or "no" mood (Brown & Pluck, 2000). Symptoms of 'negativity' such as worthlessness, failure, disappointment, and guilt are hypothesized to be related to depression. Apathy does not involve pessimism or negative self and event appraisal. Instead, what distinguishes apathy is loss of motivation. While loss of motivation can be found in depressive disorders, it may be a more 'primary' feature of apathy. When found in depression, it is secondary to sadness and "giving up."

The rationale for a loss of interest and anhedonia factor is based on the idea that these symptoms are common to both apathy and depression. In fact, a National Institute of Neurological Disorders and Stroke (NINDS) depression in PD workgroup highlighted loss of interest and pleasure as symptoms that overlaps between depression and primary apathy (Marsh, McDonald, Cummings, & Ravina, 2006). The current study will test this hypothesis. "Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day" is a criteria for a major depressive disorder (DSM-IV-TR). Furthermore, Pluck and Brown (2002) reported that their apathetic PD patients scored higher in anhedonia (based on the Snaith—Hamilton Pleasure Scale) than their nonapathetic PD patients. Lastly, the somatic factor encompasses physical symptoms such as fatigue, changes in appetite and sleep patterns, and changes in sexual drive. They are hypothesized to cluster together and to load onto their own

separate factor. Further, it seems appropriate to separate the physical symptoms because even in the absence of mood disorder, patients often experience these symptoms as part of PD.

Prior Exploratory Factor Analysis of BDI-II and AS

The factor structure of the BDI-II has been examined in large undergraduate student populations. The BDI-II manual reports a two-factor solution as the most parsimonious description of the data in an undergraduate sample. The factors corresponded to Cognitive—Affective symptoms and Somatic symptoms (Beck, 1996). This factor structure was replicated in a study of over 1,000 Canadian undergraduates (Dozois, Dobson, & Ahnberg, 1998). Two factors accounted for 46% of the variance and were labeled the Cognitive—Affective dimension and the Somatic—Vegetative dimension. The Cognitive—Affective factor consisted of items such as past failure, worthlessness, self-dislike, pessimism, self-criticalness, indecisiveness, guilty feelings, suicidality, punishment feelings, and sadness. The Somatic—Vegetative factor primarily consisted of the items of changes in sleep, fatigue, loss of energy, irritability, agitation, loss of interest in sex, loss of interest, loss of pleasure, and changes in appetite (Dozois, Dobson, & Ahnberg, 1998). Consistent with these exploratory analyses, the present study proposes a separate somatic factor. Notably, the Dozis et al. (1998) study includes loss of interest and anhedonia along side the other physical symptoms. In a clinical sample of PD patients with more prevalent mood disorders than a diverse undergraduate population, loss of interest/anhedonia are predicted to fall into a separate factor.

There are no published studies on the structure of the Apathy Scale. The original validation study of the Apathy Evaluation Scale included an exploratory factor analysis. In a population 123 subjects with either major depressive disorder, stroke, Alzheimer's disease, or normal elderly adults, three main factors were reported (Marin et al., 1991). These included a General apathy factor (Factor 1) with items involving having initiative, lack of productivity,

emotional flatness, lack of effort. Factor 2 included items that dealt with curiosity or novelty seeking, interest in things (in general), learning, new experiences, and spending time in interesting activities. Factor 3 included items involving insight, lack of concern about one's problems and needing structure for daily activities. In our laboratory, an exploratory factor analysis (EFA) study of the Apathy Scale was recently completed on 78 non-demented PD patients with clinically significant apathy. Initial analysis indicated that items 3 (Are you concerned about your condition?) and 13 (Are you neither happy nor sad, just in between?) did not correlate with the total apathy score and were excluded from the EFA. Principal axis factoring with Promax rotation was used. Results suggested a three factor solution that resembled Cognitive (items 1, 2, 6 involving learning, interest, and plans/goals for the future), Behavioral (items 4, 5, 7, 8 involving effort, seeking out activities, motivation, and energy), and Affective (items 10, 11, 14 involving emotional indifference and lack of concern) domains (Kay et al., submitted to American Academy of Neurology, 2009).

Potential Contribution of Confirmatory Factory Analysis

Prior studies have investigated the latent structure of the BDI-II and the AS. No studies have combined items from both scales into one analysis. This will allow items to load across scales and constructs can be proposed that extend across both scales. Confirmatory factor analysis (CFA) was selected over EFA because it allows a priori hypotheses to be made and tested. CFA will contribute to the PD literature because it will test discrete apathy and depression factors. Individual items can be placed onto specific factors. Additionally, CFA has the benefit of multiple indices to measure the goodness of fit of the hypothesized model to the data, whereas EFA only has one (e.g. square root mean residual).

Potential Implications

If the results support separate apathy and depression factors, this will provide increasing empirical support for the dissociability of these two mood disorders in PD. If apathy manifests as a separate disorder, this has important implications for clinical practice and for the understanding of the neural substrates involved. First of all, apathy can greatly affect PD patients' lives. A recent large scale survey of nonmotor symptoms 1,000 Italian PD patients reported that apathy was one of the symptoms most negatively impacting quality of life (Barone et al., 2009). Further, treatments specific to apathy in neurological disorders are being investigated. Amphetamines, atypical antipsychotics, dopaminergic agents, and acetylcholinesterase inhibitors have been examined (van Reekum, Stuss, & Ostrander, 2005). Methylphenidate (i.e. Ritalin) successfully treated apathy in a case study of a man with Parkinson's disease and cognitive impairment (Chatterjee & Fahn, 2002). There is preliminary support for the efficacy of some of these pharmacological interventions in neurological diseases such as Traumatic Brain Injury (TBI) and Alzheimer's Disease (Galynker et al., 1997; Kaufer, 1999; Kraus & Maki, 1997; Van Reekum et al., 1995). Moreover, a clinical trial has very recently been completed at this center (University of Florida, Movement Disorders Center) investigating repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of apathy in PD. Twenty-four PD patients experiencing either mixed apathy/depression (n = 11) or pure apathy (n = 13) underwent apathy, depression, and motor assessment prior, immediately following, one month, and three months after treatment. Treatment was either high frequency rTMS (10Hz) or sham stimulation delivered over the left dorsolateral prefrontal cortex for 10 days. Both rTMS and sham showed significant improvements in apathy immediately, at one month, and at three months post-treatment. There was no difference between the level of improvement derived from rTMS vs. sham, and no differences between the pure apathy and

mixed apathy/depression group. This study indicates that brief, daily behavioral interventions are important for apathy, but does not demonstrate a unique effect of rTMS (Fernandez et al., 2009, submitted to American Academy of Neurology).

Furthermore, different neural mechanisms may underlie apathy and depression in PD. Orbito-frontal-subcortical connections may underlie depression whereas mesial frontal/anterior cingulate cortex-ventral tegmental connections may underlie apathy in PD. Using Positron Emission Tomography (PET), Mayberg and colleagues demonstrated a relationship between depression in PD patients and hypometabolism in the orbital-inferior area of the frontal lobe, and the caudate, as compared to nondepressed PD patients (Mayberg, 1994; Mayberg et al., 1990). Apathy may result from dysfunction of the anterior cingulate cortex circuit. This cortico-striato-pallido-thalamo circuit consists of anterior cingulate cortex→ ventral striatum→ ventral pallidum→dorsomedial thalamus→anterior cingulate cortex. Very few studies have as of yet examined the neuroanatomical basis for apathy in PD. Yet, past research has shown that bilateral lesions in the anterior cingulate cortex (ACC) leads to a severe form of apathy called akinetic mutism. The patient makes no attempt to act, speak, or initiate activity. Patients can recover from this condition and afterwards report that they felt "empty" and had "nothing to say" and were not motivated (Damasio & Tranel, 1992). Remy and colleagues (2005) examined apathy in twenty Parkinson patients using Positron Emission Tomography with a radioactive ligand that binds selectively to dopamine and norepinephrine receptors (Remy, Doder, Lees, Turjanski, & Brooks, 2005). Decreased binding is a marker for cell loss. Higher apathy on the AES was related to reduced dopamine/norepinephrine binding in the ventral striatum. This is consistent with the circuit above. Taken together, findings may indicate that apathy is a separate

mood disorder in PD, needing more careful assessment and treatment. One area needing further assessment is the relationship between apathy and cognitive impairment.

Apathy and Cognitive Impairment

Overview of Cognitive Impairment in PD

Parkinson's disease is accompanied by a broad spectrum of cognitive impairment, ranging from mild deficits in executive functioning to fully developed dementia. Further, there is wide variability in cognitive impairment in non-demented patients. Impairment in executive functioning, language, memory, and visuospatial skills have been described in non-demented PD patients (Caballol, Marti, & Tolosa, 2007; Dubois & Pillon, 1997; Pillon, Czernecki, & Dubois, 2003; Taylor & Saint-Cyr, 1995). Although not pervasive across all individuals with PD, memory, psychomotor speed, and executive functioning, can be impaired as early as when the patient is initially diagnosed with PD (Levin & Katzen, 1995, 2005; Levin, Llabre, & Weiner, 1989; Muslimovic, Post, Speelman, & Schmand, 2005).

Two domains that are commonly impaired in PD are memory and executive functioning. Memory impairment in PD is characterized by deficits in free recall, with benefit from cuing and preserved recognition. This memory impairment profile is considered secondary to executive dysfunction. Specifically, it is thought that PD patients find it difficult to organize information for encoding and retrieval (Brandt, Shpritz, Munro, Marsh, & Rosenblatt, 2005). Subcortical dementias (i.e. also called fronto-subcortical dementias such as Parkinson's disease, Huntington's disease, and Progressive Supranuclear Palsy) are considered to exhibit memory deficits that are not "true amnesia," but secondary to inefficient strategies of encoding/retrieval that are due to pathology of fronto-striatal connections. This memory profile can be contrasted with cortical dementias like Alzheimer's disease that have prominent memory deficits, rapid

forgetting, little benefit from cuing, and impaired recognition (Albert, Feldman, & Willis, 1974; Elias & Treland, 1999; Pillon, Deweer, Agid, & Dubois, 1993).

Executive functioning impairment in PD are widely reported in the literature, and is common even in patients without otherwise significant cognitive impairment (Caballol et al., 2007; Muslimovic et al., 2005; Perry & Hodges, 1996; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). The type and severity of executive impairment can vary across patients. However, deficits in attentional set-shifting, planning, concept formation, and inhibition of responses have been consistently described (Owen et al., 1992; Dubois & Pillon, 1997; Weintraub et al., 2005; Muslimovic, Post, Speelman & Schmand, 2005; Williams-Gray et al., 2007; Caballol et al., 2007). A further review of executive functioning will be continued in the next section. Before turning to this, a brief overview of PD related dementia is provided next.

The estimated prevalence of dementia in PD is between 25-30% of patients (Aarsland et al., 2005). The DSM-IV diagnostic criteria do not capture all of the characteristics of dementia in PD because of their focus on memory and on impaired activities of daily living. Memory deficits are not always prominent in PD dementia. Also, it can be difficult to determine if impairment in activities of daily living in PD are due to cognitive impairment or due to motor disability. Dementia in PD begins insidiously and is characterized by a slowly progressive cognitive decline. Initial complaints frequently involve concentration, poor immediate recall, slowed information processing, and word finding problems (Caballol et al., 2007). Factors that are associated with increased risk of dementia in PD are older age and greater severity of motor symptoms (Aarsland, Andersen et al., 2001; Hobson & Meara, 2004); Hughes et al., 2000). Further, a longitudinal study by Levy et al. (2002) found support for the combined effect of age

and severity of motor symptoms. Results indicated that age was an important risk factor for dementia only when coupled with more severe motor symptoms. Older age without severe motor symptoms was not associated with increased risk of dementia (G. Levy et al., 2002).

Executive Functions: Definition and Review of Findings in PD

The term executive functions is an "umbrella" term encompassing functions such as planning, shifting mental sets, abstract reasoning, mental flexibility, and problem solving (Burgess, Veitch, de Lacy Costello, & Shallice, 2000; Damasio, 1995; Stuss, Shallice, Alexander, & Picton, 1995). Executive functions are the most complex of human behaviors, and are key in our ability to respond and adapt to novel situations (Lezak, 1982; Lezak, Howieson, & Loring, 2004). Impairment in one or more executive functions can have devastating effects on people's everyday lives, including occupation/educational performance, independent functioning at home, and developing and maintaining social relationships (Chan, Shum, Toulopoulou, & Chen, 2008; Green, Kern, Braff, & Mintz, 2000).

An important aspect of executive functions is how it fractionates into specific subcomponents and skills. A patient's performance on one type of executive function may have no predictive value for another type of executive function (Burgess, Alderman, Evans, Emslie, & Wilson, 1998). Over the last two decades, progress has been made in isolating what areas of the prefrontal cortex are involved in which particular cognitive processes. For example, the dorsolateral prefrontal circuit is involved in planning, goal selecting, sequencing, and working memory, whereas the orbitomedial circuit and anterior cingulate circuit are involved in response inhibition (MacDonald, Cohen, Stenger, & Carter, 2000).

As it might be imagined, many cases involving executive functioning involve frontal lobe damage. However, importantly, subcortical structures and their connections to prefrontal lobe are also involved. This is especially relevant for PD. Many of the "frontal-like" executive

deficits in PD have been ascribed to dysfunction in the connections between the striatum and prefrontal lobes (Elias & Treland, 1999; Owen, 2004; Owen et al., 1992; Zgaljardic, Borod, Foldi, & Mattis, 2003; Zgaljardic et al., 2007).

Unfortunately, the neuropsychological measurement of executive functions is difficult and sometimes controversial. First, there is a paradoxical need to structure a situation where the patient can demonstrate how well they can create structure for themselves (Lezak, 1982). In contrast, during the administration of most cognitive tests, the examiner decides what activity the subject is to do, conveys the rules, and leaves relatively little room for discretionary behavior on the part of subject (Lezak, Howieson, & Loring, 2004). To accurately measure executive functions, tests must allow the subject enough room to make decisions, and think of and chose alternatives for their own behavior and cognition (Lezak, Howieson, & Loring, 2004).

Ecological validity is another issue when measuring executive functions. Although tests can demonstrate excellent psychometric properties, they may not map on to the naturalistic tasks found in everyday life (Goldstein, 1996; Sbordone, 1996). Also, at times, patients with frontal lesions perform equally well as controls on neuropsychological tests, but experience multiple difficulties in everyday life (Shallice & Burgess, 1991). Thus, tests are not always sensitive to executive functioning difficulties. Daily life may require more complex multi-step tasks that require goal setting, prioritization, reliance on prospective memory, and inhibition of inappropriate actions than tests are able to capture (Chan et al., 2008). However, neuropsychological measures of executive functioning are often criticized for tapping a number of executive functions all at the same time, making it difficult to ascertain which specific skill is impaired. This leaves measures of executive function in a "catch 22" because when they

incorporate more tasks they are likely more ecologically valid. However, when they are more ecologically valid, they do not capture the fractionation of the executive system.

Overview of Executive Impairment in PD. Despite the difficulties with the measurement of executive functions described above, progress has been made in understanding the executive impairment in PD. Studies have compared the performance of PD patients to that of individuals with frontal lobe damage. Like patients with frontal lobe damage (Milner, 1964), PD patients both "on" and "off" their levodopa medications showed set-shifting impairment on the Wisconsin Card Sorting Task (WCST) (Canavan et al., 1989; Lees & Smith, 1983; Taylor, Saint-Cyr, & Lang, 1986). This set-shifting difficulty has been found on other tests in addition to the WCST. Downes et al. (1989) found that PD patients were impaired on visual discrimination learning when required to shift response sets between two stimulus dimensions (Downes et al., 1989). This was replicated and extended by Owen et al. (1991). PD patients and frontal lobe patients were impaired on this task, but patients with unilateral temporal lobe damage or amygdala-hippocampal damage were not impaired (Owen, Roberts, Polkey, Sahakian, & Robbins, 1991).

Studies have also found that PD patients are impaired in planning abilities. PD patients were impaired in organizing "picture stories" on the Picture Arrangement subtest of the WAIS. Authors interpreted this as impairment in sequencing and forward planning (Growdon, Corkin, & Rosen, 1990). Further, PD patients were impaired (increased) in terms of the amount of time spent thinking about their solution to the Drexel Tower of London planning test. However, accuracy on this test was only impaired in patients with more severe Hoehn and Yahr disease staging (Owen et al., 1992).

Weintraub and colleagues (2005) found that increased severity of parkinsonism was associated with reduced inhibitory control on the Stroop interference condition. They administered the Drexel Tower of London test, the Trail Making Test, and the Stroop Color Word Test, Golden version, to 46 PD patients. Subscores from the measures were factor analyzed. Two factors emerged: 1) a planning factor that encompassed total moves, time violations, and execution time from the Drexel Tower of London test, and 2) an inhibitory control factor consisting of errors on Trails B, errors on Stroop Color Word task, Interference condition, and rule violations on the Drexel Tower of London test. The inhibitory control factor was negatively correlated with motor slowing, increased parkinsonism, and lower educational level. The planning factor was negatively correlated with apathy as measured by the Apathy Scale (Weintraub et al., 2005). However, this study was limited by a 96% male population (limiting generalizability), a relatively small sample size compared to the number of factors analyzed, and the use of principal component (PCA) extraction. PCA is controversial and generally discarded in favor of exploratory factor analysis because it does not separate shared and unique variance, and therefore is less helpful in revealing latent variables (Gorsuch, 1990; Costello & Osborne, 2005).

As with most PD symptoms, executive function impairment is thought to be associated with dopaminergic dennervation of the striatum. This, in turn, leads to a cascade of dysfunction including the connections between subcortical and cortical brain structures. It is thought that connections between the striatum and differential areas of cortex can account for some of the non-motor symptoms of PD. For instance, disruptions between basal ganglia and dorsolateral prefrontal cortex is thought to affect working memory and set shifting ability. Disruptions between basal ganglia and anterior cingulate cortex is though to disrupt motivation and response

initiation (Zgaljardic, 2003, Lichter, 2000). However, this represents a broad generalization of the effects of complex neurodegenerative processes. In addition to dopamine systems, it is likely that non-motor symptoms also involve other systems such as the cholinergic system. Dopaminergic treatment consistently improves motor functioning in PD, but it does not always improve cognition (Cooper et al., 1992; Zgaljardic et al., 2003; Gotham, Brown, & Marsden, 1998).

Cognitive Impairment: Association with Demographic and Disease Variables

General demographic variables as well as disease specific variables are known to be related to cognitive impairment. In normal aging, it has been well established that older age and fewer years of education are associated with poorer cognitive functioning (Collie, Shafiq-Antonacci, Maruff, Tyler, & Currie, 1999; Scuteri, Palmieri, Lo Noce, & Giampaoli, 2005). In PD, age and education have been found to be associated with executive impairments, particularly on planning tasks (Taylor et al., 1986). In a meta-analysis of 25 longitudinal studies of cognition in PD, age was significantly related to decline global cognitive abilities (measured by dementia rating scales such as MMSE) and memory. Lower educational levels were associated with decline in all cognitive domains (e.g. global cognitive abilities, memory, verbal abilities including verbal fluency, reasoning, attention, processing speed, visuo-perceptial and visuo-spatial abilities) (Muslimovic, Schmand, Speelman & De Hann, 2007). Further, disease severity has been shown to be an important predictor of cognitive impairment. Studies have demonstrated that patients at different stages of PD can be differentiated in terms of executive functions (e.g. specifically, planning on the Drexel Tower Test, and attentional set-shifting on a computerized test of visual stimulus dimensions where subjects had to shift each time to focus on the previously irrelevant stimulus dimension), working memory, and short-term spatial memory (Morris et al., 1988; Owen et al., 1992).

Mood Disorders in PD: Effect on Cognition.

The fact that impairment in executive functions often accompanies PD is clear. What seems less well established is the effect of mood disorders on cognitive impairment in PD. It is notable that even in young, neurologically intact individuals with Major Depressive Disorder (MDD) studies find that depression has variable effects on cognition. Some studies suggest MDD is related to decreased concentration (one of the diagnostic criteria for MDD), slowed information processing and impaired working memory (reviewed by Mayberg et al., 2002). Other studies find no neuropsychological distinctions between moderately depressed individuals and non-depressed individuals matched on age and education (Crews et al., 1999).

Depression's Effect on Cognitive Functioning in PD. The situation is more complex when examining depression in PD because it is a neurological disorder commonly associated with cognitive impairment such as slowed information processing, executive deficits, and memory retrieval problems. There are mixed findings regarding whether depression exacerbates cognitive impairment in PD. Some studies report no differences in cognitive performance between depressed and non-depressed PD patients (Beliauskas et al., 1989; Santamaria et al., 1986; Taylor et al., 1986; Huber et al., 1988). Others report that depressed PD patients have worse general cognitive functioning on the Mini Mental Status Exam (MMSE) and the Dementia Rating Scale (Troster, Stalp et al., 1995; Troster, Paolo et al., 1995; Starkstein et al., 1990; Starkstein et al., 1992). More recent studies are more methodologically sophisticated because they match depressed PD patients and non-depressed PD patients on demographic, disease variables, and general dementia screening measures. These studies find that depression is associated with greater impairments in executive functioning and working memory (Kuzis, Sabe, Tiberti, Leiguarda, & Starkstein, 1997; Santangelo et al., 2009; Uekermann et al., 2003).

