2011-06-29

Expanding the Model of Apathy in Parkinson's Disease: Exploration of Conceptual Domains and Identification of Neuropsychological Correlates

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EXPANDING THE MODEL OF APATHY IN PARKINSON'S DISEASE: EXPLORATION OF CONCEPTUAL DOMAINS AND IDENTIFICATION OF NEUROPSYCHOLOGICAL CORRELATES

By

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A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

August 2011

UNIVERSITY OF MIAMI

A dissertation submitted in partial fulfillment of
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MYERSON, CONNIE E. (Ph.D., Psychology)
Expanding the Model of Apathy in Parkinson's Disease: Exploration of Conceptual Domains and Identification of Neuropsychological Correlates. (August 2011)

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Phillip M. McCabe, Ph.D., and Bonnie E. Levin, Ph.D.
No. of pages in text (178)

Apathy is a debilitating non-motor symptom in Parkinson's disease (PD) that is closely associated with cognitive dysfunction, depression, and caregiver burden. The proposed etiology and operational definition of apathy involves a tripartite model that includes cognitive, behavioral, and emotional manifestations. This theoretical model has not been statistically validated. We examined the tripartite structure of apathy in PD, and subsequent associations between apathy factors and demographic, disease, and neuropsychological measures. One hundred forty-one patients with idiopathic PD underwent neurological examination and comprehensive neuropsychological testing including the Apathy Evaluation Scale (AES). Statistical analyses included correlation, means comparison, item analysis, and confirmatory factor analysis using SEM. The AES was found to be a valid and reliable measure of apathy. Although a tripartite model of apathy was not supported, a novel 3-factor structure of apathy (R-Apathy) emerged characterized by Cognitive/Emotional and Behavioral factors. Both education and depression were significantly associated with R-Apathy. When these were controlled, R-Apathy was associated with impairment in select executive function and visuospatial skills. Apathy remains an important dimension in understanding nonmotor changes in PD. As a whole, apathy correlated with specific areas of neuropsychological dysfunction

apart from the influence of depression. Manifestations of apathy such as mental disengagement and behavioral withdrawal are key features of the disease presentation. The importance of evaluating apathy as a contributing factor to patients' neurocognitive status, mood, and psychosocial functioning should not be underestimated. Furthermore, an apathy evaluation should be included as a standard part of a Parkinson's evaluation.

TABLE OF CONTENTS

Chapter 1: Introduction

Parkinson's disease has long been associated with motor symptoms and also mood and cognitive alterations. More recently, other neuropsychiatric symptoms such as apathy have been documented. Apathy, or the apathy syndrome, is defined broadly as a lack of goal-directed cognition, behavior, and emotional concomitants of goal-directed behavior. Apathy is a product of the frontal subcortical neurodegeneration inherent in Parkinson's disease and recent literature appears to lend support for pathophysiological evidence of three apathy domains (i.e., cognitive, emotional, behavioral).

The purpose of the current study is to confirm existing findings regarding the construct of apathy including the reliability and validity of the Apathy Evaluation Scale- Self-Report version (a common measure of apathy in PD), and the relationship of apathy to depression and cognitive decline. Additionally, the study aims to enhance current knowledge of apathy in PD through exploration of the presence of cognitive, emotional, and behavioral domains, identification of additional neuropsychological correlates of each domain, and investigation of potential risk factors and outcomes.

This proposal will examine the literature regarding Parkinson's disease and apathy before exploring their co-occurrence and implications for the individual. Finally, a detailed outline of the proposed study including specific aims and methods will be presented.

The detection of apathy and other neuropsychiatric non-motor symptoms is imperative as they may contribute to cognitive decline, greater disability, declining quality of life, and increased caregiver burden. Identification of apathy also provides the clinician with more information in evaluating a patient's strengths and limitations in regard to their disease, enabling individualized and tailored treatments in the hopes of achieving optimal patient outcomes.

Chapter 2: Parkinson's Disease

Epidemiology

Prevalence, incidence, and risk factors.

The clinical features of Parkinson's disease were first described by James Parkinson in 1817 in "An essay on the shaking palsy" (Parkinson, 1817). Parkinson's disease is a neurologic illness in which the main clinical features have a chronic, progressive, insidious, and usually asymmetric onset due to the unexplained loss of pigmented dopaminergic brainstem neurons, particularly within the basal ganglia (Diamond & Jankovic, 2006; Lew, 2007; Kasten, Chade, & Tanner, 2007). Other pathologic hallmarks of the disease include the presence of Lewy bodies, or cytoplasmic aggregations of alpha-synuclein proteins in brain neurons (Samii et al., 2004) visible through magnetic resonance imaging and in post-mortem evaluations. Degradation of dopaminergic neural networks results in both motor (i.e., bradykinesia, resting tremor, rigidity, postural instability) and nonmotor symptoms (i.e., cognitive decline, neuropsychiatric disturbance, sensory disturbance, and autonomic dysfunction) that together contribute to increasing disability and diminished quality of life (Lew, 2007; Ferrara & Stacy, 2008; Schrag, Jahanshahi, & Quinn, 2000).

Parkinson's disease is the second most common neurodegenerative disease (next to Alzheimer's disease) and the most common movement disorder (Tanner & Aston, 2000). While the full clinical presentation of PD will soon be discussed in great detail, the basic diagnostic criteria include the 'unequivocal' presence of at least

two of four cardinal motor signs which are tremor, rigidity, bradykinesia and postural instability (Alves, Forsaa, Pedersen, Gjerstad, & Larsen, 2008). The most common PD presentation arises in the sixth to seventh decades of life with unilateral motor slowing, stiffness, or tremor in the most distal portion of an extremity. Symptoms usually respond well to levodopa and severe postural instability and hallucinations may develop following 10 years duration (Lees, 2009). Idiopathic PD refers to progressive parkinsonism following degeneration of pigmented aminergic brainstem neurons without an identifiable cause, while "parkinsonism" refers to the secondary syndromes of tremor, rigidity, bradykinesia, and postural instability (Kasten, Chade, & Tanner, 2007).

While a definitive diagnosis may require post-mortem evaluation, there are atypical clinical features that help to distinguish PD from other parkinsonian disorders such as multiple system atrophy or progressive supranuclear palsy. These include frequent falls, eye movement disorders, autonomic, pyramidal, or cerebellar features, and a lack of response to dopaminergic treatment (Alves et al., 2008; Litvan et al., 2003). No feature decisively differentiates between PD and other parkinsonian disorders, and in fact, there is often considerable overlap between disorders, e.g., asymmetric motor features are also seen in corticobasal degeneration, a considerable portion of patients with Alzheimer's disease also display parkinsonian features, and according to current guidelines, the diagnosis of dementia with Lewy bodies should be given for patients developing motor symptoms, dementia within one year following onset, and other cognitive and neuropsychiatric disturbances (Alves et al., 2008).