An early study by Starkstein and colleagues (1992) examined approximately 100 PD patients and categorized them into major depression, minor depression, and non-depressed based on psychiatric interview with DSM-III criteria (Starkstein, Mayberg, Leiguarda, Preziosi, & Robinson, 1992). Authors re-assessed these patients after one year and reported the differences between groups. The PD patients with major depression had significantly: 1) greater decline in MMSE scores than the other two groups, 2) a longer duration of illness, 3) greater declines in activities of daily living over 1 year, and 4) greater impairments in motor scores. Authors concluded that major depression in PD is related to faster progression of PD (Starkstein, Mayberg, Leiguarda et al., 1992). Yet, the patients with major depression had longer duration of illness (i.e. more years with PD) than the other two groups. This confounds the conclusions because duration of illness could account for the cognitive and ADL declines.

Other studies matched disease and demographic variables. Troster and colleagues (1995) carefully matched 44 depressed PD patients, 44 nondepressed PD patients, and 44 normal elderly controls on disease variables (PD groups only) and demographic factors, and compared neurocognitive profiles (Troster, Stalp, Paolo, Fields, & Koller, 1995). Results indicated that the depressed PD group, but not the non-depressed PD group, had poorer performance on phonemic fluency, semantic fluency, and confrontation naming than healthy controls. Comparing depressed PD and non-depressed PD groups revealed worse immediate recall and semantic fluency in the depressed PD group (Troster et al., 1995). However, authors reported that the DRS scores were significantly lower in the depressed PD group. They then matched the two groups on overall DRS score, using a subsample of 15 depressed and 15 non-depressed PD patients, and found that the significant differences between PD groups disappeared. Authors discussed the importance of matching to general cognitive functioning/dementia level.

Several studies have matched all three: demographics, disease variables, and general cognitive functioning/dementia measure scores. These studies find that depressed PD patients perform more poorly on measures of executive functioning than non-depressed PD patients. Kuzis and colleagues (1997) included four matched groups: MDD without PD, depressed PD, non-depressed PD, and normal controls. The MDD and depressed PD patients were more severely impaired than the other two groups on verbal auditory attention (i.e. digit span) and phonemic verbal fluency. Depressed PD patients were worse than all three other groups on abstract visual reasoning (i.e. Ravens Progressive Matrices) and set shifting/mental flexibility (i.e. Wisconsin Card Sorting Task). Depressed PD patients completed fewer categories than the three other groups. Uekermann et al.(2003) also found that reasoning and verbal fluency were impaired in depressed PD patients relative to normal controls. This study examined patients early in the course of PD. There were two control groups—MDD without PD, and healthy controls. Depressed and non-depressed PD groups were matched on MMSE scores and all groups were matched on demographics and IQ. The depressed PD patients were depressed based on a BDI score of > 10 (e.g. DSM criteria was not used to diagnose MDD in the PD group). Depressed PD patients, but not non-depressed PD patients, were impaired compared to normal controls on alternating semantic verbal fluency (alternating between first names and vegetable names), working memory (i.e. Digit Span), and abstract verbal concept formation (i.e. Similarities subtest from the Wechsler Abbreviated Scale of Intelligence) (Uekermann et al., 2003).

Similarly, in a recent study using DSM-IV MDD diagnostic criteria, depressed PD patients showed more executive impairment than non-depressed PD patients (Santangelo et al., 2009). Depressed PD patients performed worse on the Frontal Assessment Battery, semantic

fluency, copy of visuospatial figures, Stroop color reading, and Stroop interference. Authors suggest that copying the visuospatial figures may be related to executive functioning because subjects exhibited poor planning in their copies (Santangelo et al., 2009).

Apathy's Effect on Cognitive Functioning in PD. Apathy, too, may affect cognitive functioning in PD. Six studies examined the relationship between apathy and cognitive functioning (Isella et al., 2002; Pluck & Brown, 2002; Starkstein, Mayberg, Preziosi et al., 1992; Zgaljardic et al., 2007). See Table 2-3. These studies classified PD patients into high and low apathy groups and examined for differences on cognitive measures. The majority of cognitive measures administered were executive functioning tasks. A few other measures of memory, visuospatial skills, and attention were interspersed across several studies. Apathy was consistently associated with worse performance on semantic and phonemic fluency (Isella et al., 2002; Pedersen, Alves et al., 2009; Pluck & Brown, 2002; Santangelo et al., 2009; Starkstein, Mayberg, Preziosi et al., 1992; Zgaljardic et al., 2007). There were mixed findings regarding cognitive inhibition, as measured by the Stroop Interference task, and set shifting/mental flexibility, as measured by the Wisconsin Card Sorting Task (WCST). Two studies found cognitive inhibition was worse in the apathetic group compared to the non-apathetic group (Pluck & Brown, 2002; Santangelo et al., 2009) and two studies did not find a difference between groups (Pedersen, Alves et al., 2009; Zgaljardic et al., 2007). Similarly, there were mixed findings regarding the WCST; one study reported that apathetic patients completed fewer categories than non-apathetic patients (Pluck & Brown, 2002), but another found no differences in number of categories completed (Starkstein et al., 1992). The Executive Interview, Frontal Assessment Battery, and Cambridge Examination of Cognition in the Elderly were all more impaired in apathetic versus nonapathetic patients (Isella et al., 2002; Santangelo et al., 2009;

Pluck & Brown, 2002, respectively). Generally, there appears to be support for a negative association between apathy and executive functioning. Further studies are needed to determine whether certain aspects of executive functioning are consistently related to apathy. All studies find a relationship between impaired verbal fluency and higher levels of apathy, but other results are mixed.

Several memory, visuospatial, and attention tasks were also given. There were mixed findings regarding memory/new learning, and visuospatial functioning. Paired word learning was worse in apathetic than nonapathetic patients (Starkstein et al., 1992). Yet, verbal story recall (an Italian-normed story), word list learning and recall (California Verbal Learning Test-II), and visual figure recall (Rey-Osterreith figure—recall) were not different between groups (Isella et al., 2002; Pedersen et al., 2009). Visuospatial skills, specifically visual object perception (Silhouettes from the Visual Object and Space Perception battery) and copying simple and complex figures were impaired in apathetic patients (Pedersen et al., 2009; Santangelo et al., 2009). However, visual space perception (Cube Test from the Visual Object and Space Perception battery) and copying of a complex figure (Rey-Osterreith figure—copy) were not different across groups (Pedersen et al., 2009; Isella et al., 2002). Attention and working memory, as measured by Digit Span and Spatial Span, were not different between apathetic and nonapathetic groups (Starkstein et al., 1992; Isella et al., 2002; Zgaljardic et al., 2007). This was a consistent finding across studies that measured attention/working memory.

Although progress is being made in the understanding of how apathy affects cognition, there are several confounding factors in the interpretation of the data. First, three out of six studies included patients with probable dementia. The recommended cut-off for dementia in PD based on the MMSE is <26 (Dubois et al., 2007). Starkstein et al. (1992), Isella et al. (2002),

and Santangelo et al. (2009) included patients below this threshold. This is problematic for the purposes of examining apathy and cognition because of unequal distribution of dementia cases across apathetic and non-apathetic groups. Based on the MMSE means for each group, there are more individuals with probable dementia in the apathetic group for Starkstein et al. (1992) and Isella et al. (2002). Santangelo et al. (2009) collected MMSE scores, but did not compare them across their apathetic/anhedonic group classifications. More dementia in apathetic groups confounds conclusions that apathy is related to impaired cognitive functioning because the impairment could be driven by the overall deficits in general cognitive functioning in the unequal distribution of individuals with dementia.

On the same note, depression was often not controlled for across groups. Depressive symptoms were greater in the apathetic groups versus the nonapathetic groups in two studies (Zgaljardic et al., 2007; Pederson et al., 2009). Differences in depression across apathetic/anhedonic group classifications in Santangelo et al. (2009) is unknown. As with dementia, greater depression in the apathetic groups—given the relationship between depression and cognitive impairment reviewed earlier—clouds conclusions that cognitive deficits are related to apathy.

Lastly, most studies do not measure multiple cognitive domains in their sample. Mostly, studies administered executive tasks plus a sampling of one or two other domains. This likely contributed to the inconsistencies in findings regarding memory/new learning and visuospatial tasks. Studies have different sample characteristics and use different apathy scales and hence different cut-off scores to create their groups.

Addressing Current Confounds. The present study aims to address these confounds by controlling for dementia, depression, and assessing a wide range of cognitive domains within the

same sample. It is critical to control for the effects of depression and other demographic and disease variables to determine if apathy has a unique effect on cognition. The present study is designed to address the unique contribution of apathy to cognitive functioning above and beyond that of other variables. This will help determine whether or not apathy is an important factor influencing cognitive performance in PD.

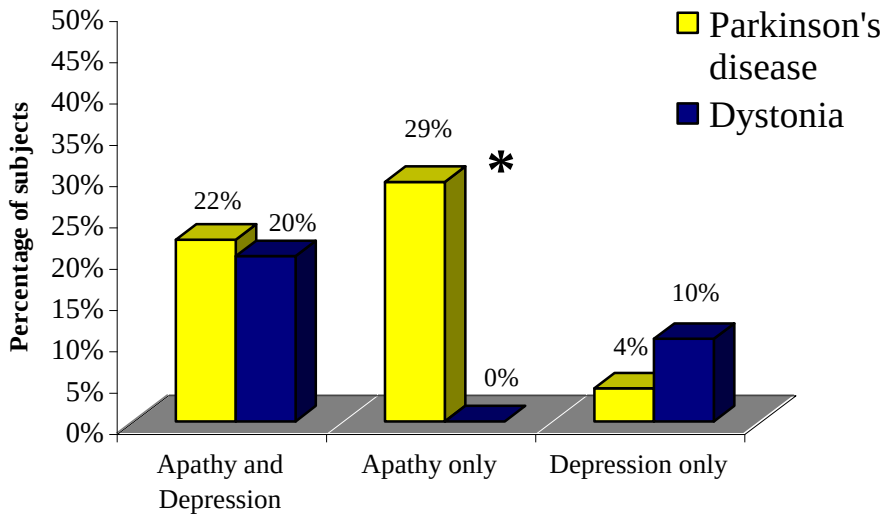

Figure 2-1. Overlap between apathy and depression, apathy alone, and depression alone between groups.

Table 2-1. Marin's proposed criteria for the syndrome of apathy

Lack of motivation, relative to patient's previous level of functioning or the standards of his or her age and culture, as evidenced by all three of the following:
BEHAVIOR
1) Diminished goal-directed overt behavior as indicated by:
Lack of productivity
Lack of effort
Lack of time spent in activities of interest
Behavioral compliance or dependency on others to structure activity
Diminished socialization or recreation
COGNITION
2) Diminished goal-directed cognition as indicated by:
Lack of interests, lack of interest in learning new things, lack of interest in new experiences
Lack of concern about one's personal, health, or functional problems
Diminished importance or value attributed to such goal-related domains as socialization, recreation, productivity, initiative, perseverance, curiosity
EMOTION
3) Diminished emotional concomitants of goal-directed behavior as indicated by:
Unchanging affect
Lack of emotional responsivity to positive or negative events
Euphoric or flat affect
Absence of excitement or emotional intensity

Table 2-2. Proposed consensus criteria for a syndrome of apathy from the European Psychiatric Association

For a diagnosis of Apathy, the patient should fulfill criteria A, B, C, and D.
A. Loss of, or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observation of others.
B. Presence of at least one symptom in ***at least two of the three following domains*** for a period of at least four weeks and present most of the time:
Domain B1: **Loss of, or diminished, goal-directed behavior** as evidenced by at least one of the following: 1) Loss of self-initiated behavior (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices 2) Loss of environment-stimulated behavior (for example: responding to conversation, participating in social activities)
Domain B2: **Loss of, or diminished, goal-directed cognitive activity** as evidenced by at least one of the following: 1) Loss of spontaneous ideas and curiousity for routine and new events (i.e. challenging tasks, recent news, social opportunities, personal/family and social affairs. 2) Loss of environment-stimulated ideas and curiosity for routine and new events (i.e. in the person's residence, neighborhood, or community).
Domain B3: **Loss of, or diminished emotion** as evidenced by at least one of the following: 1) Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observations by others of a blunted affect) 2) Loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)
C. These symotoms (A-B) cause clinically significant impairment in personal, social, occupationa., or other important areas of functioning.
D. These symptoms (A-B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effect of a substance (e.g. drug of abuse, a medication).

Table 2-3. Summary of PD studies examining cognition in apathetic versus nonapathetic groups

Study	***N***	**Apathy Measurement**	**Exec. Functioning Tests Significantly Worse in Apathetic vs. Nonapathetic PD Patients**	**Exec. Functioning Tests Similar Between Groups**
Starkstein et al., 1992	*N* = 50	Apathy Scale	Letter fluency TMT, Part B	WCST categories TMT, Part A
Isella et al., 2002	*N* = 30	Apathy Scale	Letter fluency Semantic fluency Executive Interview	None
Pluck & Brown, 2002	*N* = 45	Apathy Evaluation Scale	Letter fluency Semantic fluency WCST, categories Stroop Word, Color, and Interference Cambridge Examination of Cog. in the Elderly	WCST, perseverative errors
Zgaljardic et al., 2007	*N* = 32	Frontal Systems of Behavior Scale	Letter fluency Semantic fluency	Stroop Word, Color, and Interference Twenty questions from D-KEFS
Pedersen et al., 2009	*N* = 175	Neuropsychiatric Interview	Semantic fluency	Stroop Interference
Santangelo et al., 2009	*N* = 125	Apathy Evaluation Scale	Letter fluency Stroop Interference Frontal Assessment Battery Planning aspects of copying 2-D spatial figures	Semantic fluency

Note: WCST = TMT = Trail Making Test; Wisconsin Card Sorting Test; D-KEFS = Delis-Kaplan Executive Functioning Scale;

CHAPTER 3
SPECIFIC AIMS OF THE PRESENT STUDY

The specific aims of the study are twofold. Aim 1 is to empirically validate the distinctness of apathy symptoms from depressive symptoms using theory-guided confirmatory factor analysis. Although apathy and depression are related constructs and have overlapping symptomatology, studies suggest they may occur independently (Isella et al., 2002; M. L. Levy et al., 1998; Pluck & Brown, 2002). A study from our laboratory found that apathy occurred separately from depression in 29% (23/80) of PD patients (Kirsch-Darrow et al., 2006). A weakness of existing studies is the manner by which patients are classified as exhibiting 'apathy' or exhibiting 'depression.' This classification has primarily been based on total scores from apathy and depression self-report measures, for example the Apathy Scale (Starkstein, Mayberg, Preziosi et al., 1992) and the Beck Depression Inventory-II (Beck, 1996). This is problematic since apathy and depression have overlapping symptoms (i.e. anhedonia, lack of interest). Thus, symptoms of apathy may be included as depression inventory total score when they actually represent apathy and vice versa. One of the major aims of this study is to address this limitation by using a statistical approach—that of confirmatory factor analysis. This approach will examine whether items from these two commonly used mood measures will load onto discrete apathy and depression factors. This is proposed to be a stronger test of whether apathy and depression are indeed separable in PD.

Hypothesis 1: Apathy and depression are related, but distinct constructs that are dissociable in Parkinson disease. Prediction 1: Patients' item level scores on the Apathy Scale and Beck Depression Inventory-II will load onto 4 factors: 1) an apathy factor representing loss of motivation, 2) a dysphoric mood factor representing sadness and negativity, 3) a loss of interest and anhedonia factor representing the overlap between apathy and depression, and 4) a somatic

factor representing bodily complaints (e.g. sleep, appetite, fatigue). Theory guided confirmatory factor analysis will be used to examine the fit of the individual items to the proposed factors.

Aim 2 is to investigate the relationship between apathy and cognitive functioning controlling for other important variables such as depression, disease severity, disease duration, and demographics. Previous studies have reported a negative correlation between apathy and executive functioning in PD (Isella et al., 2002; Pluck & Brown, 2002; Starkstein, Mayberg, Preziosi et al., 1992; Zgaljardic et al., 2007). However, several of these studies fail to control for dementia and depression and assess only a limited range of cognitive functions. This study aims to overcome these limitations by examining apathy in relation to the multiple cognitive domains of processing speed, working memory, language, verbal episodic memory, and executive functioning. This study also controls for dementia and depression. This will help clarify whether apathy in and of itself is related to impaired cognitive functioning in PD.

Hypothesis 2: Apathy in PD is related to impaired frontal lobe function as evidenced by poor performance on executive functioning tasks. Prediction 2: Apathy will predict poor functioning specifically in the executive functioning domain. Other cognitive domains will only be predicted by other variables such as depression, demographics, and disease variables.

CHAPTER 4
PARTICIPANTS AND METHODS

Participants

Participants included one-hundred sixty-one patients with idiopathic Parkinson's disease who underwent a clinical neuropsychological evaluation at the University of Florida Neuropsychology clinic between the dates of 8/2004 and 5/2009, and agreed to have their data stored for research purposes. Prior to participating in this study, informed consent was obtained according to university and federal guidelines. To be included, PD patients had to be between 40 and 90 years of age and meet the United Kingdom Brain Bank diagnostic criteria for idiopathic PD (Hughes, Ben-Shlomo, Daniel, & Lees, 1992; Hughes, Daniel, Kilford, & Lees, 1992). These criteria are based on the presence of at least two of the four cardinal motor signs of PD: 1) bradykinesia (e.g. slowness of initiation of voluntary movement and reduction in speed of voluntary movement), 2) muscular rigidity, 3) resting tremor, and 4) postural instability. Further, at least one of these signs must be bradykinesia. Patients must have demonstrated a good response to dopaminergic therapy, as defined by a marked improvement in parkinsonian motor signs assessed by the motor subscore of the Unified Parkinson's Disease Rating Scale-Third Edition (UPDRS-III; Fahn & Elton, 1987). The UPDRS-III is a standard rating tool designed to assess the severity of motor symptoms over the course of the disease. Demonstrating a positive response to levodopa therapy is required to exclude patients with Parkinson's plus syndromes (e.g., Shy-Drager, Multiple Systems Atrophy, Lewy Body disease, Corticobasal Degeneration).

Specific exclusion criteria were: 1) co-morbid neurological illness (e.g. stroke, traumatic brain injury, brain tumor, comorbid movement disorder), 2) previous neurosurgical treatments such as deep brain stimulation or pallidotomy, 3) evidence of dementia as assessed by the Dementia Rating Scale II (DRS-II; Jurica, Leitten & Mattis, 2001). The DRS-II covers the

domains of attention, initiation/perseveration, visuoconstruction, conceptualization/reasoning, and memory. There are 144 possible points. Since one of the purposes of this study is to examine the relationship between apathy, depression, and cognition in a non-demented PD sample, patients scoring < 130 total DRS-II points were excluded from the study.

Of the 161 participants, 111 were men and 50 were women (see Table 4-1). Participants ranged in age from 42 to 84 years (*M* = 64.1, *SD* = 8.7). The majority of patients were Caucasian of non-Hispanic origin (95%), with a small number of other races and ethnicities (1 patient was African American, 1 patient was Asian American, and 6 patients were Hispanic). On average, PD patients had been experiencing parkinsonian symptoms for eight and a half years (i.e. *M* = 101.8 months, *SD* = 54.3 months, range 12 - 251 months). Severity of motor symptoms based on the UPDRS-motor section evaluated on levodopa medications was an average of 25.13 (*SD* = 8.6, range 9 to 47). Approximately one third of the patients were pre-surgical candidates for Deep Brain Stimulation (DBS). In the sample as a whole, the average apathy, depression, and anxiety symptoms were as follows: The mean AS score was 10.8 (SD = 6.3, range 0-31), and the mean BDI-II score was 9.5 (SD = 7.2; range 0-34). Average anxiety levels were based on age and gender relevant manual norms for the State Trait Anxiety Scale (STAI) (STAI manual, Spielberger, 1968). The mean STAI-state percentile was 56th %ile (SD = 30, range 5 - 99th %ile) and the mean STAI-trait percentile was 53rd %ile (SD = 31, 3 - 99.9th %ile).

Ninety-eight percent of PD patients were taking dopaminergic medications (e.g., levodopa, dopamine agonists) at the time of the evaluation. Three patients (1.9%) were not taking levodopa because they were in the early stages of disease and the movement disorders physician had decided to wait before beginning levodopa treatment. In all but those three patients, leovodpa equivalent dosages (LEDs) were calculated to quantify the total amount of levodopa patients

were taking. The LEDs were created by converting the dopamine agonists (e.g., bromocriptine, pergolide, ropinirole, pramipexole) into levodopa equivalent doses using the formula described by Hobson and colleages (Hobson et al., 2002). The results of this calculation were then added to the total amount of regular levodopa that the patients were taking. In the current sample of Parkinson patients, levodopa equivalent dosage was an average of 813.9 (*SD* = 511.4, range 0 – 2600). Of the total group of patients, 30% were prescribed antidepressants (49 out of 161) and 25% were prescribed anxiolytic medication (40 out of 161). Breaking this down further, 11% were taking both antidepressants and anxiolytics (18/161), 19% were taking only antidepressants (31/161), and 14% were taking only anxiolytics (22/161).

Procedure

Overview of Design

Two studies were completed, both involving the same participants described above. The first study investigated whether apathy symptoms could be distinguished from depression symptoms using theory-guided confirmatory factor analysis. The second study examined the relationship between apathy and cognitive functioning while controlling for depression, demographics, and disease variables.

Study 1: Examining Apathy and Depression Factors

Specific Aim 1: The purpose of Study 1 is to determine whether apathy and depression items can be distinguished using confirmatory factor analysis.

Mood Assessment Measures. These included the Beck Depression Inventory-II (BDI-II) and the Apathy Scale (AS). The BDI-II is a 21 item scale that assesses symptoms of depression experienced over the last two weeks (Beck, 1996). Example items include, "I feel like a failure," and "I feel sad much of the time" and are measured rated on a 0 to 3 Likert scale. The BDI-II is an updated version of the BDI-I (Beck, 1978). The BDI-II retained the original format of the

BDI-I (21 items with 0-3 Likert scale) and deleted four items (i.e. body image change, work difficulty, weight loss, somatic preoccupation) and replaced them with four items on agitation, worthlessness, loss of energy, and concentration difficulty. Due to these updates, the BDI-II better reflects the DSM-IV diagnostic criteria (Arbisi, 2001).

Researchers have not yet repeated reliability studies with the BDI-II specifically in PD patients, however literature has shown that the BDI-I has excellent reliability and validity in PD patients (e.g. internal consistency reliability = .88, test-retest reliability = .89, criterion validity with DSM IV depression criteria) (Levin, Llabre, & Weiner, 1988; Visser, Leentjens, Marinus, Stiggelbout, & van Hilten, 2006). The Apathy Scale (AS) is a 14 item scale measuring cognitive, emotional, and behavioral symptoms of apathy (Starkstein, Mayberg, Preziosi et al., 1992). Sample items include: "Are you interested in learning new things?" "Are you indifferent to things?" Items are rated on a 0 to 3 Likert scale. The scale is abridged from the original 18 item version developed by Robert Marin (Marin et al., 1991). The original scale was shortened by 4 items, and wording was simplified by Starkstein et al. in 1992. The AS was selected because it has previously been used in studies comparing apathy and depression and has shown good psychometric properties in PD (Internal consistency reliability=.76, test-retest one week r = .90).

Anxiety Assessment Measure. To assess anxiety, participants were given the State Trait Anxiety Inventory (STAI). The STAI is a 40 item, 1-4 Likert scale measuring state and trait anxiety (Spielberger, 1970). Sample items include, "I feel tense," "I feel nervous," and "I am presently worrying over possible misfortunes." Trait-anxiety scale test-retest reliability ranges from .65 to .86. The STAI correlates highly with other anxiety measures such as the Taylor

Manifest Anxiety Scale and the Institute of Personality and Ability Test (IPAT) Anxiety Scale (r =.80; r = .75). (STAI manual, Spielberger, 1970).

Analytic Approach

First, the prevalence of apathy and depression was examined in this sample of 161 PD patients. Apathy was defined using the recommended cutpoint of ≥ 14 (Starkstein, Mayberg, Preziosi et al., 1992). Depression was defined using the recommended cutpoint from the BDI-II manual of ≥ 14 (i.e. minimal depression ≤ 13, mild = 14-19, moderate = 20-28, severe ≥ 29). Further, Leentjens and colleagues have also recommended using 14 as a cutpoint for the original BDI-I (Leentjens, Verhey, Luijckx, & Troost, 2000). We also examined the frequency of pure apathy (≥14 AS without ≥14 BDI-II), pure depression (≥14 BDI-II without ≥ 14 AS) and mixed apathy and depression symptoms (≥ 14 on AES and BDI-II).

Then, four groups were created based on these classifications. This resulted in the following groups: a) pure apathy, b) pure depression, c) mixed apathy-depression, and d) neither apathy nor depression [no symptoms]. One-way analyses of variance (ANOVAs) were used to analyze groups for differences in age, education, disease variables (i.e. UPDRS motor score on levodopa and months with PD), depression, anxiety, and LED. Gender, antidepressant usage, and anxiolytic usage were dichotomous variables, therefore chi square tests were used to evaluate significant differences between groups.

Next, the reliability of each item from the AS and BDI-II was examined using item-total scale correlations and Cronbach's alpha. Unreliable items were not used in the analyses. Items were analyzed using confirmatory factor analysis (CFA). Table 4-2 shows the hypothesized loadings of each item onto the factors. Confirmatory factor analysis was chosen to examine the factor structure because it allows one to propose a priori hypotheses about the underlying structure of the data and then empirically test and evaluate the proposed factor structure.

Parameters of Confirmatory Factor Analysis. The CFA was conducted with statistical software AMOS 17.0, using maximum likelihood estimation. Before factoring, items were examined for univariate normality (e.g. skewness and kurtosis). Since most items were non-normally distributed, item parcels were created instead of factoring raw items. The rational for this is that CFA has an assumption of multivariate normality. Items on psychopathology scales were skewed towards the lack of psychopathology (e.g. 0 or 1) and thus present a non-normal, positively skewed, and kurtotic distribution. Parceling helps correct for this. Further, parceling creates fewer indicators, requires fewer parameters of estimation, and thus provides a better fit (Gorsuch 1983; Little, Cunningham, Shahar, & Widaman, 2002). Models were examined for fit based on the following goodness of fit criteria: minimum fit function chi square, root mean square error of approximation (RMSEA), root mean square residual (RMR), normed fit index (NFI), comparative fit index (CFI), incremental fit index (IFI), relative fit index (RFI), and the Tucker-Lewis Index (TLI). Conventional standards were used to determine goodness of fit (e.g. ratio of chi square to degrees of freedom 2:1 or less, RMSEA below .05 and nonsignificant, RMR below .05, and NFI, CFI, IFI, RFI, TLI above .9. As is conventional, no single fit index is the primary indicator, but the preponderance of evidence must be in support of the fit of the model.

Further, a nested model approach was used to test alternatives to the full four factor model. These included a one factor model where "depression" subsumed apathy, dysphoric mood, loss of interest, and somatic complaints. A two factor model was also tested, where only "apathy" and "depression" factors were represented without loss of interest or somatic factors. Finally, 2 three factor models (one without loss of interest/pleasure and one without somatic complaints)

were tested. The resulting chi-squared statistics were tested against the hypothesized four factor model.

Study 2: Apathy and Cognitive Impairment

Specific Aim 2. The purpose of Study 2 is to examine the effect of apathy on cognitive functioning, controlling for depression, demographics, and disease variables. It was hypothesized that apathy would significantly relate to impaired executive functioning. However, for other cognitive domains, only depression, demographic and disease variables would be related to cognitive functioning.

Neuropsychological domains and measures: The PD participants completed cognitive and mood testing during a clinical neuropsychological evaluation that lasted approximately 4-5 hours. This evaluation was done solely for clinical purposes and conducted through the University of Florida's Psychology Clinic or through the Department of Neurology. Raw scores were converted to age, education, and gender based norms per the test manual or Heaton-based norms (Heaton, Miller, Taylor, & Grant, 2004). Heaton norms were used for the following measures: Trail Making Test, Parts A and B, Boston Naming Test, COWA [F,A,S] letter fluency, Animal fluency. Test manual norms were used for the following measures: Digit Symbol from the Weschler Adult Intelligence Scale-III (WAIS-III), Vocabulary from the Weschler Abbreviated Scale of Intelligence (WASI), Logical Memory subtests (I,II) from the Wechsler Memory Scale-III, Hopkins Verbal Learning Test-II, form I (HVLT-II), Judgment of Line Orientation, Facial Recognition Test, Wisconsin Card Sorting Test, and the Stroop Color Word Test. Normative scores from these measures were converted to z scores using a standardized table. This was done for ease of comparison across tests. Of note, all measures were administered to the full sample of PD patients (N = 161) with one exception, the Wisconsin Card Sorting Test (WCST). Only 68 of the 161 PD participants had data from the WCST, due to

the fact that this measure was not incorporated into the battery of tests until 2007. Moreover, the WCST was frequently not administered due to time constraints. Due to the relatively small number of individuals receiving this measure, data from the WCST was analyzed separately but grouped with the "executive" function tasks. It is considered as a test of executive functioning because it is thought to measure mental flexibility, ability to develop abstract concepts, and shift mental sets in response to examiner feedback (Lezak, Howieson, & Loring, 2004). Two dependent variables from the WCST were examined: the total number of categories achieved, and the total number of perseverative errors. Perseverative errors refer to the incorrect repetition of a response when either a) the subject continues to sort according to a previously successful principle that is now incorrect, or b) the subject continues to sort according to an initial incorrect guess.

Table 4-3 depicts the cognitive tests used in this study and grouped into rationally derived domains based on the cognitive processes they are thought to tap. These domains include: 1) Executive functioning, 2) Processing speed, 3) Verbal episodic memory, 4) Working memory, and 5) Language functioning. In assigning tasks to these domains, the approach of Sheline et al. (2006) was followed by grouping tasks into rationally derived domains based on the cognitive processes tapped by each task (Sheline et al., 2006).

Analytic Approach

Hierarchical Multiple Regression. Cognitive domains composites were created by averaging the z scores for each test within the proposed domain. These cognitive domain composite scores were then used as the outcome variables (i.e. dependent variables) in regression analyses. Advantages to using composite scores rather than each individual test include better reliability with multiple measures per construct of interest and fewer overall analyses, lowering Type I error rate. Hierarchical regression was used to determine whether apathy has a significant

effect on cognitive domains above and beyond the effects of demographics, disease variables, depression, and anxiety. Predictor variables included demographics (age, gender, education), disease variables (UPDRS motor score on levodopa, and months with PD), BDI-II score, STAI-trait anxiety score, AS score, and "group type." Group type was defined as the apathy-depression symptom classification described above (i.e. pure apathy, pure depression, mixed apathy-depression, or no-symptoms). This was used to examine whether group type explained significant variance in any cognitive domain. Group type was a categorical variable with four levels, therefore dummy variables were created with the "no-symptom" group as the reference group (i.e. group against which the others were compared). Five regressions, one for each cognitive domain, were performed with each cognitive domain as the outcome variable. If apathy significantly contributed unique variance to any domain, that domain was examined in terms of individual tests. Predictor variables were entered simultaneously in blocks: age, education, gender (Block 1), UPDRS motor severity (on levodopa), months with PD (Block 2), BDI-II score (Block 3), STAI-trait anxiety score (Block 4), AS score (Block 5), group type (Block 6).

Table 4-1. Patient characteristics

Characteristic	PD patients
	(N=161)
Age	64.1 (8.7), range 42-84
Men: Women	111:50, (68.9% male)
Years of Education	15.1 (2.8), range 7-22
On DOPA meds	98%
On Anti-depressants	30%
On Anxiolytics	25%
Levodopa Equivalent Dosage	813.0 (511.4), range 0-2600
Disease Subtype	77% Tremor Predominant 17.4% Akinetic/Rigid 1.9% Postural Instability/Gait 3.7% were either missing or not given a subtype diagnosis
Months Symptoms	101.8 (54.3), range 12-251
Motor score (UPDRS, on levodopa)	25.5 (8.6), range 9-47
DRS-II Total Score	138.8 (3.5), range 130-144
Apathy Scale	10.8 (6.3), range 0 – 31
Beck Depression Inventory-II	9.5 (7.2), range 0-34
State Trait Anxiety Inventory-State Percentile	56^{th} %ile (SD = 30), range 5-99^{th} %ile
State Trait Anxiety Inventory-Trait Percentile	53^{rd} %ile (SD = 31), range 3-99.9^{th} %ile

Note: N = 161. However, four patients were missing UPDRS on scores, (N = 157), 7 patients were missing anxiety scales (N = 157), and 6 patients did not have a subtype diagnosis (N = 155).

Table 4-2. Proposed loadings of each item.
Italic = apathy factor, Underlined = dysphoric mood factor, *Italic & Underlined* = overlap factor of loss of interest/pleasure, **Bold = somatic factor**

Apathy Scale Items	Beck Depression Inventory-II Items
Are you interested in learning new things?	I feel sad much of the time.
Does anything interest you?	I feel more discouraged about my future than I used to.
Are you concerned about your condition?	I have failed more than I should have.
Do you put much effort into things?	*I don't enjoy things as much as I used to.*
Are you always looking for something to do?	I feel guilty over many things I have done or should have done.
Do you have plans and goals for the future?	I feel I may be punished.
Do you have motivation?	I have lost confidence in myself.
Do you have the energy for daily activities?	I am more critical of myself than I used to be.
Does someone have to tell you what to do each day?	I have thoughts of killing myself, but would not carry them out.
Are you indifferent to things?	I cry more than I used to.
Are you unconcerned with many things?	I feel more restless or wound up than usual.
Do you need a push to get started on things?	*I am less interested in other people or things than before.*
Are you neither happy nor sad, just in between?	*I find it more difficult to make decisions than usual.*
Would you consider yourself apathetic?	I don't consider myself as worthwhile and useful as I used to.
	I sleep somewhat more/less than usual.
	I have less energy than I used to have.
	I am more irritable than usual.
	My appetite is somewhat less/greater than usual.
	I can't concentrate as well as usual
	I get more tired or fatigued more easily than usual.
	I am less interested in sex than I used to be.

Table 4-3. Tests categorized into rationally derived cognitive domains. DV = dependent variable.

Cognitive Domain	Test and Description
Executive functioning	*Trail Making Test, Part B* - a test of psychomotor speed and mental set shifting; Subject must rapidly alternate between connecting numbers and letters over a page, DV= time (in seconds) to completion; maximum time is 300" *Verbal Fluency* – a test of speeded word production to either a letter of the alphabet (F, A, S) or to a category (animals), DV 1 = total number of words produced to letters F, A, and S over 60 second trials, DV 2 = total number of animals produced in a 60 second period *Stroop Color Word Test* - a measure of cognitive inhibition; Subject must inhibit automatic response of word reading and instead name the color of the ink the word is printed, DV = number of correct responses over a 45 second trial *Wisconsin Card Sorting Test* – a measure of mental flexibility, ability to develop abstract concepts, and shift mental sets in response to examiner feedback; Subject must sort cards according to a principle [color, form, number] that the subject must deduce from examiner feedback, DV 1 = number of categories achieved, DV 2 = number of perseverative errors
Processing speed	*Trail Making Test, Part A*- a test of psychomotor speed; Subject must rapidly connect numbers in a series spread throughout the page, DV = time to completion in seconds; maximum time is 300" *Digit Symbol, Wechsler Adult Intelligence Test (WAIS-III)*- a test of psychomotor speed; Subject must rapidly write the correctly paired symbol below each number, DV = number of correctly filled in symbols during a 120" period *Stroop Color Word Test, Reading Trial*- a test of speeded single word reading of 'color' words [red, green, blue], DV = number of words read aloud during 45 second trial
Verbal episodic memory	*Logical Memory I and II, Wechsler Memory Scale-III (WMS-III)* – a test of recent memory for detailed stories read aloud to the subject, DV1 = total correctly recalled details immediately after presentation, DV2 = total of correctly recalled details after a 30 min delay *Hopkins Verbal Learning Test-II (HVLT-II)*- a test of learning and memory of a list of 12 words that can be organized into three categories, DV1 = total number of correctly recalled words over the 3 learning tria1, DV2= total correctly recalled words after a 20 min delay
Working Memory	*Digit span forward*, (WAIS-III)- a test of auditory attention that involves repeating a number sequence in correct order, DV = highest number of digits repeated forwards *Digits Span backward (WAIS-III)*- a test of auditory working memory that involves repeating number sequences in reverse order, DV = highest number of digits repeated backwards

Table 4-3. Continued

Cognitive Domain	Test and Description
Language	*Boston Naming Test (BNT)*- a 60 item test of visual confrontation naming; DV = total number of correctly named items *Vocabulary (Weschler Abbreviated Scale of Intelligence*)- a measure of verbal knowledge of word definitions, DV = number of correctly defined words with 1 or 2 point answers depending on degree of elaboration

CHAPTER 5
RESULTS

Aim 1: Relationship Between Apathy and Depression

Frequency of Apathy and Depression Symptoms

Initial analyses examined the frequency of mood symptoms in the Parkinson sample. Results indicated that 54 out of 161 (i.e. 33.5%) Parkinson's patients had clinically significant levels of apathy (defined by ≥ 14 on the Apathy Scale). Further, 41 out of the 161 patients (i.e. 25.3%) had clinically significant depressive symptoms (defined by ≥ 14 BDI-II score). The relationship between apathy and depression was examined by calculating the number of individuals who exhibited "pure" apathy (i.e. ≥ 14 AS without ≥ 14 BDI-II), those who exhibited "pure depression" (i.e. ≥ 14 BDI-II without ≥ 14 AS), and those who exhibited mixed apathy and depression (i.e. ≥ 14 on both scales). As shown in Figure 5-1, results indicated that 17.4% (28/161 patients) had pure apathy, 9.3% (15/161 patients) had pure depression, and 16% (26/161) had mixed apathy and depression.

Differences Between Apathy-Depression Groups on Demographics, Disease Variables, and Medication Usage

In order to examine differences between groups with pure apathy, pure depression, mixed apathy-depression, and no symptoms, four groupings (as defined with the cutpoints described above) were created. This resulted in the following groups: a) pure apathy (n = 28), b) pure depression (n = 15), c) mixed apathy-depression (n = 26), and (d) neither apathy nor depression [no symptoms] (n = 92). The groups were then compared in terms of demographic variables (age, gender, education), disease variables (disease duration, disease severity), and medication usage (levodopa equivalent dosage, antidepressant usage, anxiolyic usage). Separate one-way ANOVAs with Bonferroni post-hoc comparisons were used to examine differences among groups in age, education, disease duration (i.e. months with PD), disease severity (UPDRS motor

score on levodopa), and amount of levodopa equivalent dosage (i.e. LED). Chi squared tests were used to evaluate differences across groups in gender distribution, antidepressant usage, and anxiolytic usage. Means, standard deviations, ranges, F and χ^2 statistics, and significance values for each analysis are displayed in Table 5-1.

Age. One-way ANOVA results indicated a significant effect of Group on age, $F(3, 157 = 3.35, p = .021)$. Follow-up post hoc analyses indicated that the pure apathy group ($M = 68.07$ years, $SD = 8.4$) was significantly older than the mixed apathy-depression group ($M = 61.27$ years, $SD = 10.22$, $p = .021$). No other groups were significantly different from each other (see Table 5-1).

Gender. Chi square analyses indicated that gender distribution was not significantly different between groups. The percentage of males in each group were as follows: 75% of the apathy only group, 73% percent of the depression only group, 69% percent of the mixed apathy-depression group, and 66% percent of the no-symptom group. The gender distribution was not significantly different among groups, χ^2 (3, N = 161) = .915, $p = .822$.

Education. One-way ANOVA results indicated a significant effect of Group on education, $F(3, 157 = 3.23, p = .024)$. Follow-up post hoc analyses indicated that the mixed apathy-depression group ($M = 13.58$ years, $SD = 2.5$) had significantly less education than the no-symptom group ($M = 15.48$ years, $SD = 2.78$, $p = .013$). No other groups were significantly different from each other.

Disease severity and duration. Of note, seven UPDRS on motor scores were missing so the n was 154. One-way ANOVA results suggested that there was not a significant effect of Group on disease severity as measured by the UPDRS motor score "on levodopa medications" among groups, $F(3, 153 = 1.76, p = .158)$. One-way ANOVA results indicated no significant

effect of Group on disease duration as measured by number of months with PD among groups, [$F(3, 157 = 2.10, p = .102)$, (see Table 5-1 motor scores and number of months of PD for each group)].

LED. One-way ANOVA results indicated a trend for an effect of Group on LED, $F(3, 58.6 = 2.55, p = .058)$. Post-hoc tests revealed that the pure depression group ($M = 1121$, $SD = 412.1$) was taking significantly more levodopa than the pure apathy group ($M = 698.58$, $SD = 418.09$), $p = .047$). No other groups were significantly different from each other.

Antidepressant usage. Chi square analyses indicated that groups differed significantly in terms of percentage of patients taking antidepressants, χ^2 (3, N = 161) = 8.46, $p = .037$. The percentage of patients taking antidepressants were as follows: 25% (freq = 23/92) of the no-symptom group, 25% (freq = 7/28) of the pure apathy group, 33.3% (freq = 5/15) of the pure depression group, and 53.8% (freq = 14/26) of the mixed apathy-depression group. Further chi-squared analyses were undertaken to determine where the significant difference was. Results indicated that the mixed apathy-depression group (53.8%, 14/26) was taking significantly more antidepressants than the no-symptom group (25.0%, 23/92), χ^2 (1, N = 118) = 7.84, $p < .01$. The mixed apathy-depression group was also taking significantly more antidepressants than the pure apathy group, χ^2 (1, N = 54) = 4.75, $p = .030$. No other groups were significantly different from each other.