The prevalence of PD is estimated to be between 100 and 200 cases per 100,000 in North America and Europe (as reviewed in Kasten et al., 2007). In general, prevalence for industrialized countries is estimated at 0.3% of the entire population and 1% in those individuals over the age of 60 (Nussbaum & Ellis, 2003). PD is rare before the age of 50 and is characterized by increased incidence in the sixth through eighth decades of life, with juvenile-onset (e.g., before age 20) and young-onset disease (e.g., around age 30) accounting for only a small proportion of cases (Inzelberg, Schechtman, Paleacu, 2002; Kasten et al., 2007). Studies suggest greater frequency of PD in Caucasian populations (Van Den Eeden et al., 2003), and a greater relative risk for men than women regardless of geographic location or race (Tanner & Goldman, 1996; Baldereschi et al., 2000; Wooten et al., 2004). Additional risk factors include rural living and use of well water (Priyadarshi, Khuder, Schaub, & Shrivastava, 2000), obesity (Korell & Tanner, 2005), hysterectomy and/or supplemental estrogen (Benedetti et al., 2001), dietary factors such as excessive milk consumption in male cohorts, animal fats, iron, and manganese (Chen, Zhnag, Hernan, Willett, & Ascherio, 2002; Park et al., 2005; Powers et al., 2003; Kaur et al., 2003), synthetic opioid drug use (i.e., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]; Langston & Ballard, 1983), rapid eye movement sleep disorder (REM behavior sleep disorder; Britton & Chaudhuri, 2009), family history of PD (DeMichele, Filla, Volpe, Gogliettino, Ambrosio, & Campanella, 1996; Marder et al., 1996), repeated head trauma (Maher et al., 2002; Goldman, Tanner, Oakes, Bhudhikanok, Gupta & Langston, 2006), and possible toxic exposures (e.g., pesticides, asbestos, polychlorinated biphenyls; Corrigan et al., 1998; Pryardarshi et

al., 2000). Interestingly, increased smoking and tobacco use, and greater caffeine and alcohol intake are linked to reduced risk of PD, in addition to increased physical activity and non-steroidal inflammatory drug use (de Lau & Breteler, 2006; Kasten et al., 2007).

At a genetic level, increased risk of PD may be due to a number of dominant and recessively inherited genetic mutations. While most people with Parkinson's disease report no family history, about 15% can identify a first degree relative who also has/had the disorder (Payami, Larsen, Bernard, & Nutt, 1994). Results of a twin study have also suggested that genetic susceptibility plays a greater role in early-onset PD, as there was little concordance in twins who developed PD after age 50, but complete concordance in those who developed it earlier (Tanner et al., 1999). Five genes in particular (as reviewed by Samii, Nutt & Ransom, 2004) have been linked to familial PD and generated substantial interest in genetic contributions to the disorder. The first, PARK1, codes for the alpha synuclein protein which is a major component of Lewy bodies (Polymeropoulos, et al., 1997; Bostantjopoulou, Katsarou, Papadimitriou, Veletza, Hatzigeorgiou, & Lees, 2001; Kruger et al., 1998), while PARK2 codes for the parkin protein and has been linked to an autosomal recessive juvenile onset form of PD (Kitada et al., 1998; Abbas et al., 1999). Several different parkin mutations have been found to cause autosomal recessive disease and could be responsible for up to half of early –onset cases and perhaps even more of juvenile-onset PD (Lucking & Brice, 2000). Interestingly, pathological findings in young onset PD show cell loss in the locus coeruleus and substantia nigra but without the presence of Lewy bodies. Given that parkin has been found to be a ubiquitin-protein

ligase and that alpha synuclein is ubiquitinated by parkin, it has been suggested that the failure of the ubiquitin-proteasome system is the common factor in the pathogenesis of PD (McNaught, Olanow, Halliwell, Isacson, & Jenner, 2001; Shimura et al., 2000,2001). Next, a genetic mutation at loci PARK5 was reported in two German siblings, and codes for an enzyme which is involved in labeling abnormal proteins for proteasomal degradation. However, its importance is questionable as it has only been found in one family with two affected individuals (Leroy et al., 1998; Gasser, 2003). PARK7 is the fourth gene which is linked to an autosomal recessive early-onset form of PD and has been implicated in the response to oxidative stress (van Duijn et al., 2001; Bonifati et al., 2003). Finally, the fifth gene, PARK6, has been linked to mutations in PINK1, which is located in the mitochondria of the cell and may have a protective function (Valente et al., 2004). Further investigation of the protein products of these genes may reveal more information regarding nerve cell death in parkinsonism, and more attention is being paid to the role of key proteins (e.g., alpha synuclein) and molecular pathways leading to neural degeneration (Kasten et al., 2007). In addition to causative genes, susceptibility genes which result from complex interactions between environmental and genetic factors have begun to be explored. Genes that are likely candidates include those involved in dopamine and mitochondrial metabolism, detoxification, other neurodegenerative diseases, familial PD, and those associated with putative risk factors (de Lau & Breteler, 2006). For example, studies focusing on polymorphisms in mitochondrial DNA have suggested that these variants may modify susceptibility to PD (van der Walt et al., 2003), however further work is needed in this area to fully

understand the pathophysiological significance of each gene or polymorphism and their complex interactions with specific environmental exposures which may in turn lead to the presentation of PD.

Hyposmia may be an additional risk factor for PD with a potentially broad application. The first reports of an association between PD and hyposmia date to the 1980's, and since then the presentation of olfactory dysfunction has been firmly established as one of the first and most prevalent clinical manifestations of PD (Berendse & Ponse, 2006). Estimates of olfactory impairment in PD are as high as 80-90%, with symptoms often occurring well before the clinical onset of the disease (Doty, Deems, & Stellar, 1988; Hawkes, Shephard, & Daniel, 1997). A study of 361 first degree relatives of PD patients found 10% of those identified as having idiopathic hyposmia developed PD within a two year follow-up, in comparison to none of the non-hyposmic controls. Another 12% of the hyposmic individuals demonstrated a decline in dopamine transporter binding via SPECT, raising the risk of developing PD in the first-degree relatives to 20% in just two years (Abbot, 2001; Poewe, 2009). Many odor identification tests (e.g., University of Pennsylvania Smell Identification Test) are relatively inexpensive, can be self-administered, and if properly validated in their ability to detect at risk persons, carry great potential for use as community and clinical screening tools.

Progression and mortality.

Prior to the introduction of levodopa pharmacotherapy, PD patients had a much higher mortality rate than that of the general population. Following implementation, the mortality rate for PD patients dropped, but still remains elevated in relation to non-Parkinson cohorts (Fall, Saleh, Fredrickson, Olsson, & Granerus, 2003). The majority of epidemiological studies consistently suggest that PD reduces life expectancy, despite differing methodologies. In a review by De Lau & Breteler, mortality hazard ratios, or the risk of mortality for PD patients versus a control group range from 1.5 to 2.7 (2006). A nine year follow-up study of survival time, mortality, and cause of death in PD patients found the mortality ratio to be 1.6, the mean age of death for PD patients to be 81.9 years compared to 82.9 in the control group, and a significantly shorter survival time for PD patients (Fall et al., 2003). There was also a significant increase in deaths from pneumonia. Variables associated with progression of disability and increased mortality include more symmetrical parkinsonism signs, non-tremor symptomotology at disease onset (i.e., gait dysfunction, bradykinesia), increased severity and rate of worsening of parkinsonism prior to study enrollment, higher age at onset, increasing age, depression and dementia (Post et al., 2007; Louis, Tang, Cote, Alfaro, Mejia, & Marder, 1999; Marras et al., 2005; Marras, Rochon, & Lang, 2002; de Lau & Breteler, 2006; Schrag, Dodel, Spottke, Bornschein, Siebert, & Quinn, 2007). Risk factors for progression of motor and nonmotor-related disability will be discussed below.

Pathophysiological Mechanisms

The pathologic hallmark of Parkinson's disease includes the degeneration of dopaminergic neurons in the substantia nigra pars compacta, and the presence of Lewy bodies which are cytoplasmic collections of the alpha synuclein protein found in brain neurons (Samii et al., 2004; Lew, 2007). In PD, the severity of rigidity and bradykinesia in PD is closely linked to the degree of pigmented nigral cell loss in the pars compacta and also dopamine levels in the putamen. Nigral cell loss in PD patients is much faster than that of normal aging, following an exponential curve at 8-10 times the rate of normal loss (Greffard et al., 2006; Fearnley & Lees, 1991). Studies have also shown that dopamine reduction and bradykinesia severity appear to progress most rapidly in the first 5 years of disease, leveling off after 10 years (Jankovic, 2005; Morrish, Rakshi, Bailey, Sawle, & Brooks, 1998). Interestingly, by the time the first motor signs appear at least 30% of all nerve cells in the pars compacta have already disappeared, and within five years of diagnosis 50% will have died with an additional 7% of the surviving neurons further degenerating each year (as reviewed in Lees, 2009).

Neurodegeneration could be due to a variety of mechanisms including oxidative stress, mitochondrial dysfunction, excitotoxicity, apoptosis, and inflammation (Pal, Samii, & Calne, 1999). The discovery of genetic mutations mentioned previously (i.e., PARK1, PARK2, PARK5, PARK7, PARK6) which code for alpha synuclein, parkin, and ubiquitin C-terminal hydrolase L1 suggest that the common denominator of the neurodegenerative pathway is that of the failure of the ubiquitin-proteasome system (McNaught et al., 2001). In short, ubiquitin molecules

normally attach to damaged proteins as a signal for cellular degradation. Parkin acts as a catalyst for the ligation of ubiquitin to proteins which need to be broken down, and polyubiquitin chains that are released from degraded proteins are disassembled back into monomers to again re-enter the cycle of normal protein degradation. However, malformed alpha synuclein protein may misfold, aggregate, and generally resist degradation by the ubiquitin proteasome. In addition, mutations in parkin and ubiquitin themselves may interfere with the degrading process (Samii et al., 2004). Lewy bodies, which contain various proteins that have not been properly degraded, are often found in the substantia nigra pars compacta of PD patients where high amounts of proteins that are resistant to proteasomal degradation may accumulate (Samii et al., 2004).

The Lewy body is the "pathologic inclusion" that has been traditionally associated with PD, and without confirmation via histochemical stains many neuropathologists are reluctant to confirm the clinical diagnosis (Lees, 2009). Lewy bodies are located in the somata of neurons and are found most often in the substantia nigra, dorsal motor nucleus of the vagus, locus coeruleus, nucleus basalis of Meynert, pedunculopontine nucleus, raphe nuclei, periaqueductal grey matter, thalamus, amygdala and olfactory system, the intermediolateral column of the spinal cord and Onuf's nucleus. The core of Lewy bodies are rich in ubiquitin, while higher levels of alpha synuclein can be found in the periphery (Lees, 2009). Mass spectrometry has also identified more than 70 other molecules in Lewy bodies including those involved in protein folding, oxidative stress, and membrane trafficking. In addition, kinases and ubiquitin ligases may be candidate genes or directly involved in the pathological

mechanisms that are responsible for PD (Wakabayashi, Tanji, Mori, & Takahashi, 2007). However, debate regarding the pathologic significance, and actual mechanistic contribution of Lewy bodies to PD progression continues. Lewy bodies have been found in brain regions such as the neocortex where cell loss has not been identified, and in elderly individuals who have died without signs of PD. Together these findings support the view that the presence of Lewy bodies alone is not sufficient for cell death (Lees, 2009). In addition, the prevalence of Lewy body pathology in individuals over 80 years of age may approach 20%, and Lewy bodies are also found in those with Alzheimer's disease, subacute sclerosing panencephalitits, and autosomal dominantly inherited PD. Despite this seeming lack of specificity for PD, the finding of Lewy bodies is still considered a significant pathologic change in the aging brain (Gibb & Lees, 1988).

In 2003, Braak and colleagues proposed a framework by which pathological progression in PD may occur, commonly referred to as "Braak's staging". Based on a series of post-mortem anatomic studies focusing on the deposition of alpha synuclein, the investigators proposed that pathology associated with PD begins in the medulla oblongata (specifically in the dorsal motor nucleus of vagus) and also in the olfactory bulbs (Stage 1). Stage 2 and 3 define the period of abnormal alpha synuclein aggregation that ascends the brainstem, and continues accumulating towards the mesocortex and basal forebrain (Stage 4) before finally arriving at the cerebral neocortex (Stage 5 and 6) (Del Tredici, Rub, De Vos, Bohl, & Braak, 2002; Braak, Ghebremedhin, Rub, & Del Tredici, 2004; Lees, 2009). An advantage of Braak's theory of staging is that it may account for autonomic symptoms and hyposmia as

early disease features in PD. These symptoms will soon be discussed in greater detail, but it should suffice to say that the potential explanatory power of Braak's staging has led it to find favor and resonance with both movement disorder specialists and neuropathologists alike (Lees, 2009).

Pharmacologic and Surgical Treatment

The discovery of levodopa in the 1960's revolutionized treatment of Parkinson's disease and is one of the most common forms of pharmacotherapy used today with PD patients. Despite its efficacy, safety, and availability, levodopa is not a viable option for long-term care given its association with the development of disabling motor complications and inability to slow the progression of disease pathology. The short half-life of levodopa results in fluctuating plasma levels which translate into fluctuating striatal dopamine concentrations and pulsing stimulation (Olanow et al., 2004). As a result the patient may experience "wearing off", sudden unpredictable "offs", dystonias, dyskinesias, dose failures, medication-refractory tremors, and freezing (Diamond & Jankovic, 2006). The risk for developing levodopa-related dyskinesias and motor complications has been linked to several factors including disease state and loss of striatal dopamine terminals, the age of the patient, and the dosage and duration of exposure to levodopa (Olanow et al., 2004). Controlling levodopa-induced motor fluctuations may be handled in several ways. Levodopa-based strategies include dietary modification to control absorption and metabolism, alternate routes of administration (e.g., oral vs. transdermal), and the

addition of catechol-*O*-methyl transferase (COMT) inhibitors to prolong motor response (Heikkinen et al., 2001; Ruottinen & Rinne, 1996; Kaakkola, 2000; Diamond & Jankovic, 2006).

Non-levodopa based strategies such as dopamine agonists (e.g., lisuride, apomorphine) are an additional avenue of treatment for Parkinson's disease as they offer a longer half-life than levodopa and prolonged dopaminergic activation of the striatum (as reviewed in Diamond & Jankovic, 2006). Monoamine oxidase (MAO-B) inhibitors may also provide improvement in "on" time in those patients experiencing wearing off and on-off phenomenon (Hubble, 1999; Seager, 1998). In addition, N-*methyl*-D-*aspartate* (NMDA) receptor agonists have also shown promise in patients who experience dyskinesias and wearing-off (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004; Diamond & Jankovic, 2006). Still, these methods fail to match the efficacy of levodopa (Poewe, 2009). The best results overall are currently found in invasive strategies such as intraduodenal or subcutaneous delivery of levodopa or apomorphine (a dopamine agonist), or surgical deep brain stimulation of the subthalamic nucleus (Poewe, 2009).

Brain stimulation in awake patients has been used since the 1960's for mapping cortical functions during epilepsy and tumor surgery. While it was first thought that such stimulation activated circuits, it was soon found that high-frequency stimulation could temporarily disrupt normal neural activity producing a functional lesion (Penfield, 1968; Albe-Fessard et al., 1961). Several decades later an approach using high frequency thalamic stimulation through implanted electrodes opened many new avenues in functional PD surgery (Benabid, Pollak, Louveau, & Henry, 1987).