Anxiolytic usage. Chi square analyses indicated that groups did not differ significantly in terms of the percentage of patients taking anxiolytics, χ^2 (3, N = 161) = 3.48, $p = .32$. The percentage of patients taking anxiolytics was as follows: 20.7% (freq = 19/92) of the no-symptom group, 25% (freq = 7/28) of the pure apathy group, 26.7% (freq = 4/15) of the pure depression group, and 38.5% (freq = 10/26) of the mixed apathy-depression group.

Differences Between Apathy-Depression Groups on State and Trait Anxiety

In order to examine the relationship between apathy, depression, and anxiety, the four groups were compared on their state and trait anxiety percentile scores from the STAI (see Table 5-2, and Figures 5-2 and 5-3). Two separate one-way ANOVAs were used for state and trait anxiety. Seven of the 161 patients were missing anxiety scores, resulting in a total N of 154 for this analysis. Since Levene's test for the homogeneity of variance was significant, the Brown – Forsythe F correction was used. Results indicated a significant effect of Group on state anxiety, $F(3, 74.82 = 19.96, p < .001)$, and on trait anxiety, $F(3, 58.6 = 43.83, p < .001)$. For state anxiety, follow-up post-hoc tests revealed that the pure apathy group ($M = 56^{th}$ percentile, $SD = 30.35$) did not significantly differ from either the no-symptom group [($M = 47^{th}$ percentile, $SD = 28.2$), $p = .4$] or the pure depression group [($M = 68^{th}$ percentile, $SD = 21.2$) $p = .5$)]. However, the pure apathy group had significantly lower state anxiety scores than the mixed apathy-depression group [($M = 86^{th}$ percentile, $SD = 14.5$), $p < .001$]. These findings are depicted in Figure 5-2.

Next, trait anxiety scores were compared across groups in post-hoc follow-up tests. As shown in Figure 5.3, the pure apathy group had significantly higher trait anxiety ($M = 60^{th}$ percentile, $SD = 24.69$) than the no-symptom group [($M = 37^{th}$ percentile, $SD = 25.05$), $p = .001$], but significantly lower trait anxiety than the mixed apathy-depression group [($M = 90^{th}$ percentile, $SD = 14.30$), $p < .001$]. There was no difference between the pure apathy group and the pure depression group [($M = 76.5^{th}$ percentile, $SD = 25$) $p = .26$]. Finally, the pure depression group did not differ in trait anxiety scores from the mixed apathy-depression group ($p = .27$).

In addition to looking at the mean differences between groups, it is important to look at the relative proportions of clinically significant anxiety in each group. The Spielberger manual lists a raw score of 40 as a cut-score for individuals with high anxiety, however in medically ill

patients and geriatric patient populations the cut score with the best sensitivity and specificity has found to be higher, ranging from 41 to 55 (Stark et al., 2002; Stanley et al., 2001; Kvaal et al., 2005). The corresponding percentile ranks between these two raw scores range between 81st - 100th percentile. In the present study, 93rd percentile was chosen as the cutpoint for significant anxiety because it represents a mid-point between these two percentile ranges from the literature, and is one and a half standard deviations from average. Chi squared statistics were used to examine the difference in the occurrence of elevated trait anxiety across groups using $\geq 93^{rd}$ percentile as the cut-point. Results indicated that the proportion of individuals with elevated trait anxiety scores differed across the apathy-depression groups, $\chi^2(N = 154, df = 3) = 64.5$, $p < .001$. As shown in Figure 5.4, the percentages of patients with elevated trait anxiety scores were as follows: 1.1% (1 out of 89) of the no symptom group, 7.4% (2 out of 27) of the pure apathy group, 30.8% (4 out of 13) of the pure depression group, and 64% (16 out of 25) of the mixed apathy-depression group. Breaking these down into post-hoc comparisons, the pure apathy group (7.4%) did not significantly differ from the no-symptom group (1.1%) (Fisher's exact significance, used to correct for less than 5 per cell, $p = .135$). The pure apathy group (7.4%) was lower than the pure depression group (30.8%) at trend (Fisher's exact significance = .075) and significantly lower than the mixed apathy-depression group (64.0%), $p < .001$. Further, the pure depression group was significantly lower than the mixed apathy-depression group at trend ($p = .052$). These results indicate that the prevalence of high anxiety is greatest in the group with mixed apathy and depression. The pure apathy group has a low prevalence of high anxiety, and it is not significantly different from the no-symptom group.

Factor Structure of Apathy and Depression: Confirmatory Factor Analysis

In addition to using total scores, a primary aim of this study was to examine the individual items on the apathy and depression scales. It was predicted that items from the Apathy Scale

(AS) and Beck Depression Inventory-II (BDI-II) would load onto 4 factors: 1) an apathy factor representing loss of motivation, 2) a dysphoric mood factor representing dysphoria and negativity, 3) a loss of interest/pleasure factor representing the overlap between apathy and depression, and 4) a somatic factor representing bodily complaints (e.g. sleep, appetite, fatigue).

Prior to conducting a confirmatory factor analysis (CFA) on the AS and BDI-II items, these items were first screened for internal consistency reliability and for normality. This was done by examining the means, standard deviations, and item-total correlations for the 21 items of the BDI-II and the 14 items of the AS. As is conventional for reliability analysis, negatively worded AS items were reverse scored. Cronbach's alpha was examined for each of the total scales, and in terms of whether deleting items improved overall alpha. For the AS, most items positively correlated with the total apathy score between .4 and .7. The one exception was AS item 3. This item (reverse scored) had a negative correlation with the total score (r = -.14). This item states: "Are you concerned about your condition?" The negative correlation with the total apathy score indicates that as patients endorse higher apathy on this item they score lower in overall total apathy. Furthermore, internal consistency reliability item-total statistics indicated that deleting this item improved internal consistency reliability (i.e. Cronbach's alpha) from .831 to .855. This indicates that AS item 3 is a psychometrically poor item. Due to its unreliability, AS item 3 was not used in the confirmatory factor analysis. For the BDI-II, all items positively correlated with the total depression score (between .36-.68) and alpha was not improved by deleting any items. The overall alpha was .89.

Items were then checked for normality. Results indicated that individual items on both scales tended to be skewed towards the lack of psychopathology (positively skewed and positively kurtotic). Item parcels were created by summing items into pairs. This is done

pseudorandomly by combining items randomly within hypothesized factors. Item parcels improve normality, an assumption for CFA. Because some item parcels were still non-normal, the data were transformed by taking the square root ($\sqrt{(x + 1)}$) of each item parcel to further reduce the positively skew.

Confirmatory factor analyses. One-hundred forty-six participants had complete item data for both the AS and BDI-II. Fourteen patients had skipped at least one item on either scale, so their item data was incomplete and was not analyzed. The remaining one-hundred forty-six participants' item parcels were constrained to the hypothesized 4-factor solution. These factors and indicators were: 1)*"Apathy/Loss of Motivation"* (5 item parcel indicators, A7_A10, A9_A4, A5_A14, A11_A6, A12_A13), 2)"*Dysphoric mood"* (6 item parcel indicators, B6_B8, B3_B17, B9_B2, B1_14, B5_10, B7_11), 3)"*Loss of Interest and Pleasure"* (3 item parcel indicators, B4_B12, A1_A2, B13), and 4)*"Somatic Complaints"* (4 item parcel indicators, B16_B18, B21_A8, B15_B20, B19).

The overall fit of the model to the data was: χ^2 (129, N = 146) = 213.3, p <.01 (NFI = .844, CFI = .931, IFI = .932, RFI = .815, TLI = .918). The RMSEA was .067 (p = .04), and the RMR was .011. The overall fit was good in terms of the ratio of chi square to degrees of freedom ratio being less than a ratio of 2:1, fit indices close to 1, and RMR less than .05. However, the RMSEA was significant and greater than .05. Modification indices were examined to see if there was a single parameter that would greatly improve the fit of the model. Interestingly, it was a correlated uniqueness (unexplained variance) among two *"Dysphoric Mood"* indicators (B6_B8 and B7_B11) that the modification indices provided as improving fit the most. These items have to do with feelings of punishment, self criticalness, and crying and guilt. This means that there is unexplained variance in these parcels that "clusters together." Allowing the unexplained

variance of these indicators to correlate improved the model by 17.05 chi squared points. This improved the fit to: χ^2 (128, N = 146) = 194.9, p <.01 (NFI = .858, CFI = .945, IFI = .946, RFI = .830, TLI = .934). The RMSEA was .060 (p = .16) and the RMR was .011. The chi square to degrees of freedom ratio is slightly lower (1.5:1 versus 1.65:1 before) and fit indices are closer to 1; additionally RMSEA is nonsignificant, indicating a better fit. Table 5-3 shows these four factors, items, standardized loadings and uniquenesses.

All the loadings were high, ranging from .59-.87. For the *Apathy/Loss of Motivation factor*, the loadings ranged from .65 to .87. The highest loadings were for items A7_A10, "Do you have motivation?," "Are you indifferent to things?," (.87) and items A4_A9, "Do you put much effort into things?," "Does someone have to tell you what to do each day" (.76). For the *Dysphoric Mood factor*, loadings ranged from .59-.87. The highest loadings were items B7_B11, "I have lost confidence in myself," "I feel more restless or wound up than usual" (.87) and items B1_B14, "I feel sad much of the time," "I don't consider myself as worthwhile and useful as I used to." The *Loss of Interest and Pleasure factor* ranged from .65-.72, with the highest loading for items A12_A13, "Do you need a push to get started on things?, "Are you neither happy nor sad, just in between?" Finally, the *Somatic factor* ranged from .63-.70, with the highest loading B19, "I can't concentrate as well as usual" and B21_AS8 "Do you have the energy for daily activities," "I am less interested in sex than I used to be."

Alternative nested models.

A nested model approach was used to test alternatives to the four factor model. This was done to determine if the four factor model has a significantly lower χ^2 (indicating a better fit) than other alternative models. These nested models were identical in structure to the original model except for the number of factors (i.e. they included the correlated uniqueness). The results

are summarized in Table 5-4. A one factor model, subsuming dysphoric mood, apathy, loss of interest/pleasure, and somatic into one overarching "Depression" factor was tested. This model was significantly worse than the four factor model (one factor $\chi^2 = 433.3$, vs. four factor $\chi^2 = 194.9$, $p < .01$). We also tested two factors ("Apathy" and "Depression"), a three factor solution without the Somatic factor, and a three factor solution without the Loss of interest/pleasure factors. All of these models were significantly worse than the four factor model ($p < .01$). See Table 5-4 for chi square change and significance statistics. Worse (higher) chi square indicates a greater discrepancy between the original and reproduced correlation matrix, and hence a worse fit to the data.

Thus, the four factor model separating the constructs of apathy, depression, loss of interest/anhedonia, and somatic complaints was supported. This lends support to the hypothesis that apathy and depression are separable constructs in PD. Further studies will be important to disentangle the discrete effects of apathy versus depression. One such area involves examining the separate effects of apathy and depression on cognitive functioning. The next part of this study sought to do this by investigating the unique effects of apathy on cognition in PD. An important aspect of this aim was to control for demographics (age, gender, education), disease variables (duration, severity), and depression in order to understand the unique effects of apathy on cognitive functioning.

Aim 2: Relationship between Apathy and Cognition

The second overarching aim of the present study was to investigate the relationship between apathy and cognitive functioning in PD. It was hypothesized that apathy is related to impaired frontal lobe functioning, and that deficits would be evidenced on tasks of executive functioning. Specifically, it was predicted that apathy would be related to poor performance on the executive functioning domain, while other cognitive domains (e.g. episodic memory, etc)

would only be predicted by other variables such as demographics, disease variables, and depression.

First, patients' norm based scores on each cognitive test were converted to z score equivalents using a standardized table. See Table 5-5 for means and standard deviations of each cognitive measure. Then, composite scores were created by averaging the z scores across tasks in each rationally derived domain. These domains consisted of: *Executive functioning* (Trail Making Test, Part B, letter fluency, animal fluency, and Stroop Color Word), *Processing speed* (Trail Making Test, Part A, Digit Symbol, Stroop Color Naming), *Episodic memory* (HVLT total, HVLT delay, WMS Logical Memory I, Logical Memory II), *Working memory* (Digit span forwards, Digit span backwards), and *Language processing* (Boston Naming Test, Vocabulary). See Table 4-3 for a summary of each test and the associated domain. The means, standard deviations, and ranges of each domain are presented in Table 5-6. Correlations between cognitive domains are presented in Table 5-7. The correlation between each and every cognitive domains were significant (p <.001). The lowest correlation was between Working memory and Executive functioning (r = .254) and the highest correlation was between Processing speed and Executive functioning (r = .659).

Cognitive Domain Regression Analyses

Next, the cognitive domains were entered as dependent variables in regression analyses. Predictors were regressed upon each cognitive domains using hierarchical multiple regression. Five hierarchical regressions, one for each cognitive domain, were performed with simultaneous entry of variables in sequential blocks. Demographic variables were entered on Block 1 (age, gender, education). Disease variables were entered on Block 2 (duration of disease, disease severity). Depression (BDI-II score) was entered on Block 3, and anxiety (STAI-trait percentile) was entered on Block 4. Apathy score (AS score) was entered on Block 5. The dummy coded

variable of group type (i.e. pure apathy, pure depression, mixed apathy-depression, no symptoms) was entered on Block 6.

Multicollinearity statistics of tolerance and Variance Inflation Factors (VIFs) are presented in Table 5-8. The VIFs for the models range from 1.0-5.0. The VIF indicates whether the predictor has a strong linear relationship with the other predictors. Values greater than 10 indicate concern that multicollinearity is biasing the models (Fields, 2005). The tolerance statistics range from .20-.99. Values below .20 indicate concern that multicollinearity is biasing the models (Fields, 2005). Results of hierarchical multiple regression analyses are provided in Tables 5-9 through 5-15, and include total model R^2 change in R^2 for each set of predictors, b values, standard errors, and betas (β).

Executive functioning. First, the Executive functioning domain was examined. The final model, with all predictors included (demographics, disease variables, depression, anxiety, apathy, and group type), explained 13.8% of the variance in Executive functioning (p = .031, see Table 5-9). Breaking this down by set of predictors and significance of R^2 change statistics, the set of demographic variables did not contribute significant variance to Executive functioning (p = .69). The set of disease variables did not explain significant variance, but was at trend (R^2 change = 3.5%, p =.073). However, neither severity of PD (p = .108), nor duration of PD (p = .426) had significant βs in the final model. Apathy contributed 3.5% of the variance in Executive functioning (p =.02). Apathy and Executive functioning were inversely related (β = -.369, p =.012). Neither anxiety (p =.145) nor depression (p =.273) contributed significant variance to Executive functioning. Additionally, group type did not explain significant variance (p = .135).

Thus, as predicted, apathy contributed an incremental increase in variance explained in Executive functioning, with increased apathy related to decreased performance in the Executive functioning domain.

Next, the remaining cognitive domains were examined. These included: Processing speed, Verbal episodic memory, Working memory, and Language processing. It was predicted that apathy would not add incremental variance explained in these cognitive areas.

Processing speed. The final model, with all predictors included, significantly explained 21.8% of the variance in Processing speed (p <.001, see Table 5-10). Breaking this down by predictors, the set of demographic variables accounted for 7.4% of the variance (p = .011). This variance was completely contributed by gender, with males performing more poorly than females (β = -.209, p = .008). The set of disease variables contributed an additional 5.9% of variance (p =.008). Severity of PD was inversely related to Processing speed (β = -.175, p =.036), while duration of PD was not related (p = .22).

Depression explained an additional 2.4% of variance in Processing speed (p = .048). Depression was inversely related to Processing speed (β = -.414, p = .014). Neither anxiety (p = .255) nor apathy (p = .939) contributed significant variance to Processing speed. Group type explained 5.3% of variance in Processing speed (p = .027). This was driven by a trend for the *no symptom group* to score better in Processing speed than the *depression only group* (β = .184, p = .065).

Verbal episodic memory. The final model explained 24.5% of the variance in Verbal episodic memory (p <.001, see Table 5-11). The set of demographic variables explained 16.4% of the variance in Verbal episodic memory (p <.001). Gender significantly predicted Verbal episodic memory, with males performing more poorly than females (β = -.274, p <.01).

Education also significantly predicted list learning memory, with higher education related to better list learning scores (β = .272, p = .001).

There was a trend for the set of disease variables to add incremental variance (R^2 change = 2.8%, p =.09). In the final model, disease severity was significantly and inversely related to Verbal episodic memory (β = -.163, p = .048). Disease duration was not significantly related (p = .653). There was also a trend for depression to contribute variance (R^2 change = 1.6%, p =.09). However, depression's β was not significant in the final model (p = .829). Neither anxiety (p = .47), apathy (p = .84), or group type (p = .11) explained significant variance in Verbal episodic memory.

Working memory. The final model did not explain significant variance in Working memory performance (p = .204, see Table 5-12). However, in earlier models, education contributed significant variance to Working memory. Education was the only predictor that accounted for significant incremental variance (5.6%, p = .038). Education was positively related to working memory (β =.190, p = .027). Disease variables (p = .37), depression (p = .14), anxiety, (p = .36), apathy (p = .56), and group type (p = .81) did not explain significant variance in Working memory.

Language functioning. The overall model explained 16.1% of the variance in Language functioning (p <.01, see Table 5-13). Demographic variables contributed a significant 5.2% (p = .049). Education was positively related to Language functioning (β = .197, p =.018). There was a trend for the disease variables to contribute variance (R^2 change = 3.8%, p =.054). This was driven by a significant inverse relationship between disease severity and Language functioning (β = -.192, p = .027). Disease duration was not significantly related to Language functioning (p = .254).

Depression contributed a significant variance of 4.0% to Language functioning (p = .011). However, its β weight was insignificant in the final model (p = .8). Anxiety contributed significant variance at trend (R^2 change = 2.0%, p =.072). The β weight for anxiety was at trend in the final model, with anxiety inversely related to Language functioning (β = -.201, p =.073). Apathy (p = .318) and group type (p = .86) did not contribute significant variance to Language functioning.

Summary of Regression Results

It was predicted that the Executive functioning domain would be related to apathy over and above the effects of demographics, disease variables, depression, and anxiety. This prediction was supported, as increasing apathy was related to impaired Executive functioning.

Next, it was predicted that the other cognitive domains (Processing speed, Verbal episodic memory, Working memory, Language functioning) would be related to demographics, disease variables, depression, and anxiety only. The effect of apathy was predicted to be specific to Executive functioning. This was also supported. Apathy did not contribute incremental variance to Processing speed, Verbal episodic memory, Working memory, or Language functioning.

Apathy's Relationship to Individual Executive Functioning

In order to fully understand the relationship between apathy and Executive functioning, the composite domains were broken down into specific tests. For the Executive functioning domain, four hierarchical regressions were completed—one each for Trail Making Test Part B, letter fluency, animal fluency, and the Stroop color word test.

Executive Functioning Tests The same predictors (demographics, disease variables, depression, anxiety, apathy, group type) were entered in Blocks as above. For the Trail Making Test Part B, the final model explained 14.9% of the variance (p <.019). Apathy did not contribute significant variance to the test (p = .58). Group type also did not contribute significant

variance (p = .53). However, the set of disease variables contributed a significant 6.8% of the variance (p < .01). Duration of PD was inversely related to performance on the test (β = -.197, p =.019), but disease severity was not related (p = .28). Demographics (p = .10), depression (p = .19), and anxiety (p = .154) did not contribute significant variance to Trail Making Test Part B.

Next, speeded verbal fluency measures were examined. For letter fluency, the final model with all the predictors included did not explain significant variance (p =.59). Apathy did not contribute significant variance to letter fluency. In fact, no variable examined contributed significant incremental variance to letter fluency. Group type did not contribute variance (p = .5). Demographics (p = .59), disease variables (p = .46), depression (p = .63), and anxiety (p = .4) did not contribute significant variance to letter fluency.

For animal fluency, the final model explained 11.9% of the variance at trend (p =.091). There was a trend for apathy to explain variance in animal fluency (R^2 change = 2.3%, p =.063). Apathy was inversely related to animal fluency (β = -.320, p = .032). Group type also explained variance in animal fluency at trend (R^2 change = 4.2%, p =.097). This was driven by the *no symptom group* scoring significantly better on animal fluency than the *mixed apathy-depression group* (β = .435, p = .017). Demographics (p = .725), disease variables (p = .152), depression (p = .152), and anxiety (p = .470) did not explain significant variance in animal fluency.

Stroop Color Word, interference condition, was also examined. The final model significantly 12.6% of the variance at trend (p =.069). Apathy explained a significant 5.5% of the variance in Stroop Color Word (p < .01), and was inversely related (β = -.433, p < .01). No other variables explained significant incremental variance. Demographic variables (p = .28), disease variables (p = .33), depression (p = .41), anxiety (p = .16), and group type (p = .64) did not contribute significant variance in Stroop Color Word.

In summary, apathy contributed significant variance to Stroop Color Word. Apathy contributed variance at trend to animal fluency. However, apathy did not contribute variance to letter fluency. Apathy also did not contribute significant variance to Trail Making Test Part B. Thus, apathy was related to some aspects of executive functioning such as cognitive interference and semantic verbal fluency, but was not related to phonemic verbal fluency, or psychomotor speed and switching mental sets.

Subsample's Performance: Wisconsin Card Sort Test

A subsample of the total of Parkinson patients (65 of 161 Ss) was also administered the Wisconsin Card Sort Test (WCST). This test was incorporated into the battery in 2007 (sample collection began in 2004). This variable was not used in the domain-specific regressions analyses due to the small sample size. However, because a primary aim of this study was to examine the relationship between executive functioning and apathy, regression analyses were carried out in this limited sample. Of note, there were no significant differences between the subjects who received the Wisconsin versus those who did not. Furthermore, demographic, disease, and apathy, depression, and anxiety characteristics of the samples that were administered the WCST versus not administered the WCST were compared. They did not differ on any variable.

Using the same methodology of hierarchical linear regressions, the dependent variables of number of categories and number of perseverative errors (PE) were regressed upon predictors (e.g. demographics, disease variables, depression, apathy). Raw scores were used due to the limited range of the scores once they were normed (e.g. most people get a score of $>16^{th}$ percentile for number of categories). The descriptive statistics were as follows: number of raw categories achieved (M = 3.31, SD = 2.1, range 0-6), number of perseverative errors (M = 24.6, SD = 13.6, range 4-57).

Hierarchical regression results indicated that the final model did not explain variance in number of categories achieved (p = .40, see Table 5-14). However, demographics contributed significant incremental variance in number of categories achieved (R^2 change = 14.9%, p =.019). The variance was completely due to age. Age was inversely related to the number of categories achieved (β = -.314, p = .049). No other demographic variable was related. Disease variables (p = .83), depression (p = .81), anxiety (p = .93), apathy (p = .62), and group type (p = .69) did not explain significant variance in number of categories achieved.

Further, raw number of perseverative errors was also examined. Regression results indicated that the final model did not explain significant variance in number of perseverative errors (p = .14). Similar to categories achieved, significant incremental variance was contributed by demographic variables (p <.01). Older age was related to more perseverative errors (β = .318, p = .046). More education was related to fewer perseverative errors (β = -.363, p <.01). The regression model and parameters are shown in Table 5-15; as before, disease variables (p=.49), depression (p = .87), anxiety (p = .82), apathy (p = .79), and group type (p = .68) did not explain variance in number of perseverative errors.

Interestingly, apathy was not related to WCST performance, either with regards to total categories achieved or in regards to number of perseverative errors. This is counter to the a priori prediction. Nor was apathy related to the Trail Making Test Part B, another task that involves "switching" of mental sets.

Summary of Hierarchical Regression Results

Aim 2 of the current study was to examine the relationship between apathy and cognitive functioning in Parkinson disease. Hierarchical regressions were used to quantify whether apathy had a unique and incremental effect of explaining variance in specific cognitive domains of Executive functioning, Processing speed, Verbal episodic memory, Working memory, and

Language functioning. Apathy was predicted to be specifically related to Executive functioning and not to other domains. This was supported. Apathy explained incremental variance in Executive functioning. Apathy explained 5.5% of the variance in Executive functioning. Apathy did not explain incremental variance in Processing speed, Verbal episodic memory, Working memory, or Language functioning.

The relationship between apathy and Executive functioning was further examined by turning to individual test performance. Apathy significantly explained variance in Stroop Color Word performance. Apathy explained variance at trend in animal fluency performance. However, apathy did not explain significant variance in letter fluency, Trail Making Test Part B, Wisconsin Card Sorting Test number of categories achieved, or the Wisconsin Card Sorting Test number of perseverative errors.

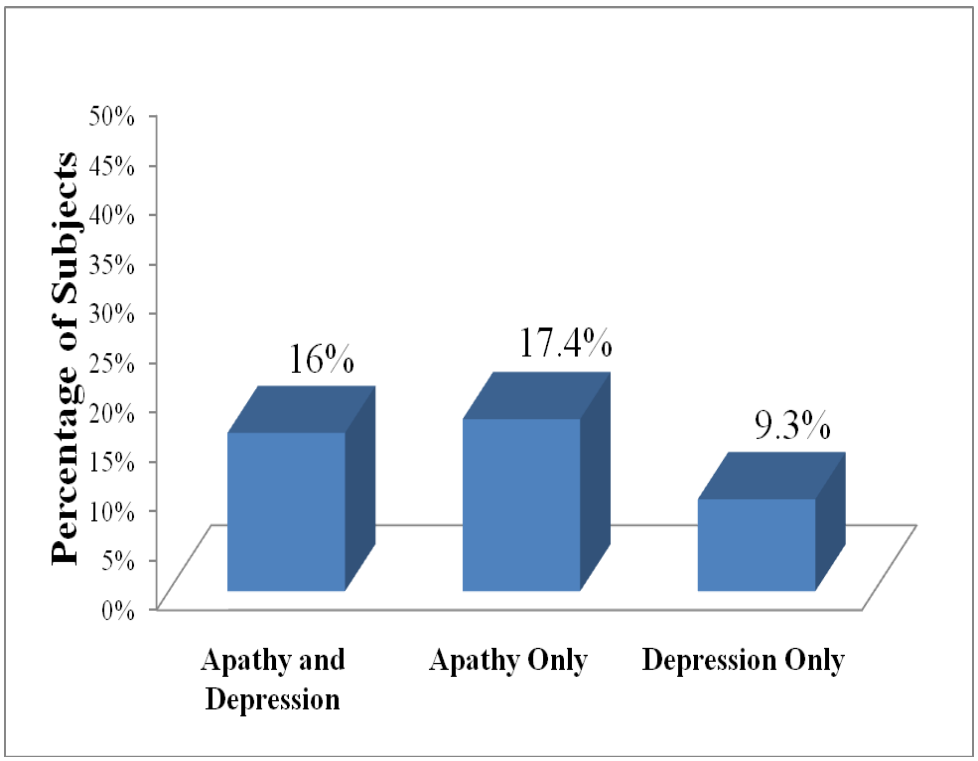

Figure 5-1. Prevalence of apathy and depression in 161 Parkinson patients

Table 5-1. Demographic, disease variable, and medication average scores, standard deviations, and ranges between no symptom, pure apathy, pure depression, and mixed apathy-depression groups

Characteristic	No symptoms	Pure Apathy	Pure Depression	Both	*F* or χ^2 value (df = 3, 157)	*p* value
	N = 92	*N = 28*	*N = 15*	*N = 26*		
Age	64.05 (8.38), range 43-80	68.0 (8.4), range 47-84	61.67 (6.76), range 51-77	61.27 (10.2), range 42-84	3.35	.021
Men: Women	61:31 (66.3% male)	21:7 (75% male)	11:4 (73.3% male)	18:8 (69.2% male)	.915	.822
Yrs of Education	15.48 (2.78), range 12-21	15.32 (2.80), range 11-20	15.33 (3.33), range 12-22	13.58 (2.47), range 7-18	3.23	.024
% on Anti-depressants	25.0%	25.0%	33.3%	53.8%	8.45	.037
% on Anxiolytics	20.7%	25.0%	26.7%	38.5%	3.48	.324
Levodopa Equivalent Dosage	784.4 (525.99), range 0-2600	698.56 (418.09), range 150-1875	1121.72 (412.56), range 434-2100	865.06 (552.39), range 288-2025	2.55	.058
Months of Symptoms	94.8 (50.03), range 12-228	110.75 (65.11), range 24-240	129.6 (48.27), range 54-251	101.27 (57.31), range 12-241	2.10	.102
Motor score (UPDRS, on levodopa)	24.51 (8.69), range 9-47	28.0 (8.09), range 13-46	22.29 (7.85), range 10-35	24.99 (8.43), range 13-42	1.76	.158

Note: N = 161. However, five patients were missing UPDRS on scores, (N = 157). Results are presented as means (standard deviations) and ranges.

Table 5-2. STAI State and Trait average scores, standard deviations, and ranges between no symptom, pure apathy, pure depression, and mixed apathy-depression groups

Characteristic	No symptoms	Pure Apathy	Pure Depression	Both	*Browne-Forsythe* F or χ^2 value	*p* value
	N = 89	*N = 28*	*N = 13*	*N = 25*		
STAI state percentile	46th %ile (28.20), range 5-97	56th %ile (30.39), range 11-99	68th %ile (21.2), range 28-97	87th %ile (14.54), range 39-99	19.96	<.001
STAI trait percentile	37th %ile (25.1), range 3-96	61st %ile (24.69), range 6-97	76th %ile (24.97), range 14-98	91th %ile (14.3), range 37-100	43.83	<.001
Percentage of patients > 93%ile on STAI trait	1.1% (1/89)	7.4% (2/28)	30.8% (4/13)	64.0% (16/25)	64.5	<.001

Note: Seven patients were missing anxiety scores, (N = 154). Results are presented as means (standard deviations) and ranges.

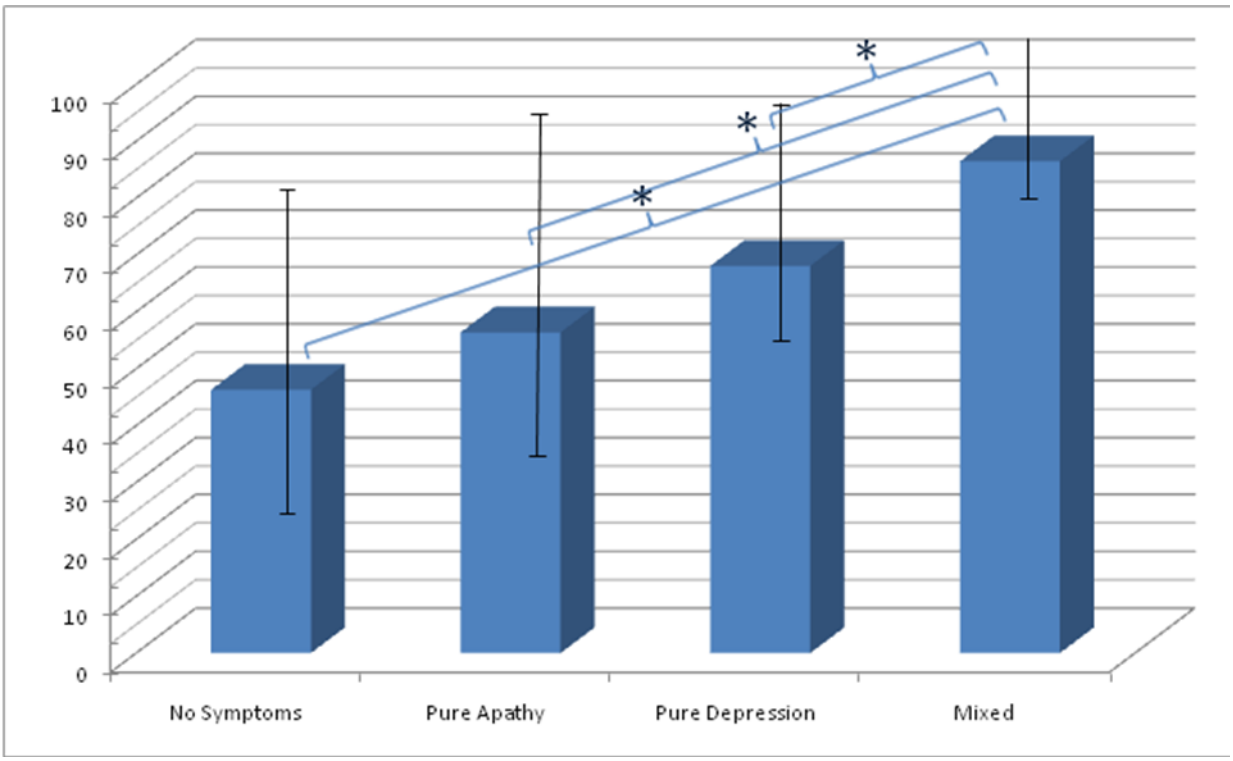

Figure 5-2. Mean State Anxiety Scores across Apathy-Depression subgroups.

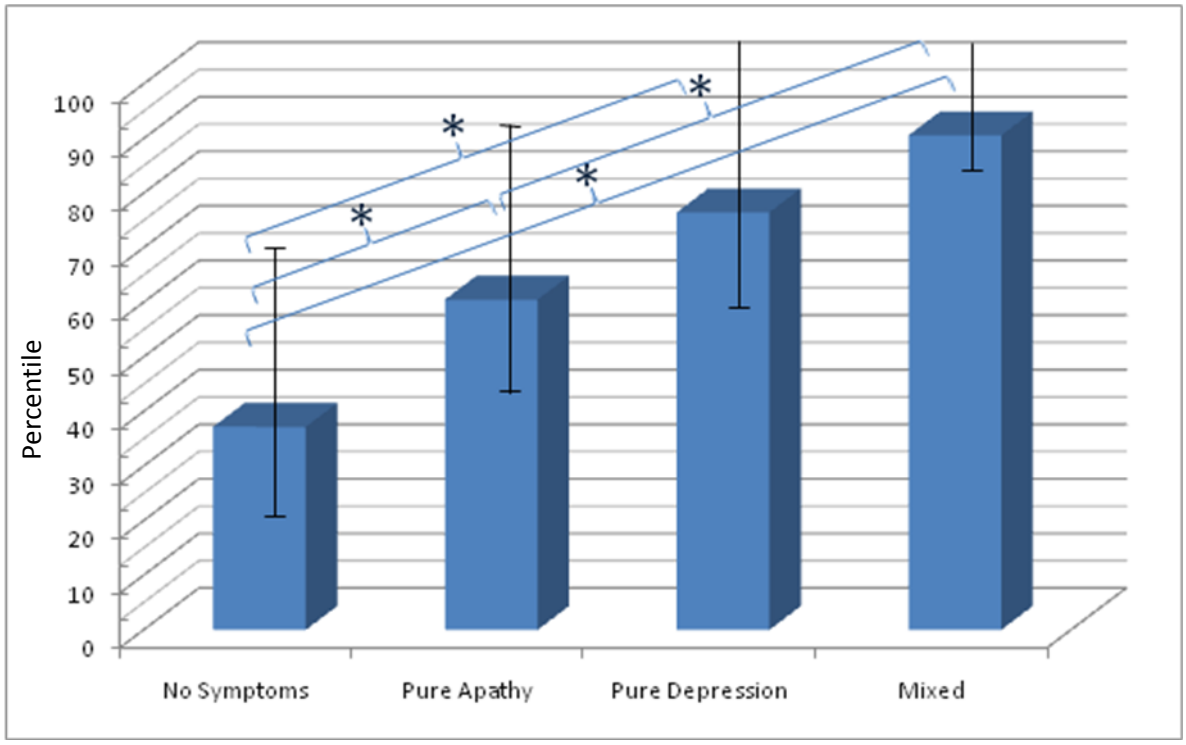

Figure 5-3. Mean Trait Anxiety scores across Apathy-Depression subgroups

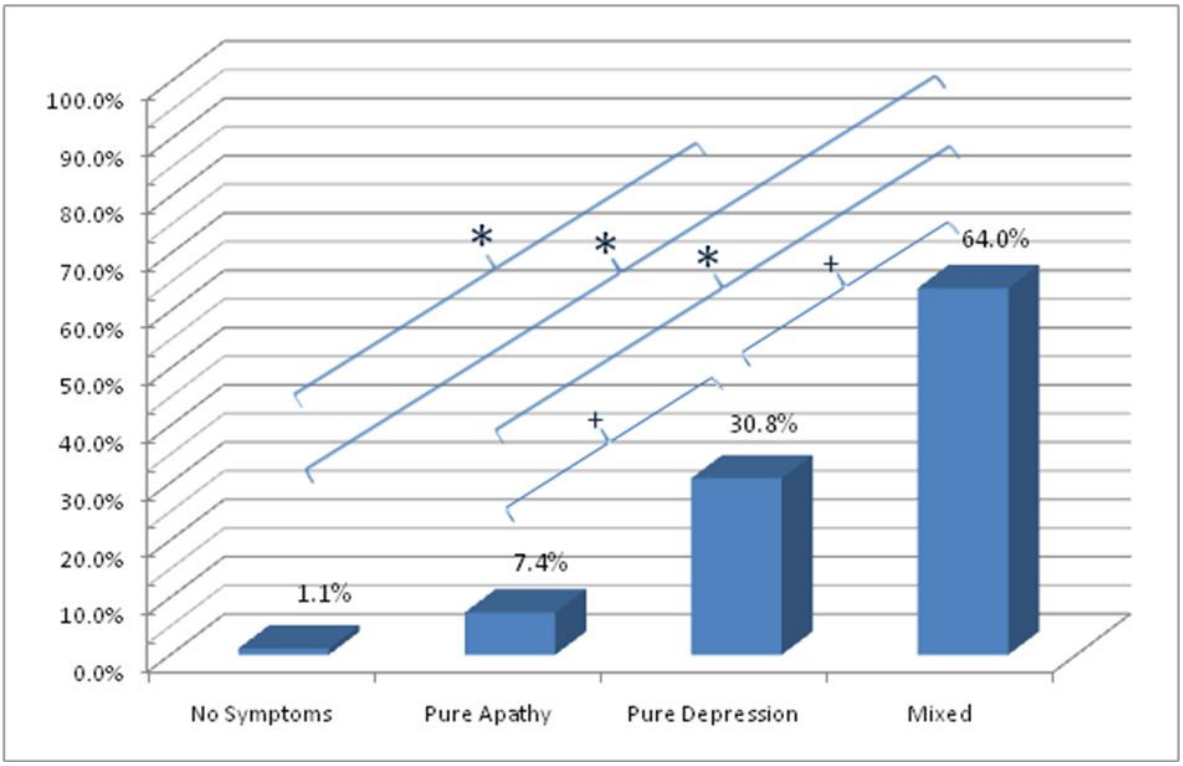

Figure 5-4. Percentages of patients with clinically elevated trait anxiety across Apathy-Depression subgroups.

* Indicates significant differences, + indicates trends

Table 5-3. Confirmatory factor analysis loadings and uniquenesses

Factor	Items	Loading	Uniqueness
Apathy	A7_A10	.870	.242
	A4_A9	.758	.425
	A14_A5	.646	.582
	A11_A6	.687	.528
	A12_A13	.724	.476
Dysphoric Mood	B6_B8	.668	.553
	B3_B17	.770	.407
	B9_B2	.671	.549
	B1_B14	.794	.369
	B5_B10	.585	.658
	B7_B11	.868	.247
Loss of Interest/ Pleasure	B4_B12	.761	.420
	A1_A2	.453	.795
	B13	.650	.577
Somatic	B19	.701	.508
	B15_B20	.640	.591
	B21_A8	.671	.550
	B16_B18	.630	.603

Table 5-4. Factor correlations

Factor	Apathy	Dysphoric mood	Loss of interest/pleasure	Somatic complaints
Apathy	--	.526	.801	.735
Dysphoric mood	.526	--	.895	.584
Loss of interest/pleasure	.801	.895	--	.870
Somatic complaints	.735	.584	.870	--

Table 5-5. Goodness-of-fit statistics for confirmatory factor analysis of full four factor model and alternative nested models

Model	χ^2	*df*	$\Delta\chi^2$	Δdf	$p_{difference}$
Four factor	194.9	128	--	--	--
One factor	433.3	134	238.3	6	$p < .01$
Two factor	278.9	133	84	5	$p < .01$
Three factor, without somatic	295.2	132	100.2	4	$p < .01$
Three factor, without loss of interest	212.8	132	17.81	4	$p < .01$

Note: p values indicate the chi square difference between the alternative models and the four factor model, indicating significantly worse fit for all alternative models.