The procedure of deep brain stimulation (DBS) came at a time when primate models were used to explore various changes in basal ganglia circuitry which could be responsible for parkinsonian akinesia. Results indicated that both the globus pallidus interna and subthalamic nucleus (STN) likely played integral roles in these processes (Bergman, Wichmann, & DeLong, 1990; DeLong, 1990). DBS of these structures was then the rational therapeutic modality to explore, with the proposed pathophysiological mechanism being the induction of a functional lesion, cancellation of error messages, or possibly the liberation of transmitter either at local or more distant locations from the point stimulated (Saint-Cyr & Albanese, 2006). STN DBS has since evolved into what some have called the second major breakthrough in PD following the discovery of levodopa, or the "holy grail" of treatment for advanced PD (Poewe, 2009; Saint-Cyr & Albanese, 2006). Indeed, several studies have found the procedure to dramatically reduce drug-resistant motor fluctuations and dyskinesias, reduce the use of dopaminergic medication by about 50% and also provide long-term improvement of motor symptoms (Moro & Lang, 2006; Voon, Kubu, Krack, Houeto, & Troster, 2006; McIntyre, Savasta, Kerkerian, & Vitek, 2004). One study in particular by Houeto and colleagues demonstrated impressive findings after following twenty PD patients up to two years following surgery. Results indicated that parkinsonism motor disability measured at two timepoints (i.e., on-stimulation and off-medication) was improved by 81% and 67% respectively. Levodopa-equivalent daily dose was decreased by 79% and 66%, respectively, and the severity of levodopa-related motor complication was improved by 84% and 70%. Depression and anxiety, in addition to global quality of life scores were all significantly improved

(Houeto et al., 2006). Despite these achievements, STN DBS does not prevent disease progression and additional limitations include the cost of surgery and hardware-related complications, potential neuropsychological dysfunction, and psychosocial maladjustment (Krack et al., 2003; Houeto et al., 2002; Moro & Lang, 2006; Voon et al., 2006; Poewe, 2009). Further investigation regarding nonmotor symptoms following STN-DBS in PD is needed.

Disease Severity and Disability Rating Scales

The most widely used and accepted tool for evaluating motor severity and disability in PD patients is the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS was first created and introduced in 1987 by a group of international movement disorder specialists, and has since undergone several revisions (the most recent in late 2008) to more accurately capture a wide range of nonmotor symptoms (to be discussed shortly) (Goetz et al., 2008; Fahn & Elton, 1987). The scale is divided into four subscales covering mood, behavior, and mental status (Part I), activities of daily living (Part II), motor symptoms (Part III), and treatment complications (Part IV) (Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002). An additional measure that is used as an indicator of disease stage is the Hoehn and Yahr (H&Y) scale developed in 1967. It addresses motor, balance, and gait impairments and ranges from Stage 0 (no signs of disease) to Stage 5 in which the individual is bedridden, wheelchair-bound and dependent on others for many, if not all, activities of daily living. Of note, it does not include evaluation of non-motor features. Still, the H&Y is an accepted instrument used in conjunction with the UPDRS, and

together they enable the clinician to follow the patient's disease course and have been shown to be valid and reliable measures (Alves et al., 2008; Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002; Hoehn & Yahr, 1967). Finally, the Schwab and England Activities of Daily Living Scale is commonly used to evaluate patient disability in relation to activities of daily living (Gillingham, Watson, Donaldson, & Naughton, 1960). Unlike the UPDRS and H&Y, the Schwab and England scale is completed by the patient or caregiver. The rater assigns a global functioning score from 0 (vegetative functions only) to100 (complete independence) based on the patient's perceived independence in activities of daily living, and can offer a unique perspective on the disease process. While many other measures of activities of daily living may be also employed (*see* Methods), the Schwab and England is used quite often in Parkinson's disease literature.

Primary Motor Symptoms and Initial Presentation

Most often the initial symptoms of PD are so slight they may go unnoticed, and it is not until the disease has progressed that the patient and family, through retrospective analysis, may be able to identify the precise time of onset. Subtle changes in body posture, reduced speed of movement and cognition, and complaints of stiffness may present months or years before noticeable tremor, but instead are overlooked or incorrectly dismissed as part of the normal ageing process (Lees, 2009). While clinical diagnosis of PD requires precise detection of progressive decline in fine motor function, the patient or family is more likely to notice diminished arm swing and/or a lack of facial expression (e.g., "poker face") (Lees,

2009). However, the most commonly reported cardinal sign at disease onset is a resting tremor (Alves et al., 2008); Hughes, Daniel, Blankson & Lees, 1993; Jankovic et al., 1990; Schrag, Ben-Shlomo & Quinn, 2000). It is usually asymmetric and most apparent in the distal part of an extremity (e.g., pinkie finger, toe), is reduced during movement, not present during sleep, and is exaggerated by apprehension, anxiety, or excitement (Alves et al., 2008). Still, tremor does not develop in all patients with one quarter (25%) never experiencing this primary symptom (Hughes et al., 1993). Less frequent than tremor but still common at the onset of PD are bradykinesia and rigidity. Bradykinesia refers to a general slowing of movement in addition to difficulty in initiation and maintaining motions, while rigidity describes increased resistance to the passive stretch of skeletal muscles (Alves et al., 2008). Other signs-termed axial symptoms, are not typically seen at disease onset but become more common as the disease progresses. These include speech impairment and postural instability. In a community based study, while only 1% reported these symptoms at disease onset, 64% experienced postural instability with falls and 49% demonstrated speech difficulties after a disease duration of six years (Alves et al., 2008; Schrag et al., 2002). Also worth noting is freezing of gait, a gait disorder characterized by the inability to initiate or sustain movement and which is often a source of falls. Freezing of gait occurs suddenly, is usually transient, may be triggered by environmental stimuli (e.g., narrow spaces), and most often appears in the medication-off state (Alves et al., 2008; Stolze, Klebe, Zechlin, Baecker, Friege, & Deuschle, 2004). Severe freezing is atypical in early stage PD and may suggest other diagnosis such as progressive supranuclear palsy. Identified risk factors for the development of

freezing of gait include absence of tremor and longer disease duration. Indeed, the frequency and severity increase with the disease progression (Giladi et al., 2001).

Motor symptoms most often present in an asymmetrical fashion and are localized to the upper extremities. Over time they may affect the contralateral limb and lower extremities, however in terms of severity the asymmetrical pattern is usually preserved (Uitti, Baba, Wszolek, & Putzke, 2005; Aarsland et al., 2003; Poewe & Wenning, 1998). In addition, it has been found that while the severity of rigidity, bradykinesia, and postural instability tends to progress over time, tremor severity appears to be stable lending support to the notion that different pathophysiological process may underlie the various motor presentations (Louis, Tang, Cote, Alfaro, Mejia, & Marder, 1999).

Nonmotor Symptom Presentation

Nonmotor symptoms resulting from subcortical dysfunction in PD include cognitive decline, autonomic disturbance, hyposmia, and neuropsychiatric presentations (e.g., hallucinations, anxiety, depression, apathy). Detection is important as they may serve as markers for developing disease or dementia, and are often more problematic for the patient and for the physician to treat than motor counterparts. In general, the progression of motor symptom severity has been found to decrease as the disease progresses, while disability related to nonmotor symptoms continues to deteriorate over time and is likely related to additional extrastriatal pathology (Schrag et al., 2007). Aarsland et al. (2003) found that all patients who experienced motor fluctuations also had atleast one nonmotor problem during the

medication “off phase”, and a third of the patients rated their nonmotor symptoms as disabling as motor complications. In addition, a 15-year follow-up study found that in advanced patients, dementia and falls were more important and more difficult to manage than motor complications (Hely, Morris, Reid, & Trafficante, 2005; Diamond & Jankovic, 2006). In general, as PD advances nonmotor symptoms may actually become more prominent than their motor counterparts, and result in further deterioration of quality of life and increase caregiver burden (Diamond & Jankovic, 2006).

Cognitive Function

Cognitive impairment in Parkinson’s disease is considered a natural part of the disease progression, and even in the absence of full-blown clinical dementia, patients often exhibit select impairments in several cognitive domains (Dubois & Pillon, 1997). Deficits can occur early in the disease process and at times may only be detectable through specific neuropsychological testing (Muslimovic, Post, Speelman, & Schmand, 2005). For example, Muslimovic et al. (2005) found 24% of newly diagnosed PD patients displayed impaired performance on at least three neuropsychological tests, compared to only 4% of controls. The pattern and frequency of impairment in different domains is often debated, however many deficits resemble those seen in patients with frontal lobe damage and this would be consistent with the neuroanatomy of basal ganglia thalamocortical circuits in PD. It should also be noted that PD patients demonstrate deficits in different areas, and also more severe deficits than those associated with the normal ageing process. Deficits related to

normal ageing may include memory impairments and slowing of metacognitive processes (Perlmutter & Hall, 1992;Basic, Katic, Vranic, Zarevski, Babic, & Mahovic-Lakusic, 2004). In contrast, noted symptoms in PD patients may include olfactory disturbance, depression, contrast sensitivity deficits, decline in visuospatial skills and memory function, attentional deficits, and executive dysfunction (as reviewed in Levin & Katzen, 1995). Basic et al. (2004) also found PD patients demonstrated a significant drop in nonverbal abilities (e.g., parallel processing and fluid intelligence), while verbal intelligence (i.e., serial processing and crystallized intelligence) remained intact. It is generally thought that deficits in memory ability and executive function present in the early stages of PD, while difficulty with other skills such as visuospatial abilities appear to present later in the disease course and are often the product of executive decline (Muslimovic et al., 2007). Overall, neuropsychological deficits in PD are likely related to the degeneration of frontal lobe and right hemisphere functions including abstraction, planning, evaluating (executive deficits), and visuospatial tasks, respectively (Basic et al., 2004).

Language.

Language skills appear relatively preserved with only subtle impairments, and those impairments are often due to deficits in other areas of cognitive function (Levin & Katzen, 1995; Mohr et al., 1995). For example, Lees & Smith found patients had higher rates of perseverative intrusions on a phonemic word fluency task, likely due to the patients' difficulty shifting between letter categories while under time constraints, which is a decidedly executive skill (1983). In addition, one study

demonstrated that PD patients have poorer comprehension of complex sentences due to slowed lexical activation (Angwin, Chenery, Copland, Murdoch, & Silburn, 2007). The slowing of activation was linked to the dopaminergic influence on processing speed, again pointing to alternative underlying neuropsychological deficits other than language skills per se (Angwin et al., 2007).

Visuospatial skills.

Abnormalities in visuospatial skills are among the most common deficits reported in PD, and they are also the most controversial as there is little agreement on the definition of visuospatial deficits, and assessments are often compounded by motor demands and time constraints. There is also a view that visuospatial deficits reported early in PD may actually reflect changes in executive skills, or when tasks involve set-shifting and other aspects of executive function (Brown & Marsden, 1986; Levin & Katzen, 1995). Still, others have found that Parkinsonian patients consistently show visuospatial impairment which declines as a function of both advancing motor disease and dementia severity, even while controlling for potentially confounding variables such as age, manual dexterity, reaction time, and overall cognitive status (Mohr et al., 1995).

Attention and memory.

Specific areas of memory deficits in early PD include recall of semantically related words, immediate memory, deficient source memory, and increased sensitivity to interference (Taylor, Saint-Cyr, & Lang, 1990, Muslimovic, 2005). It is thought

that these changes likely stem from planning deficits interfering with acquisition of novel stimuli resulting from frontostriatal dysfunction (Taylor et al., 1990; Levin & Katzen, 1995). The decision-making process is also compromised in early PD particularly under conditions with high cognitive demand. This prolonged response time, or bradyphrenia, is thought to be nondopaminergic in origin (Zimmerman et al., 1992).

Executive dysfunction.

Executive functions include inhibition, abstraction, aspects of attention, cognitive flexibility, reasoning, sequencing, planning, problem solving, working memory, modulation of ongoing activity, and simultaneous operation of multiple cognitive processes (as reviewed in Higginson, King, Levine, Wheelock, Khamphay, & Sigvardt, 2003). The domain of executive function is said to encompass the "highest order" of cognitive ability and is associated with the frontal lobes (Stuss & Benson, 1984; Higginson et al., 2003). In particular, studies have found cognitive switching deficits in patients with focal striatal lesions indicating that the striatum may play an integral role in cognitive flexibility (Cools, Ivery, & D'Esposito, 1983). Monchi and colleagues extended this finding as they found mesocortical dopaminergic substrate in addition to nigrostriatal pathways played a role in cognitive deficits in PD patients (Monchi, Petrides, Mejia-Constain, & Strafella, 2006).

Executive dysfunction is widely acknowledged as a common occurrence in early PD and plays an important role in the clinical expression of later Parkinson's

disease dementia (Levin & Katzen, 1995; Mohr, Mendis, & Grimes, 1995; Muslimovic, Post, Speelman, & Schmand, 2005; Muslimovic et al., 2007). PD patients have been found to perform more poorly than controls on a number of neuropsychological tasks including verbal fluency, verbal and visual recall, visuoconstruction, and those requiring formulation, maintenance, and switching of instruction or response sets (Brown & Marsden, 1986; Cooper, Sagar, Tidswell, & Jordan, 1994; Lees & Smith, 1983; Taylor et al., 1990)

There is also body of evidence suggesting that many cognitive symptoms found in PD are secondary to executive dysfunction. For example, Bondi et al. found that when they held executive function as a constant statistically, the memory of non-demented PD patients was similar to that of controls (1993). Similarly, planning and organization deficits that interfere with the acquisition of novel stimuli (as mentioned above) could impact performance on a number of cognitive tasks. The findings of Higginson et al. also supported the hypothesis that various cognitive symptoms (in this study, specifically memory impairment) in PD may be secondary to executive deficits. Further study of the relationship between executive function and other cognitive deficits in PD is needed. An even more interesting question might be the impact of executive dysfunction on neuropsychiatric symptoms such as depression and apathy.

Parkinson's disease dementia.

As PD progresses, mild cognitive dysfunction is evident in nearly all patients, however it is estimated that only 20-31% will advance to dementia (PDD) (Mohr et al., 1995; Aarsland, Zaccai, & Brayne, 2005). Of those with dementia in the general population, approximately 3-4% is thought to be due to PDD, and prevalence of PDD in individuals age 65 years and over is estimated to be 0.2 to 0.5% (Aarsland et al., 2005). Studies have consistently shown that among Parkinson's patients, increasing age and severity of extrapyramidal signs are risk factors for incipient dementia. (as reviewed in Levy et al., 2002). Additonal associations have been found between verbal memory, executive function, and PDD (Levy et al., 2002).

Dementia is defined as an acquired brain dysfunction manifested by abnormalities in multiple neuropsychological domains including persistent deficits in atleast three areas such as language, memory, visuospatial skills, cognition, personality, and emotional function (Cummings, Benson, & LoVerme, 1980; Assal & Cummings, 2002). Symptoms of a subcortical dementia differ from a dementia of an Alzheimer's type in which greater cortical involvement produces aphasia, apraxia, recall and recognition deficits, diminished verbal (semantic) fluency, and prominent indifference (Cummings & Benson, 1988).