Table 5-6. Descriptive statistics for individual cognitive tests

Domains and Cognitive tests	Mean (SD)	Range	N
Executive functioning			
Trail Making Test Part B	-.706 (1.15)	-3.00 - 2.55	159
Letter fluency	-.298 (1.07)	-2.80 - 2.40	158
Animal fluency	-.115 (1.12)	-3.00 - 3.00	158
Stroop Color Word	-.271(1.05)	-2.80 - 3.00	155
Processing speed			
Trail Making Test Part A	-.579(1.13)	-3.00 – 2.80	161
Digit Symbol	-.280(.935)	-2.35 – 2.00	158
Stroop Color	-.785(.77)	-2.80 - 1.70	156
Verbal episodic memory			
Logical memory I (total)	.150(1.04)	-2.35 – 2.35	160
Logical memory II (delay)	.354 (1.03)	-2.65 – 2.65	161
HVLT-II total	-.632 (1.15)	-3.00 – 1.70	161
HVLT-II delay	-.768 (1.31)	-3.00 – 1.30	161
Working memory			
Digit span forwards	.208(.89)	-1.85 – 2.35	161
Digit span backwards	.183 (.92)	-1.70 – 3.00	161
Language functioning			
Vocabulary	.609 (.79)	-1.64 – 2.33	153
Boston Naming Test	.389 (1.01)	-2.10 – 3.00	159

Table 5-7. Descriptive statistics for cognitive domains used in hierarchical regressions (z score metric)

Cognitive domain	Mean (SD)	Range	N
Executive functioning	-.304 (.769)	-2.40 - 1.88	150
Processing speed	-.514 (.740)	-2.60 - 1.67	150
Verbal episodic memory	-.192 (.882)	-2.53 - 1.90	150
Working memory	.205 (.781)	-1.55 - 2.68	150
Language functioning	.527 (.738)	-1.72 - 2.50	150

Table 5-8. Correlations among cognitive domains (Pearson correlations).
All cognitive domains were significantly correlated ($p < .001$).

Cognitive domain	Exec. functioning	Processing speed	Verbal episodic memory	Working memory	Language functioning
Exec. functioning	_	.659	.534	.254	.462
Processing speed	.659	_	.437	.271	.317
Verbal episodic memory	.534	.437	_	.289	.431
Working memory	.254	.271	.289	_	.328
Language functioning	.462	.317	.431	.328	_

Table 5-9. Multicollinearity statistics for hierarchical multiple regressions

Model	Predictor	VIF	Tolerance
1	Age	1.010	.990
	Gender	1.019	.981
	Education	1.029	.972
2	Age	1.132	.884
	Gender	1.039	.963
	Education	1.036	.965
	Months PD	1.039	.963
	UPDRS on	1.168	.856
3	Age	1.164	.859
	Gender	1.051	.951
	Education	1.065	.939
	Months PD	1.051	.952
	UPDRS on	1.168	.856
	BDI-II	1.090	.917
4	Age	1.165	.858
	Gender	1.051	.951
	Education	1.074	.931
	Months PD	1.057	.946
	UPDRS on	1.168	.856
	BDI-II	1.905	.525
	STAI-T	1.807	.553
5	Age	1.210	.826
	Gender	1.052	.951
	Education	1.092	.916
	Months PD	1.062	.941
	UPDRS on	1.188	.842
	BDI-II	2.494	.401
	STAI-T	1.851	.540
	AS	1.876	.533
6	Age	1.218	.821
	Gender	1.057	.946
	Education	1.106	.905
	Months PD	1.096	.912
	UPDRS on	1.210	.826
	BDI-II	4.897	.204

Table 5-9. Continued

Model	Predictor	VIF	Tolerance
	STAI-T	2.034	.492
	AS	3.391	.295
	Group: Pure apathy	2.079	.481
	Group: Pure depression	1.733	.577
	Group: Mixed apathy-depression	5.009	.200

Note: VIF = Variance Inflation Factor

Table 5-10. Hierarchical multiple regression results, showing the relationship between predictors and Executive functioning

Model	Variance explained	Predictor	B	SE B	β	*p* value
1	Total R^2 = .010	(Constant)	.023	.553		
	ΔR^2 = .010,	Age	-.004	.007	-.052	.533
	p = .686	Gender	-.146	.137	-.088	.291
		Education	.004	.023	.014	.864
2	Total R^2 = .045	(Constant)	.237	.568		
	ΔR^2= .035,	Age	-.001	.008	-.013	.884
	p = .073+	Gender	-.106	.137	-.064	.441
		Education	.007	.023	.027	.749
		UPDRS on	-.016	.009	-.159	**.073+**
		Months PD	-.001	.001	-.093	.265
3	Total R^2 = .053	(Constant)	.456	.601		
	ΔR^2= .008,	Age	-.003	.008	-.029	.744
	p = .273	Gender	-.089	.138	-.054	.517
		Education	.003	.023	.011	.892
		UPDRS on	-.015	.009	-.158	**.075+**
		Months PD	-.001	.001	-.083	.321
		BDI-II	-.010	.009	-.093	.273
4	Total R^2 = .068,	(Constant)	.479	.599		
	ΔR^2 = .014	Age	-.002	.008	-.025	.777
	p =.145	Gender	-.093	.137	-.056	.499
		Education	.006	.023	.022	.792
		UPDRS on	-.015	.009	-.158	**.073+**
		Months PD	-.001	.001	-.073	.379
		BDI-II	.001	.012	.014	.903
		STAI-T	-.004	.003	-.160	.145
5	Total R^2 = .103,	(Constant)	.460	.590		
	ΔR^2 = .035	Age	.001	.008	.015	.863
	p =.020*	Gender	-.100	.135	-.061	.460
		Education	.000	.023	-.003	.969
		UPDRS on	-.013	.009	-.131	.134
		Months PD	-.001	.001	-.087	.292
		BDI-II	.017	.014	.158	.211
		STAI-T	-.003	.003	-.120	.270
		AS	-.031	.013	-.258	**.020***

Table 5-10. Continued

Model	Variance explained	Predictor	B	SE B	β	*p* value
6	Total R^2 = .138,	(Constant)	.390	.747	.549	.390
	ΔR^2 = .035	Age	.828	.108	.426	.747
	p = .135	Gender	.696	.215	.012	.549
		Education	.614	.533	.030	.828
		UPDRS on	.390	.747	.549	.108
		Months PD	.828	.108	.426	.426
		BDI-II	.696	.215	.012	.696
		STAI-T	.614	.533	.030	.215
		AS	.390	.747	.549	**.012***
		Group: Pure apathy vs. No sym	.828	.108	.426	.614
		Group: Pure depression vs. No sym	.696	.215	.012	.533
		Group: Mixed apathy-depression vs. No sym	.614	.533	.030	**.030***

Note: UPDRS = Unified Parkinson Disease Rating Scale, BDI-II = Beck Depression Inventory II, AS = Apathy Scale, * indicates significant at p < .05; + indicates significant at p <.1

Table 5-11. Hierarchical multiple regression results, showing the relationship between predictors and Processing speed

Model	Variance explained	Predictor	B	SE B	β	*p* value
1	Total R^2 = .074	(Constant)	-.166	.515		
	ΔR^2 = .074,	Age	.000	.007	.004	.960
	p = .011*	Gender	-.426	.128	-.268	**.001***
		Education	-.005	.021	-.019	.813
2	Total R^2 = .133	(Constant)	.121	.521		
	ΔR^2= .059,	Age	.004	.007	.051	.540
	p = .008*	Gender	-.378	.126	-.238	**.003***
		Education	-.001	.021	-.004	.960
		UPDRS on	-.018	.008	-.196	**.021***
		Months PD	-.002	.001	-.133	.096+
3	Total R^2 = .157	(Constant)	.481	.547		
	ΔR^2= .024,	Age	.002	.007	.023	.782
	p = .048*	Gender	-.351	.125	-.221	**.006***
		Education	-.008	.021	-.030	.705
		UPDRS on	-.018	.008	-.195	**.020***
		Months PD	-.002	.001	-.116	.143
		BDI-II	-.017	.008	-.160	**.048***
4	Total R^2 = .164,	(Constant)	.498	.546		
	ΔR^2 = .008	Age	.002	.007	.026	.754
	p =.255	Gender	-.353	.125	-.222	**.005**
		Education	-.006	.021	-.022	.782
		UPDRS on	-.018	.008	-.195	**.020**
		Months PD	-.001	.001	-.109	.170
		BDI-II	-.008	.011	-.081	.446
		STAI-T	-.003	.002	-.118	.255
5	Total R^2 = .164,	(Constant)	.497	.548		
	ΔR^2 = .000	Age	.002	.007	.027	.748
	p =.939	Gender	-.354	.126	-.222	**.006**
		Education	-.006	.021	-.023	.777
		UPDRS on	-.018	.008	-.194	**.022**
		Months PD	-.001	.001	-.109	.170
		BDI-II	-.008	.013	-.076	.531
		STAI-T	-.003	.002	-.117	.267
		AS	.000	.012	-.008	.939

Table 5-11. Continued

Model	Variance explained	Predictor	B	SE B	β	*p* value
6	Total R^2 = .218,	(Constant)	.402	.542		
	ΔR^2 = .053	Age	.003	.007	.040	.627
	p = .027*	Gender	-.333	.123	-.209	**.008***
		Education	-.003	.021	-.009	.905
		UPDRS on	-.016	.008	-.175	**.036***
		Months PD	-.001	.001	-.097	.222
		BDI-II	-.043	.017	-.414	**.014***
		STAI-T	-.002	.003	-.106	.325
		AS	.011	.016	.098	.482
		Group: Pure apathy vs. No sym	-.293	.215	-.148	.174
		Group: Pure depression vs. No sym	.501	.269	.184	**.065+**
		Group: Mixed apathy-depression vs. No sym	.523	.339	.260	.125

Note: UPDRS = Unified Parkinson Disease Rating Scale, BDI-II = Beck Depression Inventory II, AS = Apathy Scale, * indicates significant at p < .05; + indicates significant at p <.1

Table 5-12. Hierarchical multiple regression results, showing the relationship between predictors and Verbal episodic memory

Model	Variance explained	Predictor	B	SE B	β	p value
1	Total R^2 = .164	(Constant)	-1.687	.583		
	ΔR^2 = .164,	Age	.009	.008	.094	.218
	p < .001*	Gender	-.595	.145	-.314	**<.001***
		Education	.086	.024	.273	**.001***
2	Total R^2 = .192	(Constant)	-1.475	.600		
	ΔR^2= .028,	Age	.013	.008	.130	.106
	p = .088+	Gender	-.554	.145	-.293	**<.001***
		Education	.089	.024	.284	**<.001***
		UPDRS on	-.016	.009	-.143	**.080+**
		Months PD	-.001	.001	-.080	.299
3	Total R^2 = .208	(Constant)	-1.116	.631		
	ΔR^2= .016,	Age	.011	.008	.107	.187
	p = .088+	Gender	-.527	.145	-.278	**<.001***
		Education	.083	.024	.262	**.001***
		UPDRS on	-.016	.009	-.141	**.081+**
		Months PD	-.001	.001	-.066	.390
		BDI-II	-.016	.010	-.133	**.088+**
4	Total R^2 = .211	(Constant)	-1.104	.632		
	ΔR^2 = .003	Age	.011	.008	.108	.180
	p =.468	Gender	-.529	.145	-.279	**<.001***
		Education	.084	.024	.267	**.001***
		UPDRS on	-.016	.009	-.141	**.081+**
		Months PD	.000	.001	-.061	.425
		BDI-II	-.010	.013	-.084	.413
		STAI-T	-.002	.003	-.073	.468
5	Total R^2 = .211	(Constant)	-1.106	.635		
	ΔR^2 = .000	Age	.011	.008	.112	.177
	p =.842	Gender	-.530	.145	-.280	**<.001***
		Education	.084	.025	.265	**.001***
		UPDRS on	-.016	.009	-.139	**.090+**
		Months PD	-.001	.001	-.062	.419
		BDI-II	-.009	.015	-.073	.538
		STAI-T	-.002	.003	-.070	.493
		AS	-.003	.014	-.020	.842

Table 5-12. Continued

Model	Variance explained	Predictor	B	SE B	β	*p* value
6	Total R^2 = .245	(Constant)	-1.097	.635		
	ΔR^2 = .034	Age	.012	.008	.121	.140
	p = .109	Gender	-.519	.144	-.274	**<.001***
		Education	.086	.024	.272	**.001***
		UPDRS on	-.018	.009	-.163	**.048***
		Months PD	.000	.001	-.035	.653
		BDI-II	-.004	.020	-.035	.829
		STAI-T	-.001	.003	-.049	.642
		AS	-.018	.019	-.132	.333
		Group: Pure apathy vs. No sym	.066	.252	.028	.793
		Group: Pure depression vs. No sym	-.567	.315	-.175	.074+
		Group: Mixed apathy-depression vs. No sym	.208	.397	.087	.602

Note: UPDRS = Unified Parkinson Disease Rating Scale, BDI-II = Beck Depression Inventory II, AS = Apathy Scale, * indicates significant at p < .05; + indicates significant at p <.1

Table 5-13. Hierarchical multiple regression results, showing the relationship between predictors and Working Memory

Model	Variance Explained	Predictor	B	SE B	β	*p* value
1	Total R^2 = .056	(Constant)	-.699	.549		.205
	ΔR^2 = .056,	Age	.003	.007	.031	.697
	p = .038*	Gender	-.225	.136	-.134	.101
		Education	.058	.023	.208	**.012***
2	Total R^2 = .069	(Constant)	-.817	.570		.154
	ΔR^2= .013,	Age	.006	.008	.069	.418
	p = .371	Gender	-.207	.138	-.123	.135
		Education	.060	.023	.217	**.009***
		UPDRS on	-.010	.009	-.105	.229
		Months PD	.001	.001	.076	.356
3	Total R^2 = .083	(Constant)	-.521	.601		.388
	ΔR^2= .014,	Age	.004	.008	.048	.580
	p = .138	Gender	-.185	.138	-.110	.182
		Education	.055	.023	.197	**.019***
		UPDRS on	-.010	.009	-.104	.232
		Months PD	.001	.001	.089	.281
		BDI-II	-.014	.009	-.125	.138
4	Total R^2 = .089,	(Constant)	-.506	.602		.402
	ΔR^2 = .006	Age	.004	.008	.050	.561
	p =.356	Gender	-.187	.138	-.111	.177
		Education	.057	.023	.203	**.016***
		UPDRS on	-.010	.009	-.104	.232
		Months PD	.001	.001	.095	.252
		BDI-II	-.006	.012	-.058	.603
		STAI-T	-.002	.003	-.100	.356
5	Total R^2 = .091,	(Constant)	-.511	.603		.398
	ΔR^2 = .002	Age	.005	.008	.060	.495
	p =.559	Gender	-.189	.138	-.112	.174
		Education	.055	.023	.197	**.020***
		UPDRS on	-.010	.009	-.097	.269
		Months PD	.001	.001	.091	.271
		BDI-II	-.002	.014	-.022	.865
		STAI-T	-.002	.003	-.090	.412
		AS	-.008	.014	-.064	.559

Table 5-13. Continued

Model	Variance Explained	Predictor	B	SE B	β	*p* value
6	Total R^2 = .097,	(Constant)	-.577	.615		.350
	ΔR^2 = .006	Age	.005	.008	.059	.513
	p = .813	Gender	-.191	.140	-.114	.173
		Education	.053	.024	.190	**.027***
		UPDRS on	-.009	.009	-.087	.331
		Months PD	.001	.001	.087	.308
		BDI-II	-.001	.020	-.008	.965
		STAI-T	-.002	.003	-.072	.534
		AS	.004	.018	.028	.849
		Group: Pure apathy vs. No sym	-.178	.244	-.085	.466
		Group: Pure depression vs. No sym	.032	.305	.011	.916
		Group: Mixed apathy-depression vs. No sym	-.265	.384	-.125	.491

Note: UPDRS = Unified Parkinson Disease Rating Scale, BDI-II = Beck Depression Inventory II, AS = Apathy Scale, * indicates significant at p < .05; + indicates significant at p <.1

Table 5-14. Hierarchical multiple regression results, showing the relationship between predictors and Language Functioning

Model	Variance explained	Predictor	B	SE B	β	p value
1	Total R^2 = .052	(Constant)	-.594	.520		
	ΔR^2 = .052,	Age	.006	.007	.068	.403
	p = .049*	Gender	-.112	.129	-.071	.387
		Education	.055	.022	.209	**.012***
2	Total R^2 = .090	(Constant)	-.680	.533		
	ΔR^2= .038,	Age	.011	.007	.136	.111
	p = .054+	Gender	-.074	.129	-.047	.564
		Education	.059	.021	.226	**.006***
		UPDRS on	-.019	.008	-.205	.018
		Months PD	.001	.001	.075	.357
3	Total R^2 = .130	(Constant)	-.209	.554		
	ΔR^2= .040,	Age	.008	.007	.099	.240
	p = .011*	Gender	-.039	.127	-.024	.761
		Education	.050	.021	.191	**.019***
		UPDRS on	-.019	.008	-.203	**.017***
		Months PD	.001	.001	.097	.229
		BDI-II	-.022	.008	-.210	**.011***
4	Total R^2 = .150	(Constant)	-.183	.549		
	ΔR^2 = .020	Age	.009	.007	.104	.215
	p =.072+	Gender	-.043	.126	-.027	.734
		Education	.054	.021	.204	**.012***
		UPDRS on	-.019	.008	-.203	**.016***
		Months PD	.001	.001	.108	.177
		BDI-II	-.009	.011	-.083	.437
		STAI-T	-.004	.002	-.189	**.072+**
5	Total R^2 = .156	(Constant)	-.190	.549		
	ΔR^2 = .006	Age	.010	.007	.120	.159
	p =.318	Gender	-.046	.126	-.029	.718
		Education	.051	.021	.194	**.018***
		UPDRS on	-.018	.008	-.192	**.024***
		Months PD	.001	.001	.102	.201
		BDI-II	-.002	.013	-.024	.846
		STAI-T	-.004	.002	-.172	.104
		AS	-.012	.012	-.106	.318

Table 5-14. Continued

Model	Variance explained	Predictor	B	SE B	β	*p* value
6	Total R^2 = .161	(Constant)	-.128	.560		
	ΔR^2 = .005	Age	.010	.007	.117	.176
	p = .857	Gender	-.048	.127	-.030	.705
		Education	.052	.022	.197	**.018***
		UPDRS on	-.018	.008	-.192	**.027***
		Months PD	.001	.001	.093	.254
		BDI-II	-.004	.018	-.042	.807
		STAI-T	-.005	.003	-.201	**.073+**
		AS	-.017	.017	-.149	.303
		Group: Pure apathy vs. No sym	.152	.222	.077	.494
		Group: Pure depression vs. No sym	.180	.278	.066	.519
		Group: Mixed apathy-depression vs. No sym	.144	.350	.072	.681

Note: UPDRS = Unified Parkinson Disease Rating Scale, BDI-II = Beck Depression Inventory II, AS = Apathy Scale, * indicates significant at p < .05; + indicates significant at p <.1

Table 5-15. Hierarchical multiple regression results, showing the relationship between predictors and Wisconsin Card Sorting Test, raw number of categories achieved

Model	Variance explained	Predictor	B	SE B	β	*p* value
1	Total R^2 = .149	(Constant)	5.698	2.094		
	ΔR^2 = .149,	Age	-.081	.028	-.358	**.005***
	p = .019*	Gender	-.455	.524	-.104	.389
		Education	.202	.100	.246	**.047***
2	Total R^2 = .155	(Constant)	5.737	2.152		
	ΔR^2= .005,	Age	-.074	.030	-.327	**.019***
	p = .830	Gender	-.408	.539	-.094	.452
		Education	.204	.102	.248	**.051+**
		UPDRS on	-.021	.035	-.078	.559
		Months PD	.000	.005	-.008	.948
3	Total R^2 = .156	(Constant)	5.459	2.446		
	ΔR^2= .001,	Age	-.072	.032	-.318	**.029***
	p = .807	Gender	-.413	.543	-.095	.450
		Education	.206	.104	.251	**.051+**
		UPDRS on	-.021	.036	-.079	.560
		Months PD	.000	.005	-.004	.977
		BDI-II	.010	.042	.032	.807
4	Total R^2 = .156	(Constant)	5.474	2.473		
	ΔR^2 = .000	Age	-.072	.033	-.319	**.031***
	p =.928	Gender	-.412	.548	-.095	.455
		Education	.205	.105	.250	**.055+**
		UPDRS on	-.021	.036	-.078	.567
		Months PD	.000	.005	-.005	.971
		BDI-II	.007	.054	.022	.894
		STAI-T	.001	.011	.014	.928
5	Total R^2 = .160	(Constant)	5.822	2.584		
	ΔR^2 = .004	Age	-.072	.033	-.322	**.031***
	p =.617	Gender	-.461	.560	-.106	.414
		Education	.194	.108	.236	**.078+**
		UPDRS on	-.020	.036	-.074	.593
		Months PD	-.001	.006	-.016	.901
		BDI-II	.020	.060	.063	.738
		STAI-T	.002	.011	.033	.839
		AS	-.028	.056	-.087	.617

Table 5-15. Continued

Model	Variance explained	Predictor	B	SE B	β	*p* value
6	Total R^2 = .182	(Constant)	5.249	2.753		
	ΔR^2 = .022	Age	-.071	.035	-.314	**.049***
	p = .694	Gender	-.509	.617	-.117	.414
		Education	.190	.114	.231	.102
		UPDRS on	-.020	.037	-.074	.601
		Months PD	-.001	.006	-.017	.900
		BDI-II	.046	.087	.142	.602
		STAI-T	.005	.012	.072	.690
		AS	.025	.087	.076	.780
		Group: Pure apathy vs. No sym	-.667	1.204	-.105	.582
		Group: Pure depression vs. No sym	-.264	1.231	-.037	.831
		Group: Mixed apathy-depression vs. No sym	-1.616	1.374	-.291	.245