Predictors of cognitive decline

In an effort to shed light on possible "subtypes" of PD, a number of studies have examined and identified possible risk factors associated with differential patterns of disease progression. Katzen et al. (2006) found that patients whose initial

symptoms were bradykinesia or rigidity (as opposed to tremor) demonstrated greater cognitive deficits regardless of the side of onset. Patients with tremor-predominant symptomotology also demonstrated neuropsychological deficits when they had experienced a left-sided onset. In contrast, it appeared that individuals who developed right-side tremor at disease onset remained free of cognitive decline compared to other groups (Katzen, Levin, & Weiner, 2006). Specifically, results revealed a main effect for side of onset within the memory domain, with left-side onset performing more poorly than right-side onset. There was also a trend for a main effect of symptom onset among those with bradykinesia and rigidity showing greater cognitive impairment. And finally in regards to visuospatial skills, patients with right-side tremor performed better than those with left-side tremor, and left- or right-side rigidity and bradykinesia. The right-side tremor group was also the only group with preserved visuospatial skills when compared to controls (Katzen et al., 2006).

Educational level has been found to modulate cognitive performance and neuropsychiatric presentation in PD. Cohen and colleagues found patients with a higher educational level performed better on tests of neuropsychological function, particularly those pertaining to frontal lobe functions such as executive skills. Interestingly, they also found a relationship between lower education and greater prevalence of hallucinations, depression, delusions, and sleep disturbances (Cohen, Vakil, Tanne, Nitsan, Schwartz, & Hassin-Baer, 2007). These findings perpetuate earlier pathophysiological studies in which education was found to modulate the consequences of white matter hyperintensities on cognitive performance. Overall,

individuals with more education appeared protected against cognitive decline associated with cerebral vascular insults (Dufouil, Alperovitch, & Tzourio, 2003).

Additionally, studies have shown that both advanced age and disease duration predict greater cognitive decline in PD (Cumming & Benson, 1992; Salthouse, 1988). However, older age of disease onset has also been shown to predict cognitive decline independently of (and above and beyond) advanced age or disease duration (Katzen, Levin, & Llabre, 1998). In particular, age of disease onset was shown to be associated with performance on measures of immediate and delayed verbal memory, visuospatial abilities, and executive dysfunction (Katzen et al., 1998).

General investigations into the relationship between cognitive and motor symptoms of PD have revealed several additional findings. Levy et al. (2000) found that motor impairments specifically associated with nondopaminergic systems (i.e., speech and axial impairment) were significantly associated with incident dementia in PD. Further, in a study of parkinsonian signs (i.e., tremor, gait, rigidity, bradykinesia) in individuals without PD or related dementia, higher levels of gait disturbance, rigidity, and bradykinesia were related to poorer cognitive performance. However these signs only accounted for 5% of the variance in most measures, therefore the authors concluded that parkinsonian signs have a reliable, yet modest, association with cognitive function in advanced age (Fleischman, Wilson, Bienias, & Bennet, 2005).

Autonomic and Neuropsychiatric Disturbance

Autonomic dysfunction.

PD patients may experience autonomic disturbances such as gastrointestinal, urologic, and sexual dysfunction, sweating, and orthostatic hypotension. Sleep disturbances including REM behavior sleep disorder, restless legs syndrome, altered sleep wake cycles, daytime somnolence, and sleep attacks are common. Finally, sensory disturbances such as pain, burning, and paresthesia have been reported (as reviewed in Diamond & Jankovic, 2006). Autonomic failure can also be common in the clinical presentation of other diseases such as multiple system atrophy and pure autonomic failure, therefore careful evaluation is needed. Dopamine plays an important role in brain stem autonomic regulation and in PD both the central and peripheral autonomic systems may be affected (Micieli, Tosi, Marcheselli, & Cavallini, 2003). Investigations have found cell loss and Lewy bodies within the sympathetic ganglia and also antibodies to sympathetic neurons in PD patients (Rajput & Rodzdilsi, 1976). The symptoms of autonomic dysfunction are variable, and may represent a useful tool in differentiating diagnoses of various parkinsonian disorders (Micieli et al., 2003).

Hallucinations and psychotic symptoms.

Psychotic phenomena (e.g, hallucinations, delusions, delirium) may occur in 20 to 40% of medicated PD patients and have a significant impact on the prognosis of PD. In addition, they are cardinal risk factors for placement in assisted living facilities and increased mortality (Goetz & Stebbens, 1993). Of psychotic symptoms,

hallucinations are found to be most common (Papapetropoulos & Mash, 2005). Prior to the advent of levodopa, visual hallucinations were described in about 5% of patients, however since the introduction of dopaminergic drugs they have become much more prevalent with estimates up to 39.8% of an outpatient cross-sectional sample (Schwab, Fabing, & Prichard, 1950; Fenelon, Mahieux, Huon, & Ziegler, 2000). Longitudinal studies have found rates may increase substantially over time, i.e., 42% to 50% over 12 months (Doe De Maindreville, 2004) and 33% to 63% over 48 months (Goetz et al., 2001). While hallucinations may occur in several modalities, visual are the most common followed by mixed visual and auditory (10% of patients), and with somatic, tactile, and olfactory types occurring less frequently (as reviewed in Papapetropoulos & Mash, 2005). Most often visual hallucinations are drug-induced, with primary hallucinations being much less common and possibly suggestive of other neurodegenerative disorders (Haeske-Dewick, 1995; Papapetropoulos & Mash, 2005). Initially the hallucinations may seem "friendly", with the patient reporting whole or fragmented familiar people and animals. Later they may change to frightening images which induce fear and anxiety as reality testing and insight deteriorate. Further, hallucinations may become disabling and associated with confusion, aggression, agitation, delusions and delirium, until placement in a nursing home is needed (Baker, 1999; Wolters, 2001; Papapetropoulos & Mash, 2005).

Delusions, or false beliefs based on incorrect inferences, are rare in non-medicated patients but increase with advancing age and anti-Parkinson pharmacotherapy. Prevalence of delusions is estimated to be between 3 and 30% (Cummings, 1992). Delirium is defined as a disturbance of cognition and

consciousness, and is characterized by memory loss, disorientation, decreased attention, agitation, impulsiveness and inappropriate behavior, hallucinations and sleep disorders (Papapetropoulos & Mash, 2005). In non-demented medicated PD populations, they may occur in up to 20% of patients (Lieberman, 1998).

Anxiety.

Studies have found that up to 40% of PD patients meet criteria for a clinically significant anxiety disorder such as generalized anxiety, panic, and social phobia (Stein, Heuser, Juncos, & Uhde, 1990). This exceeds prevalence for the general population (5-15%), and is also greater than rates found in other neurological or medical illnesses. The association of anxiety and PD may be an important cause of morbidity for many patients (Richard, Schiffer, & Kurlan, 1996). Most often, anxiety appears after the diagnosis of PD, however it can present in the pre-clinical period. This would suggest that anxiety may not be simply a reaction to the degree of disability in terms of psychological and social adaptation issues, but instead may be linked to the specific underlying pathophysiological processes of PD. In particular, disturbances in the central noradrenergic systems, neurotransmitters, and neuropeptides, may be involved. In addition, right-hemisphere dysfunction may be especially important in the production of anxiety in PD (Richard et al., 1996). In Parkinson's, anxiety also frequently co-occurs with depression.

Depression.