Note: UPDRS = Unified Parkinson Disease Rating Scale, BDI-II = Beck Depression Inventory II, AS = Apathy Scale, * indicates significant at p < .05; + indicates significant at p <.1

Table 5-16. Hierarchical multiple regression results, showing the relationship between predictors and Wisconsin Card Sorting Test, raw number of perseverative errors

Model	Variance explained	Predictor	B	SE B	β	*p* value
1	Total R^2 = .211	(Constant)	17.785	13.909		
	ΔR^2 = .211,	Age	.547	.176	.375	**.003***
	p = .003*	Gender	1.185	3.361	.042	.726
		Education	-1.944	.674	-.343	**.005***
2	Total R^2 = .231	(Constant)	20.808	14.243		
	ΔR^2= .020,	Age	.475	.194	.326	**.018***
	p = .491	Gender	.483	3.456	.017	.889
		Education	-1.933	.680	-.341	**.006***
		UPDRS on	.208	.230	.121	.371
		Months PD	-.033	.034	-.116	.338
3	Total R^2 = .231	(Constant)	19.582	16.165		
	ΔR^2= .000,	Age	.484	.203	.332	**.021***
	p = .869	Gender	.445	3.494	.016	.899
		Education	-1.922	.690	-.339	**.007***
		UPDRS on	.208	.232	.121	.375
		Months PD	-.032	.035	-.113	.360
		BDI-II	.043	.262	.021	.869
4	Total R^2 = .232	(Constant)	19.152	16.414		
	ΔR^2 = .001	Age	.493	.209	.338	**.022***
	p =.819	Gender	.462	3.525	.016	.896
		Education	-1.903	.701	-.335	**.009***
		UPDRS on	.204	.235	.118	.389
		Months PD	-.032	.035	-.113	.368
		BDI-II	.093	.342	.045	.786
		STAI-T	-.016	.069	-.036	.819
5	Total R^2 = .233	(Constant)	17.982	17.119		.298
	ΔR^2 = .001	Age	.496	.211	.340	**.022***
	p =.789	Gender	.680	3.646	.024	.853
		Education	-1.865	.721	-.329	**.012***
		UPDRS on	.197	.238	.114	.413
		Months PD	-.030	.036	-.107	.402
		BDI-II	.048	.384	.023	.901
		STAI-T	-.021	.072	-.047	.775
		AS	.096	.356	.046	.789

Table 5-16. Continued

Model	Variance explained	Predictor	B	SE B	β	*p* value
6	Total R^2 = .256	(Constant)	23.943	18.374		
	ΔR^2 = .023	Age	.464	.226	.318	**.046***
	p = .675	Gender	.359	4.019	.013	.929
		Education	-2.059	.763	-.363	**.009***
		UPDRS on	.213	.245	.124	.389
		Months PD	-.029	.038	-.102	.450
		BDI-II	.217	.551	.106	.696
		STAI-T	-.009	.078	-.020	.908
		AS	-.276	.550	-.133	.618
		Group: Pure apathy vs. No sym	2.539	7.592	.063	.739
		Group: Pure depression vs. No sym	-7.890	7.998	-.159	.329
		Group: Mixed apathy-depression vs. No sym	2.954	8.542	.084	.731

Note: UPDRS = Unified Parkinson Disease Rating Scale, BDI-II = Beck Depression Inventory II, AS = Apathy Scale, * indicates significant at p < .05; + indicates significant at p <.1

Table 5-17. Demographic, disease variable differences between apathetic and nonapathetic groups.

Characteristic	Nonapathetic	Apathetic	p value
	(N = 107)	*(N=54)*	
Age	63.7 (8.2), range 43-80	64.8 (9.9), range 42-84	.46
Men: Women	72:35 (67% male)	39:15 (72% male)	.53
Years of Education	15.5 (2.8), range 12-22	14.5 (2.8), range 7-20	**.04***
% on Anti-depressants	26.2% (28 out of 107 patients)	38.9% (21 out of 54 patients)	.09
% on Anxiolytics	21.5% (23 out of 107 patients)	31.5% (17 out of 54 patients)	.16
Levodopa Equivalent Dosage	831.7 (523.3)	778.7 (489.9)	.33
Months of Symptoms	99.7 (51.0), range 12-251	106.2 (61.1), range 12-241	.50
Motor score (UPDRS, on levodopa)	24.2 (8.6), range 9-47	26.6 (7.9), range 13-46	.098

Note: N = 161. However, five patients were missing UPDRS on scores, (N = 157). Results are presented as means (standard deviations) and ranges.

Table 5-18. Mood and anxiety differences between apathetic and nonapathetic groups.

Characteristic	Nonapathetic	Apathetic	p value
	(N = 107)	*(N=54)*	
Apathy (AS)	7.2 (3.7)	17.92 (4.0)	---
Depression (BDI-II)	7.07 (4.86), range 0-23	14.43 (8.60), range 1-34	**<.001***
State Anxiety (STAI) Percentile	49.05 (28.3), range 5-97	70.34 (28.4), range 11-99	**<.001***
Trait Anxiety (STAI) Percentile	42.23 (28.17), range 3-98	74.98 (25.24), range 6-100	**<.001***

Note: N = 161. However, six patients were missing STAI State scores, (N = 155), and seven patients were missing STAI Trait scores (N = 154). Results are presented as means (standard deviations) and ranges.

CHAPTER 6
DISCUSSION

The present study investigated two hypotheses. The first hypothesis was that apathy and depression, although similar, are separable experiences of mood states that can be dissociated in nondemented patients with Parkinson disease. For this reason, it was predicted that individual items from two commonly used depression and apathy self-report inventories, the Beck Depression Inventory-II and the Apathy Scale, would be dissociable via factor analysis. Specifically, items from these scales were predicted to fall onto four main factors: 1) an apathy factor representing "loss of motivation," 2) a dysphoric mood factor representing "sadness and negativity," 3) a loss of interest/pleasure factor representing the "overlapping features" between apathy and depression, and 4) a somatic factor representing "bodily complaints" (e.g. fatigue, loss of appetite, insomnia). These factors were based on the concept that depression and apathy differ in terms of their core features. Namely, depression is characterized by sadness, hopelessness, and negativity, whereas the core feature of apathy involves "blunted" or "no" mood along with loss of motivation.

The second hypothesis evaluated in this study involved the relationship between cognition and apathy. Previous studies indicated a negative association between apathy and executive functioning (Starkstein et al., 1992, Isella et al., 2002, Pluck & Brown, 2002; Zgaljardic et al., 2007; Pedersen et al., 2009; Santangelo et al., 2009). It was hypothesized that apathy would be associated with worsened cognitive status, particularly dysfunction of frontal lobe systems. However, all studies until the present one have not controlled for important comorbidities such as dementia, disease variables, and depression. Previous work has also focused on executive functioning measures to the relative exclusion of other cognitive domains (language, episodic memory, processing speed, etc). Based on the idea that frontal lobe pathology (i.e. mesial frontal

cortex/anterior cingulate cortex) is putatively involved in apathy, we hypothesized that apathy was related to deteriorated frontal lobe functioning and that this would be evidenced by poor performance in executive functioning tasks. Specifically, apathy scores would predict poor scores in the executive functioning domain, but not in other cognitive domains.

Prevalence of Apathy and Depression

The current sample of 161 non-demented Parkinson patients was comparable to that of others described in the literature in terms of prevalence of apathy and depression. Apathy was present in approximately one third of the patients in the current Parkinson sample (54 out of 161 patients, 34%). Ten previous studies are known to the authors that have assessed apathy in PD using a self-report scale (Starkstein et al., 1992; Pluck & Brown, 2002; Czernecki et al., 2002; Isella et al., 2002; Kirsch-Darrow et al., 2006; Dujardin et al., 2007; Zgaljardic et al., 2007; Pedersen et al., 2009; Santangelo et al., 2009; Starkstein et al., 2009). Some of these studies excluded dementia patients, while some did not. The present results fall into the range reported in the nondemented samples of between 23%-44% (Czernecki et al., 2002; Dujardin et al., 2007; Pedersen, Alves et al., 2009; Pluck & Brown, 2002; Zgaljardic et al., 2007). In contrast, other studies did not screen out dementia patients. These studies generally have higher prevalence rates for apathy, ranging from 32%-56% (Starkstein et al., 1992; Isella et al., 2002; Kirsch-Darrow et al., 2006; Dujardin et al., 2007; Santangelo et al., 2009; Starkstein et al., 2009).

Dujardin and colleagues compared apathy in both a demented group (n = 39) and a nondemented group (n = 120) of Parkinson patients using the Lille Apathy Rating Scale (LARS). The demented group had over twice the prevalence of clinically significant apathy than the nondemented group (56% in the dementia group vs. 24% in the nondemented group) (Dujardin et al., 2007). In addition to PD, a high prevalence of apathy is also common in other dementia classifications such as Alzheimer's disease. Using the Neuropsychiatric Inventory (NPI) to

assess apathy, studies found prevalence rates of 55% - 81% (van Reekum et al., 2005). Other subcortical disorders that commonly involve dementia, are frequently associated with apathy. These include Progressive supranuclear palsy, Huntington's disease, and Corticobasal degeneration (Aarsland, Ballard, McKeith, Perry, & Larsen, 2001; Litvan, Cummings, & Mega, 1998; Litvan, Paulsen, Mega, & Cummings, 1998; Paulsen, Ready, Hamilton, Mega, & Cummings, 2001). The strong relationship between the syndromes of apathy and dementia is thought to occur because of similar underlying brain pathology (i.e. rather than an apathy syndrome being the result of impaired cognition). Both dopaminergic (Brown & Pluck, 2000) and non-dopaminergic circuits have been hypothesized as the cause (Dujardin et al., 2007; Cummings & Black, 1998).

Importantly, the results from the present study indicated that apathy can occur in the absence of depression. In the current study, 17% of patients had apathy without depression, 16% had symptoms of both apathy and depression, and 9% had symptoms of depression only. These findings are consistent with the literature. Several studies broke down their prevalence figures into apathy alone, depression alone, and apathy and depression together. Apathy alone prevalence has ranged from 12-29%, depression alone prevalence has ranged from 3-22%, and the prevalence of both apathy and depression has ranged from 12-47% (Starkstein et al., 1992; Isella et al., 2002; Kirsch-Darrow et al., 2006; Zgaljardic et al., 2007). The rates from the current study fall within each of these ranges.

Factor Structure of Apathy and Depression in PD

The majority of studies listed above classify apathy and depression using cutting scores on self-report inventories. However, this problematic because of the use of total scores. Total scores overlook the issue that apathy and depression have overlapping symptoms such that the scales overlap in content. Symptoms may be counted towards the 'wrong' total score. To

overcome this limitation, item level confirmatory factor analysis was used to examine the hypothesis that apathy and depression can be dissociated, but also share some symptomatology. A four factor model was hypothesized that involved: 1) an apathy factor representing "loss of motivation," 2) a dysphoric mood factor representing "sadness and negativity," 3) a loss of interest and anhedonia factor representing the "overlapping features" between apathy and depression, and 4) a somatic factor representing "bodily complaints." Results indicated that this four factor solution fit the data well.

Importantly, it fit the data better than all alternative nested models. The four factor model was significantly better at describing the data than a single factor model that combined apathy and depression into an overall "general depression" factor. It fit significantly better than a two factor model specified by all of the Apathy Scale items loading on an "apathy" factor and all of the Beck Depression Inventory-II items loading on a "depression" factor. Finally, it provided a significantly better fit than the two alternative three-factor models that omitted either a) the loss of interest and pleasure factor (i.e. included the apathy, depression, and somatic factors) or b) the somatic factor (i.e. included the apathy, depression, and loss of interest and pleasure factor). Taken together, these findings contribute to the growing body of literature suggesting a separation of these two mood states in PD (Levy et al., 1998; Starkstein et al., 1992 Isella et al., 2002; Kirsch-Darrow et al., 2006; Zgaljardic et al., 2007; Durjardin et al., 2007; Pedersen et al., 2009; Santangelo et al., 2009). The findings argue *against* the idea that apathy is more accurately classified as a subcomponent of depression.

Moreover, this model supports several concepts about the different characteristics of apathy and depression in PD. Depression includes sadness and negative thoughts about the self. One of the item clusters that loaded most highly on the dysphoric mood factor was: "I feel sad

much of the time," and "I don't consider myself as worthwhile and useful as I used to." Another one that loaded highly was: "I have failed more than I should have," and "I am more irritable than usual." Symptoms of guilt and self-dislike also loaded highly on the dysphoric mood factor. In contrast, apathy does not involve pessimistic self and event appraisal. Instead, apathetic individuals lack responsiveness to both negative and positive events (Brown & Pluck, 2000). Results lend support for the idea that apathy involves lack of initiation, and lack of effort. In fact, the strongest loading item clusters on the apathy factor were "Do you put much effort into things?" and "Does someone have to tell you what to do each day?"

Two additional factors were hypothesized—one involving the overlapping symptoms of loss of interest and anhedonia, and one involving somatic symptoms. Both were supported in this study. A National Institute of Neurological Disorders and Stroke (NINDS) depression workgroup highlighted loss of interest as a symptom that overlaps between depression and apathy (Marsh et al., 2006). This has never been empirically tested until the present study.

Furthermore, the depression workgroup cautioned that using loss of interest as one of the two major core symptoms of an MDD (i.e. Criteria A1 = sad mood or Criteria A2 = markedly diminished interest or pleasure) could lead to overdiagnosis of MDD because the symptom of loss of interest might be better accounted for by a syndrome of apathy (Marsh et al., 2006). The workgroup recommended omitting decreased interest as a core affective symptom when diagnosing MDD in PD. They noted similar concerns regarding anhedonia, but decided that it was a core feature of depression as well as involved in apathy; they did not recommend omitting it from diagnosis of MDD (Marsh et al., 2006).

Unfortunately, this solution leaves the symptom of anhedonia in the same scenario as loss of interest. Namely, it could count towards one of the core symptoms of depression, or it could

count towards primary apathy. Or, a patient could have both syndromes. This is especially problematic when diagnosing minor depression. Minor depression requires a total of only two symptoms. One of these must be a core depression symptom (i.e. sad mood or loss of interest/anhedonia); the other can be any of the major depressive disorder symptoms. In PD, minor depression can easily be misdiagnosed because a patient may have loss of interest or anhedonia plus another symptom associated with PD itself (e.g. psychomotor slowing, insomnia, concentration problems). Since the number of required symptoms is so few and they have a high potential to be related to apathy or to PD itself, minor depression diagnoses should be avoided in PD. They remain in the appendix of the DSM-IV TR and, as such, have an uncertain nosology and are considered diagnostic research criteria only.

Generally, this problem of misdiagnosis using the core feature of loss of interest or anhedonia could occur even when the depressive diagnosis has a clear nosology like MDD. The potential to misclassify apathetic patients as depressed using one of these criteria, although less likely because it requires at least 5 depressive symptoms, is possible. Appetite, sleep, psychomotor changes, concentration, and fatigue are five symptoms that are all in common between MDD and PD. If these were used purely to diagnose depression, alongside loss of interest or anhedonia, the potential for a false positive diagnosis of MDD is great. Careful evaluation and critical thinking is required for an accurate diagnosis of MDD in PD. Given the results of this study, we recommend the following: First, loss of interest/anhedonia symptoms should be evaluated for longitudinal course—noting when they onset, fluctuations in severity, and which symptoms they "cluster together with." Each symptom in an MDD diagnosis should be critically evaluated to make sure it is not due to PD itself. Looking at the course of each symptom and the context of their onset will help with this (e.g. did depressive symptoms begin

roughly at the same time?). For example, did loss of interest begin at the same time as decreases in appetite, middle insomnia, worsened concentration, and feelings of worthlessness?

Furthermore, it may be useful to use apathy and depression scales in a modified manner due to the overlap between the symptoms of loss of interest and anhedonia. When the "overlap" symptoms are added into the total scores, it is hard to determine whether they fall into apathy or depressive syndrome clusters. We propose an additional scoring procedure for the scales for use with PD patients. In addition to summing the items to derive total scores, a complimentary method could be used that combines items across scales to create "index scores" that map onto the four factors found in this study. This will provide four separate indices of 'pure' apathy and 'pure' depression, overlapping loss of interest/pleasure, and somatic symptoms. Future studies could use this complimentary scoring method and compare to diagnoses of MDD and apathy based on the consensus criteria recently proposed by Robert et al. and the European task force (Robert et al., 2009) to determine if they have diagnostic utility over and above total scores.

On a similar note, future studies could use discriminant function analysis to determine the symptoms that best discriminate apathy and depression in PD. Groups of patients could be classified a priori using the DSM-IV SCID for MDD and using the consensus criteria for apathy. Then, the AS and BDI-II can be administered to both groups. The items that best discriminate between the two syndromes can then determined and noted for future use of the scales. It is hypothesized that the guilt/worthlessness item, punishment item, suicidal ideation item, and irritability item will discriminate depression from apathy. Items that overlap (e.g. anhedonia, loss of interest), as well as fatigue and concentration items likely will not discriminate between groups.

As an additional next study, larger sample sizes could also be obtained in order to cross-validate the factor analysis results. A weakness of the present study is the lack of a large enough sample to cross-validate. First, an exploratory factor analysis can be performed. Then, the results of this study can be used in a confirmatory factor analysis. Combining the items into groups of two item pairs (e.g. parcels) could also be considered a weakness as well. Parceling does not allow each item to independently load on factors. A stronger item could influence a weaker item in terms of loadings on factors. Parceling was necessary in the present study because of severe non-normality of the data. A sample with a more normal distribution of apathy scores might be able to use individual items.

Apathy and Cognition

In addition to examining the relationship between apathy and depression, a second aim of the present study was to investigate the relationship between apathy and cognition. Previous studies have reported that increased apathy is associated with decreased executive functioning (Starkstein et al. 1992; Isella et al., 2002; Pluck & Brown, 2002; Zgaljardic et al., 2007; Pedersen et al., 2009; Santangelo et al., 2009). Based on the idea that frontal lobe pathology is putatively involved in apathy (i.e. mesial frontal cortex/anterior cingulate cortex), it was hypothesized that apathy was related to impaired frontal lobe functioning and that this would be evidenced by poor performance on executive functioning tasks. It was specifically predicted that apathy scores would be significantly related to poor performance in the Executive functioning domain, but not to other cognitive domains (e.g. Processing speed, Verbal episodic memory, Working memory, Language).

Apathy's Relationship to Cognitive Domains

The hypothesis presented above was supported. Apathy explained significant incremental variance in Executive functioning (3.5%), but not in any other cognitive domain.

For Executive functioning, the influence of apathy was above and beyond that of demographic variables, disease related variables, and depression. Breaking these domains down into the individual component tests, apathy explained significant variance in the Stroop Color Word task, Interference condition (5.5%, $p < .01$). Apathy explained variance in animal fluency at trend level (2.3%, $p = .06$). However, apathy did not contribute variance to letter fluency or Trail Making Test, Part B. The influence of apathy on the Wisconsin Card Sorting Task (WCST) was examined in smaller subgroup of PD patients ($n = 68$) who were administered this task. Neither the number of categories achieved, nor the number of perseverative errors made were significantly related to apathy. Only age and education were related to WCST performance.

Based on these findings, it appears that apathy is related to certain aspects of executive functioning such as *speeded semantic verbal fluency* [as measured by animal fluency] and *cognitive inhibition* [as measured by Stroop Color Word test, Interference condition]. Apathy was not related to other aspects of executive functioning such as shifting mental sets [as measured by Trail Making Test, Part B and the WCST] or phonemic fluency [as measured by F,A,S letter fluency]. Interestingly, the types of executive measures that seem most affected by apathy are those that are known to be associated with the mesial frontal lobe/anterior cingulate cortex (e.g. cognitive inhibition). This is in contrast to the ones that apathy was not associated with (e.g. shifting mental set to changing demands and phonemic fluency) which are more associated with the dorsolateral prefrontal cortex.

Apathy and Stroop color word performance: Relationship to anterior cingulate cortex

Apathy explained significant incremental variance in performance on the Stroop Color Word test. Out of all the tests that were evaluated, apathy contributed the most variance (5.5%) to the Interference condition of the Stroop Color Word test. No other predictors aside from apathy explained significant variance on the test (i.e. not demographics, disease variables, or

depression). The Stroop test has a long history (Stroop, 1935), and has become one of most widely used measures to study the effects of cognitive interference. Stroop's famous finding was that it took longer for subjects to name the color of the ink that color words were written in when the ink color and color word were incongruent (e.g. the word *red* written in blue ink), than it took for the subjects just to name the color of colored squares (Stroop, 1935). Today, the classic Golden version of the Stroop test involves three conditions: the Stroop Word condition, the Stroop Color condition, and the Stroop Color Word condition. In the Stroop Word condition, participants read words that denote color names (i.e., red, green, blue). In the Stroop Color condition, participants identify and name the color of X's that are printed in various colors (i.e. red, green, blue). Finally, in the Stroop Color Word condition, the cognitive interference condition, participants name the color of the ink of words that denote colors (i.e., word *red* printed in green ink).