Depression is regarded as the most common neuropsychiatric disturbance in PD and may begin before presentation of motor symptoms. Most patients experience mild to moderate depression, but rarely severe. A prevalence estimate of 40% is generally expected, with approximately 20% meeting criteria for major depression and the other half for dysthymia (Cummings, 1992; Starkstein, Mayberg, Leiguarda, Preziosi, & Robinson, 1992). It is also thought that while depression in early PD may be due to structural and biochemical changes related to left basal ganglia pathology, depression in later PD may arise from impaired independence in activities of daily living and progressive deterioration (Muslimovic et al., 2007). Recent studies have found associations between depression and increased disease severity and disability, reduced sense of well-being and quality of life, and motor and cognitive impairment (Papapetropoulos & Mash, 2005). Risk factors include female gender, younger age of PD onset, greater left hemisphere involvement, a non-tremor presentation (i.e., bradykinesia, gait instability), history of depression, and greater functional disability (Cummings, 1992). PD patients who are depressed may also have greater frontal lobe dysfunction and involvement of dopaminergic and noradrenergic systems than those non-depressed PD patients. Treatment most often involves selective serotonin re-uptake inhibitors or tri-cyclic antidepressants, similar to treatment of non-PD populations (Diamond & Jankovic, 2006).

Apathy.

Prevalence estimates of apathy in PD range from 16.5 to 44% across studies, depending on methodology. It is also likely that estimates of both apathy and depression vary due to their co-occurrence in PD. In a study that delineated between apathy and depression, the authors found 14% of patients to be apathetic only, 23% of patients with both apathy and depression, and 22% depressed only (Starkstein et al., 2001). Apathy is associated with cognitive impairment (particularly executive function) and dementia, and therefore there tend to be higher prevalence rates in more advanced disease stages (Alves et al., 2008).

Apathy in Parkinson's disease is a growing area of research as more attention is being paid to the possible implications of nonmotor symptom presentations. As of the present time, extant literature has yet to identify risk factors for the development of apathy. However, identified outcomes include decreased participation and motivation for therapy regimens, social isolation, vocational loss, and increased caregiver burden. Apathy has also been linked to executive function, with some investigators questioning whether a distinct apathetic-dysecutive subtype may exist within PD. The present study hopes to expand on these findings and further define the presentation of apathy in PD. In order to provide a firm foundation and understanding of apathy from which to explore its occurrence in PD, an in depth review of the syndrome is found below.

Chapter 3: Apathy

The evolution of the construct of apathy has traditionally been intertwined with concepts of motivation, awareness, and depression. However, over time apathy has evolved into an independent and cohesive entity. It's clinical significance and impact on the individual's disease process and overall well-being is only beginning to be explored. This review will include the definitions of apathy and motivation, the underlying neurocircuitry of each and how they overlap and interact to manifest the syndrome of apathy, and finally potential clinical implications for the apathetic Parkinson's patient.

Apathy and Motivation

Apathy is most commonly defined as a disorder of diminished motivation (Marin & Wilkosz, 2005; Roth, Flashman, & McAllister, 2007) consisting of primary motivational loss that is not attributable to emotional distress, intellectual impairment or diminished level of consciousness, and manifests in diminished goal-directed overt behavior, diminished goal-directed cognition, and diminished emotional concomitants of goal-directed behavior (Marin, 1991). In short, apathy is a neuropsychiatric symptom that may be broken down into cognitive, behavioral, and emotional domains. Cognitive apathy refers to a subject's interest in doing things, concerns about one's own situation, seeing friends, and how they perceive the importance of getting things done. Behavioral apathy may refer to an individual's engagement or performance in a number of activities, and emotional apathy refers to the subject's

level of emotional excitement and overall vigor for life (Andersson & Bergedalen, 2002). While there are many possible explanations for these symptoms individually as they often occur in many psychiatric and medical disorders, apathy is distinguished by the co-occurrence of diminished activity in each of the cognitive, emotional, and behavioral domains (Marin, 1996).

Apathy may present either as an independent syndrome or as part of another primary disorder. There are a myriad of neurologic conditions associated with apathy, all sharing the common presence of lesions or other abnormalities within the frontal-subcortical circuitry. These include acquired frontal lobe, basal ganglia, and internal capsule lesions, anoxia-related brain damage, traumatic brain injury, stroke, pituitary disease, thalamic tumor, mild cognitive impairment, delirium, dementia (Lewy body or Alzheimer's type), frontotemporal dementia, vascular dementia, immune disorders (e.g., hepatitis C, HIV/AIDS), psychiatric disorders (e.g., schizophrenia, major depressive disorder, substance abuse and dependence disorders), and neurodegenerative diseases (e.g., corticobasal degeneration, Huntington's disease, Machado-Joseph disease, multiple sclerosis, myotonic dystrophy, Parkinson's disease, progressive supranuclear palsy) (as reviewed in Roth et al., 2007). The process of evaluating whether apathy is secondary to another syndrome depends on the extent to which apathy dominates the clinical picture. Therefore, it is judged to be a syndrome when lack of motivation is not attributable to other syndromes such as dementia, delirium, or depression (Silva & Marin, 1999).

The construct of motivation is also essential to the understanding of apathy. Motivation may be thought of as a superordinate concept referring to the characteristics and determinants of goal-directed behaviors and is essential for adaptation (Marin, 1991; Marin & Wilkosz, 2005). Two broad categories of motivated behavior in animals and humans are appetitive and defensive behaviors, and all emotional states may be seen as a function of these two overarching motivations (Lang et al., 1998; McAllister, 2000). Motivation may also be viewed as a conscious or unconscious internal state which incites the person to act and subsequently influences many stages of behavioral planning including determination of aim, selection of elaboration of responses, and evaluation of consequences of action (Czernecki et al., 2002). The control of, and motivation for behavior then requires the extraction of reward information from a large variety of environmental stimuli and events (Schultz, 2000), also referred to as reward sensitivity. Rewards help to establish value systems for behavior and serve as key references for behavioral decisions (Schultz, 2000). They have several basic functions including acting as positive reinforcers by increasing the intensity and frequency of behaviors which lead to positive outcomes, maintaining learned behaviors by preventing extinction, and they may also act as goals in their own right to elicit approach and consummatory behaviors (Schultz, 2000). This sensitivity to reward and ability to successfully glean meaningful information from the environment in turn leads to the motivation to approach or avoid and is essential for the generation of goal-directed behaviors. Damage to motivational circuitry can then have an impact on a number of goal-directed adaptive behaviors as manifested in the apathetic individual. In short, if

one is unable to register or recognize changes in the reward significance of the environment, the individual will be "apathetic" to those stimuli (Marin and Wilkosz, 2005).