The Stroop effect is based on the finding that it takes longer to read the name of a word when the color name is different versus name the color of X's. This finding has received multiple interpretations (Lezak, Howieson, & Loring, 2004). Some researchers attribute the slowing to a defect on the "stimulus end" where individuals have trouble processing one stimulus due to a second stimulus (Bush et al., 1998; Dyer, 1973). Others have interpreted it to be a defect on the "response end." Subjects must inhibit the pre-potent response of simply reading the word instead of stating the color of the ink the word is printed in (Zajano & Gorman, 1986). Although these may occur in healthy adults, and present as a decrease in reaction time, it often occurs to exaggerated extent in persons with frontal lobe injury (Lezak, Howieson, & Loring, 2004).

In the present study, apathy explained significant variance in Parkinson patients' performance on the Stroop Color Word Interference condition (p =.001). As apathy increased, performance on Stroop Color Word condition worsened. To see if this finding was specific to the cognitive interference condition, post hoc hierarchical regressions were performed with the same predictors and with the Stroop Word reading condition and the Stroop Color naming condition as dependent variables. Apathy did not explain significant variance in either (Word reading, p = .28; Color naming, p = .09).

The relationship between Stroop Color Word task, interference condition performance and apathy is particularly intriguing because both are thought to involve the anterior cingulate cortex (ACC). Multiple studies using fMRI in healthy adults have reported a relationship between the Stroop interference condition and ACC activation (Bench et al., 1993; Carter, Mintun, & Cohen, 1995; Pardo, Pardo, Janer, & Raichle, 1990). Studies find that the ACC is significantly more active during interference than non-interference trials (Bush et al., 1998). Further, lesion studies by Stuss and colleagues (2001) have indicated that that bilateral superior medial frontal damage is associated with increased errors and slowing on the interference trial of the Stroop, whereas posterior lesions were not related (Stuss, Floden, Alexander, Levine, & Katz, 2001).

The neurobiological substrates of apathy are unknown, but are hypothesized to involve the ACC circuit (Brown & Pluck, 2000; Isella et al., 2002). Specifically, apathy is thought to involve the striato-thalamo-cortical circuit originating in the ventral tegmental area (VTA) and ending in the ACC (VTA→ ventral striatum→ventral pallidum→ medialdorsal thalamus→ ACC). These limbic structures are involved in motivation and drive, and are important in translating motivation into action (Davidson & Irwin, 1999; Groenewegen, Wright, & Beijer,

1996; Mogenson, Jones, & Yim, 1980). Lesions in the region of the ACC and supplemental motor area produce a syndrome of extremely severe apathy, called akinetic mutism. In this syndrome, patients make no effort to communicate or initiate activities: they are content to lie silent and motionless (Kant, Duffy, & Pivovarnik, 1998; Damasio & Van Hoesen, 1983; Tranel, 1992). In PD, only one study exists that examines the neuroanatomy of apathy. Remy and colleagues used Positron Emission Tomography (PET) imaging and found that apathy was inversely correlated with dopamine and norepinephrine binding in the ventral striatum (Remy et al., 2005). The ventral striatum is a key structure in the circuit described above. Dysfunction of the ACC circuit, perhaps neurochemically through loss of dopamine and neuropathologically through Lewy bodies, may be underlie both apathy and Stroop Color Word performance in PD. Future studies should continue to address the relationship between apathy, cognitive interference/Stroop, and the ACC. Future studies could use Functional Magnetic Resonance Imaging (fMRI) during performance on a Stroop task as a noninvasive alternative to PET to investigate whether apathetic PD patients have less activation of the ACC and related circuitry than do non-apathetic PD patients.

Apathy and speeded verbal fluency

In addition to Stroop Color Word, apathy explained variance at trend level for animal (semantic) fluency. In contrast, there was no relationship between apathy and phonemic fluency. An association between apathy and verbal fluency has been found in all studies that have assessed verbal fluency in the context of apathy (Starkstein et al., 1992; Pluck & Brown, 2002; Isella et al., 2002; Zgaljardic et al., 2007; Pedersen et al., 2009; Santangelo et al., 2009). Namely, increased apathy is associated with decreased performance on verbal fluency tasks. It is unknown why the present study found that apathy was related to animal fluency at trend ($p = .06$) yet found no relationship with phonemic fluency. Phonemic fluency is often considered a more

difficult task for PD patients because it requires organization and switching between categories (e.g. executive based) versus semantic fluency which relies on memory and retrieval from semantic storage. Further studies are needed to replicate that apathy has a specific effect on semantic fluency, but not on phonemic fluency. In contrast to these findings, most of the previous studies compared scores between apathetic and nonapathetic PD groups and found both phonemic and animal fluency to be significantly worse in the apathetic group (Pluck & Brown, 2002; Isella et al., 2002; Zgaljardic et al., 2007). Starkstein and colleagues found their apathetic group to be lower on phonemic fluency than their nonapathetic group, but did not assess semantic fluency (Starkstein et al., 1992).

Speeded fluency tests require an individual to rapidly produce words, either that begin with a letter of the alphabet (i.e. F, A, and S for letter fluency), or are in a particular category (i.e. animals for animal fluency). To do well on fluency tests, the individual must successfully perform several tasks: a) self-initiate responses to a single prompt, b) organize their verbal output into meaningful clusters of related words (i.e. phonologically or semantically), and c) switch between clusters (Troyer, Moscovitch, & Winocur, 1997). Generally, it is well known that frontal lobe lesions, particularly of the left dominant hemisphere, induce impairments on verbal fluency tasks (Baldo & Shimamura, 1998; Milner, 1975). Stuss and colleagues (1998) administered the phonemic [F,A,S] and animal fluency tests to seventy-four brain damaged patients and a comparison group of healthy age-matched controls (Stuss et al., 1998). They found that patients with superior medial frontal lesions (including the ACC), either alone or with other cortical lesions, were impaired on letter fluency. These patients' performances differed from the controls' in the timing of the verbal output. Patients with medial frontal lesions produced significantly fewer words in the first fifteen seconds of the task than controls. Stuss et

al. (1998) proposed that the ACC may play a role in response initiation in this task (Stuss et al., 1998).

In the current study, the mechanism of impaired verbal fluency is unknown. To further understand this relationship, it will be important for future studies to examine performance in more fine grained ways. Some possibilities include examining the relationship between apathy and aspects of fluency performance including: 1) semantic versus phonemic fluency using different prompts other than animal and F,A,S to see if the specific relationship to semantic fluency versus phonemic fluency is replicated, 2) measuring cluster size, 3) measuring the number of switches between categories, and 3) scoring the test in 15 second intervals to determine if apathy is associated with problems initiating output to the prompt.

Apathy-Depression Group Findings

Four apathy-depression groupings were created that included PD patients with: a) pure apathy, b) pure depression, c) mixed apathy-depression, and d) neither apathy nor depression. The main differences between groups were that the pure apathy group was older than the mixed apathy-depression group. No other groups differed in age. Most studies have not found a difference in age between apathetic and nonapathetic groups (Pluck & Brown, 2002; Isella et al., 2002; Zgaljardic et al., 2007; Starkstein et al., 1992; Santangelo et al., 2009). In contrast, Pedersen and colleagues (2009) also found their apathetic group to be significantly older than their nonapathetic group.

Additionally, the mixed apathy-depression group had fewer years of education than the group with neither apathy nor depression. Although other studies have examined education and have not found a difference between groups (Pluck & Brown, 2002; Isella et al., 2002; Zgaljardic et al., 2007; Starkstein et al., 1992; Pedersen et al., 2009; Santangelo et al., 2009), this is one of the largest samples size to date (N = 161). Most studies sample sizes ranged between N = 30-50

(Pluck & Brown, 2002; Isella et al., 2002; Zgaljardic et al., 2007; Starkstein et al., 1992). As such, the current study may have included a larger range (i.e., 7 to 22 years) of education than previous studies. Although the precise relationship with apathy is unknown, the number of years of education may be a proxy for other variables such as general intellectual functioning or cognitive reserve.

In terms of anxiety, groups differed in terms of state and trait anxiety as measured by the STAI. The mixed group had significantly higher state anxiety than all other groups. There were no other differences in state anxiety between groups. In terms of trait anxiety, percentiles above 93rd percentile (1.5 SD) were considered, and the percentage of patients meeting this criteria was calculated. Results indicated dramatic differences between groups. The results were as follows: 1% for the no-symptom group, 7% for the pure apathy group, 31% for the pure depression group, and 64% of the mixed apathy-depression group. Turning to the literature regarding anxiety, Pluck & Brown (2002) administered the Hospital Anxiety and Depression Scale and found no difference in anxiety levels between patients with high versus low apathy. Starkstein and colleagues (1992) administered the Hamilton Rating Scale for Anxiety, and found higher anxiety in their depressed Parkinson group than in their Parkinson group without apathy or depression (Starkstein et al., 1992). However, they did not report comparisons between their apathy only group, or their mixed apathy-depression group and their no-symptom group. Finally, Aarsland et al. (1999) factor analyzed the symptoms from the Neuropsychiatric Inventory (NPI) from a combined group of demented and nondemented PD patients (Aarsland et al., 1999). Results indicated that two factors emerged—one involving delusions, hallucinations, agitation, and irritability and another involving apathy and anxiety (Aarsland et al., 1999). Certainly, a relationship between apathy and anxiety seems counterintuitive given that apathy is thought to

involve disinterest and disengagement rather than preoccupation and worry. A detailed discussion regarding the relationship between apathy and anxiety is provided in the next section.

Comparison to the Current Literature

The results from this and previous studies support a relationship between apathy and executive functioning. What is less clear is the exact nature and pattern of the specific executive deficits that are related to apathy. Most studies, including the present one (though at trend), find a relationship between fluency and apathy, with apathetic patients performing more poorly on verbal fluency tasks than non-apathetic patients (Starkstein et al., 1992; Pluck & Brown, 2002; Isella et al., 2002, Zgaljardic et al., 2007; Pedersen et al., 2009; Santangelo et al., 2009). Findings are mixed with regards to the Stroop Color Word Test. Like the present study, all studies used the Golden version of the Stroop. Pluck and Brown (2002) and Santangelo et al. (2009) found worse Stroop interference performance in apathetic versus nonapathetic patients, whereas Zgaljardic et al. (2007) and Pedersen et al. (2009) did not.

In line with these general findings, the present study found that apathy was associated with worse performance on the Stroop interference condition and a trend for worse performance on animal fluency. In contrast, the present study did not find a relationship between apathy and the Wisconsin Card Sorting Test (WCST) in terms of the number of categories achieved or the number of perseverative errors. Previous findings for this variable, like the Stroop Color Word Test, have also been mixed. Starkstein et al. (1992) did not find a difference between apathetic and nonapathetic groups in terms of WCST categories achieved (Starkstein, Mayberg, Preziosi et al., 1992). This was true both when authors scored the measure continuously (i.e. 0-6 categories achieved), or scored it in a dichotomous manner (i.e. with patients achieving 6 categories or fewer than 6 categories). Another study found that apathetic patients achieved fewer categories

than nonapathetic patients (Pluck & Brown, 2002). However, the number of perseverative errors was not different between the apathetic and nonapathetic groups.

Relationship Between Apathy and Anxiety

A somewhat unexpected finding was the relationship between apathy and anxiety. This finding seems counterintuitive because apathy is thought to involve disinterest and disengagement rather than anxiety and worry. Consistent across all analyses was the finding of *high anxiety in the mixed apathy-depression group*. The mixed apathy-depression group had significantly higher state anxiety than all other groups. Similarly, the mixed apathy-depression group had significantly higher trait anxiety than the pure apathy group and the no-symptom group. The mixed group and the pure depression group were not significantly different on trait anxiety. When examining clinically elevated trait anxiety, the groups differed dramatically from one another. Over half of the patients in the mixed apathy-depression group had clinically elevated anxiety and one third of the patients in the pure depression group had clinically elevated anxiety. In contrast, only 7% of the pure apathy group had clinically elevated anxiety and 1% of the no-symptom group had clinically elevated anxiety. Thus, the group with mixed apathy and depression was the highest in trait anxiety. Additionally, the percentage of elevated trait anxiety in the pure depression group was over three times as high as that of the pure apathy group. These findings suggest that pure apathy is rarely associated with clinically elevated trait anxiety, whereas the mixed apathy-depression group is associated with high trait anxiety. This suggests the existence of a highly comorbid subgroup with a mixture of high apathy, depression, and trait anxiety symptoms. Interestingly, the groups were not different in terms of duration PD or severity of PD motor symptoms.

It is well established that anxiety and depression co-occur in PD (Nuti et al., 2004; Menzaet al., 1993; Henderson et al., 1992). A high degree of overlap can often be found

between patients with depression and anxiety. For example, Pontone and colleagues administered the Structured Clinical Interview for the DSM IV (SCID-DSM IV) to one-hundred twenty-seven non-demented PD patients (Pontone et al., 2009). They found that of the individuals with a current anxiety disorder diagnosis, 65% also had a current depressive disorder diagnosis.

Further, similar to the overlapping symptom content between depression and apathy measures, there is overlapping symptom content between depression and anxiety measures. For example, the STAI trait scale has patients rate how they "generally feel" from a score of 1 (almost never) to 4 (almost always). Statements that overlap in content with depression are "I feel like a failure," "I wish I could be as happy as others seem to be," "I lack self-confidence," and "I feel inadequate." Given this, depression severity was measured across groups. Results indicated that the mixed apathy-depression group had significantly higher depression severity (mean BDI-II score of 22) than the pure depression group (mean BDI-II score of 16). Thus, the addition of apathy may only appear to be related to increased clinical elevations of anxiety. Instead, it may be that the more severe depression is driving the relationship with anxiety. In any case, this subgroup with high apathy, depression, and anxiety is clearly experiencing high levels of distress, and endorsing all measures of negative symptoms. In future studies, it would be important to determine whether this group of patients might be either perceiving more functional disability from PD or experiencing more role loss (e.g. recently had to quit work due to symptoms, unable to be head of household anymore due to cognitive changes, etc) even though their motor symptoms are not significantly worse.

Limitations

The current study has several limitations. First, when collecting data from patient medical charts, only total scores for the State Trait Anxiety Inventory (STAI) were gathered.

Item level data was obtained for the Beck Depression Inventory-II and Apathy Scale, but not for the STAI. Having STAI items would have allowed further investigation into the nature of the relationship between apathy and anxiety. Specifically, apathy could be examined separately for the group of items relating to depressive content versus the group of items specific to anxiety. The ratio of the total number of items from all three measures to the sample size of the current study would not have allowed for a confirmatory factor analysis. However, collection of a larger sample could address separate apathy, depression, and anxiety factors in Parkinson disease.

Next, this study did not use psychiatric interviews and DSM-IV diagnoses in addition to the BDI-II. This would have allowed for apathy prevalence to be assessed within the context of Dysthymia or Major Depressive Disorder (MDD). However, research has shown that patients with significant depression symptoms, even without meeting full criteria for a MDD, still experience significant disability from their mood symptoms and benefit from treatment (Judd, Paulus, Wells & Rapaport, 1996; Lyness et al., 1996). Additionally, DSM-IV diagnoses would have helped discriminate the type of anxiety patients were experiencing. Some anxiety disorders are thought to overlap more with depression in PD (i.e. specific phobia and anxiety NOS) than others (i.e. agoraphobia and social phobia) (Pontone et al., 2009). Diagnoses would have allowed us to examine disorder based overlap.

Finally, this study created composite scores by combing tests together rationally based on the cognitive processes they were thought to tap. This is a common approach in studies that administer a large number of tests (Schinka, Vanderploeg, Rogish, & Ordorica, 2002; Sheline et al., 2006). Yet, rationally derived domains do not necessarily correspond to "empirically" derived domains. In fact, this was the case when we conducted an exploratory factor analysis of the cognitive tests in our study. For example, fluency loaded onto its own factor (i.e. letter

fluency and animal fluency) and Trail Making Test Part B loaded with Trail Making Test Part A and Digit Symbol. On the other hand, the individual measures that were predicted a priori to be related to apathy were so, regardless of their loadings in the exploratory factor analysis.

Conclusions and Directions for Future Research

Apathy occurred in one third of the Parkinson patients in this sample. As such, it appears to have a prominent place in the neuropsychiatric profile of nondemented Parkinson patients. Findings from the present study provide support for the hypothesis that apathy and depression are similar, but separable experiences of mood states. Support was found in terms of important discriminating characteristics of apathy and depression. Practically, this finding argues for an additional "index" or "subfactor" scoring of the Apathy Scale and Beck Depression Inventory-II into apathy, dysphoric mood, loss of interest/pleasure, and somatic complaints indices. This may help disentangle symptoms related to apathy, depression, and somatic aspects of PD.

This study found an unexpected association between apathy and anxiety. Namely, the apathetic group had significantly more anxiety than the nonapathetic group. However, additional findings suggested that pure apathy was rarely associated with clinically elevated anxiety whereas mixed apathy-depression was highly associated with clinically elevated anxiety. The mixed apathy-depression group was twice as high in anxiety symptoms as the pure depression group. At first it seemed as if the addition of apathy was related to the anxiety elevations. However, it turned out that the mixed group was significantly higher in overall depression symptoms than the pure depression group. Thus, the depression vs. the apathy is most likely related to the heightened anxiety symptoms. It also appeared that the total score from the STAI has a similar problem of overlapping features with the BDI-II as the AS does (i.e. STAI measure has statements regarding not feeling happy, feeling like a failure, lack of self-confidence, etc).

Future research using a larger sample size can delineate discrete apathy, depression, and anxiety constructs in PD and test these ideas with confirmatory factor analysis.

Further, the hierarchical regression results pointed to a relationship between apathy and executive functioning. This is consistent with the small body of literature that has previously examined the association (Starkstein et al., 1992; Pluck & Brown, 2002; Isella et al., 2002; Zgaljardic et al., 2007; Pedersen et al., 2009; Santangelo et al., 2009). What remains to be determined is the specific patterns of executive functioning impairment that are associated with apathy. This study found that some aspects were related to apathy (e.g. cognitive interference, semantic fluency), while others were not (e.g. set shifting, phonemic fluency). The findings from previous studies all point to an association with fluency, but are mixed in regards to cognitive interference and set shifting. Additionally, links between apathy and types of executive functioning impairment are interesting from a theoretical perspective of common underlying neural substrates. Future studies may develop and test more fine-grained hypotheses related to this. For example, test batteries could be specifically designed to differentially tap the anterior cingulate cortex/mesial frontal lobe functioning (initiation, cognitive interference, etc) versus dorsolateral prefrontal cortex functioning (set shifting, complex problem solving, working memory) versus orbitofrontal functioning (perseveration, impulse control, etc). Apathy would be hypothesized to relate most to anterior cingulate cortex/mesial lobe functioning.

Further support for the notion that apathy and depression are separable in Parkinson disease has broad implications for the field of movement disorders. It suggests that clinicians should screen for both conditions in order to appropriately triage and treat patients. Selective serotonin reuptake inhibitors (SSRIs) and dual serotonin and norepinephrine reuptake inhibitors (SNRIs) are frequently prescribed for depression in Parkinson's patients, but do not necessarily

improve apathy. Further, in other neurological disorders, treatments for apathy are being examined in pharmacological areas such as: amphetamines (e.g. methylphenidate), atypical antipsychotics, dopaminergic agents, and acetylcholinesterase inhibitors. These may hold promise for the treatment of apathy in PD. In small (n) studies, preliminary support has been found for two dopaminergic agents, bromocriptine and amantadine, in treating apathy in traumatic brain injury and poststroke patients (van Reekum, Stuss, & Ostrander, 2005). At the same time that pharmacological research is getting underway, non-pharmacological interventions such as psychotherapy focusing on "behavioral activation" and re-engaging the patient slowly back into activities and interests could also be investigated.

This study adds to the current literature by emphasizing the dissociability of apathy and depression symptoms, and highlighting the prominent place apathy has in the neuropsychiatric profile of PD patients. Further, it provides a carefully controlled examination of apathy and cognition in nondemented PD patients. Results indicate a clear and specific relationship between apathy and executive functioning in PD. As the concept of apathy in PD is delved into further, differential pathology, clinical correlates, and effective treatments will be discovered.

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BIOGRAPHICAL SKETCH

Lindsey Kirsch-Darrow was born in Atlanta, Georgia, and received her B.S. in neuroscience from Furman University. During college, she obtained research experience at the Centers for Disease Control and Prevention in Atlanta, GA. Currently, she is a doctoral candidate in Clinical & Health Psychology at the University of Florida, where she is specializing in neuropsychology. She has accepted a position as a neuropsychology intern at the University of Alabama/Veterans Affairs Medical Center Consortium Site in Birmingham, AL (September 2009-August 2010). This dissertation is an extension of the ideas originating from her master's thesis, originally presented at the American Academy of Neurology meeting in Miami, FL in 2005, under the mentorship of Dr. Dawn Bowers. This project was funded by a National Institutes of Health National Research Service Award.