Apathy and Depression

Apathy is commonly regarded as a "lack of interest" and is therefore often thought of as a symptom of depression or synonymous with depression itself. However, apathy is a more complex construct, and has been shown in many studies based on psychometric methods and lesion location to be a symptom of depression and also a dissociable syndrome. In a study designed to evaluate the source of overlap between measures of apathy and depression, Marin et al. (1993) found that the convergence between depression (Hamilton Rating Scale for Depression; HamD) and apathy (Apathy Evaluation Scale; AES) inventories was attributable to a subset of HamD items which were also consistent with the syndrome of apathy, and the fact that major depression is linked to both apathy and depression. Depression inventory items with the greatest correlation with the apathy scale were items addressing diminished work/interest, psychomotor retardation, anergy, and lack of insight (Marin, 1993). Similar difficulties have been found with other inventories (e.g., Beck Depression Inventory; BDI) such that the scales overlap in content. For example, endorsement of the item "I don't enjoy things the way I used to" from the BDI might better represent apathy but is instead counted towards a total depression score (Kirsch-Darrow et al., 2006). It has been suggested that what distinguishes the two syndromes of apathy and depression are dysphoric symptoms such as guilt,

hopelessness, and depressed mood which are at best minimally associated with apathy (Marin, 1993). As previously mentioned, depression may be viewed as a disturbance in mood, while apathy is a syndrome of diminished motivation (Silva & Marin, 1999). Multiple studies have also confirmed that apathy and depression are dissociable based on their variable expression in different disorders and at different levels of disease severity. In a comparison of stroke, Alzheimer's patients, and those with major depression, Marin et al. (1993, 1994) found that the relationship between apathy and depression varied among diagnostic groups. Despite significant correlations between apathy and depression within groups, absolute levels of each varied considerably. Left hemisphere stroke patients and those with major depression most frequently had low apathy scores with high depression, while Alzheimer's patients were more likely to have high apathy and low depression scores (Marin et al., 1993). Using the apathy and depression subscales of the Neuropsychiatric Inventory which have minimal item/symptom overlap, Levy et al. (1998) found no correlation between apathy and depression scores in 154 patients over 5 neurodegenerative disorders (i.e., Alzheimer's disease, Huntington's disease, Parkinson's disease, frontotemporal dementia, and progressive supranuclear palsy). They also found that the two symptoms were associated with other neuropsychiatric symptoms in differing ways. For example, apathy was associated with disinhibition and aberrant motor behavior while depression was associated with anxiety, agitation, irritability, and hallucinations. In addition, the relationship between apathy and depression appeared disease specific in this sample such that Alzheimer's disease, frontotemporal dementia and progressive supranuclear palsy had more prevalent and severe apathy,

whereas Parkinson and Huntington's patients had more prevalent and severe depression (Levy et al., 1998). Differences in apathy and depression were also evident in comparisons of Parkinson and dystonia patients. The researchers suggested that "apathy may be a core feature of Parkinson's disease and occurs in the absence of depression" (Kirsch-Darrow et al., 2006). Still other studies were able to dissociate apathy and depression using an apathy scale and structured clinical interview among patients with Alzheimer's disease, major depressive disorder, and healthy controls (Starkstein, 2001) and between Parkinson's patients and healthy controls (Starkstein et al., 1992). The complete list of studies presenting convincing evidence for the dissociating of apathy and depression may be impossible to include here, however it is sufficient to say the majority of researchers agree- that while apathy and depression may coexist, they are different entities. Collectively, the findings indicate that apathy: 1.) can occur in the absence of depression, 2.) in most cases of neurologic disease is not the consequence of depression, and 3.) within a patient may be not only clinically but also anatomically independent (Levy & Dubois, 2006).

Measurement of Apathy

As investigations into apathy and related neuropsychiatric syndromes have progressed, researchers have come to operationalize the construct so that it may be quantitatively measured in clinical settings. More recent views describe apathy as a lack of responsivity to stimuli resulting in diminished self-initiated action or quantitative reductions in self-generated or goal-directed behaviors (Stuss, van

Reekum, & Murphy, 2000; Levy & Dubois, 2006). Accordingly, a number of inventories have also been created to detect the presence of apathy in a variety of patient populations. The Apathy Evaluation Scale (AES) was the first of its kind developed to quantify and characterize apathy in adult patients (Marin et al., 1991). The scale approached the assessment of apathy as a psychological dimension that may be evaluated in patients in which apathy dominates their clinical presentation, or in those in which it exists as a secondary symptom of another syndrome. Given the association of apathy with impaired insight, three different versions were developed for the clinician (AES-C), an informant (e.g., family member, caregiver, or friend; AES-I), and patient self-report (AES-S). The scale consists of 18 questions in which the rater circles the answer which best describes their thoughts, feelings, and actions during the past 4 weeks. Example questions include: "I am interested in things", "When something good happens I am excited", and "Getting together with friends is important to me" (with slight variations in wording for clinician and informant versions). Response choices then include "not at all true", "slightly true", "somewhat true", and "very true", and are coded on a likert scale of 1 to 4, with 4 representing greater apathy. It should also be noted that several items are reverse coded such as "I put little effort into anything". Factor analysis identified three similar factors in each of the rater sources accounting for 50-65% of the total variance for different raters (Marin et al., 1991). Factors included Apathy (32-53% variance of the scale for three rater sources), Curiosity/Novelty Seeking (5-10%), and Insight/Lack of Concern/Need for ADL Structure (7-8%). All items were found to have nonsignificant correlations with depression, and items for impaired insight and

dependency and the need for structuring ADL's suggested they may be endorsed preferentially by more severely impaired subjects (Marin et al., 1991). Interrater reliability for the clinician version suggests multiple raters can be trained to use the scale in a similar fashion, and the scale was found to have sufficient test-retest reliability in evaluating the extent to which apathy changes with, or independently of, other variables. A multitrait multimethod matrix procedure supported convergent and discriminant validity (Marin et al., 1991).

While some have raised questions regarding the sensitivity and predictive ability of different versions (Glenn et al., 2002; Clarke et al., 2007), studies have generally confirmed the internal consistency and validity of the measure (Glenn et al., 2002) and found comparable factor structures (e.g., "apathy", "interest", and "other" factors; Clarke et al., 2007). Cutoff scores appear to vary between studies depending on the clinical sample and version of the scale implemented, however it is generally accepted to be two standard deviations below the mean (36.5- 37.5 for self-report versions; Marin et al., 1991; Clarke et al., 2007). The developers of the AES also examined each of the hypothesized cognitive, behavioral, and emotional domains of apathy and labeled each item accordingly. Eight items are labeled as cognitive, five are behavioral in nature, two emotional, and three labeled as "other" (Marin et al., 1991).

One point of controversy is whether self-report versions of apathy such as the AES above are reliable measures given the potential for a lack of self-awareness in several degenerative diseases, following traumatic injury, or in those who are demented. Patients with AD and apathy may be unaware of the magnitude of their

cognitive and behavioral changes suggesting that assessment of apathy or other behavioral disorders should be done in the presence of caregivers (Starkstein, 2001). However, others point out that apathy may be less apparent to caregivers or clinicians particularly when parkinsonian symptoms become more severe and may be susceptible to misinterpretation (Isella et al., 2002). Using external sources may result in misattributions of decreased goal-directed behaviors as laziness or decreased motivation to perform ADL's may be misinterpreted as a product or emotional processing deficits or motor difficulty (Shulman, 2000; Aarsland, Cummings, & Larsen, 2001; Zgaljardic et al., 2003, 2007). In addition, apathy does not always mean unawareness and like other self-report ratings insight into a patient's perception of their dysfunction is an important aspect for treatment. Similar to other neuropsychiatric syndromes, apathy is an internal experience and not just an external manifestation of behavior with studies lending support for the feasibility of using self-report measures as a means to assess symptoms related to apathy in nondemented samples (Zgaljardic et al., 2007).

Despite the development of additional measures (discussed below) and any misgivings regarding self-report scales, the use of the AES remains the "gold standard" (Kirsch-Darrow et al., 2008) and has been cited in numerous studies and publications across various populations such as traumatic brain injury, schizophrenia, stroke, Alzheimer's disease, and Parkinson's disease (e.g, Kant, Duffy, & Pivovarnik, 1997; Andersson, Krogstad, & Finset, 1999; Andersson & Bergedalen, 2002, Kant & Smith-Seemiller, 2002; Roth et al., 2007; Clarke et al., 2007; Van Rao et al., 2007).

Due to its widespread acceptance, the self-report form of the Apathy Evaluation Scale was utilized in the present study.

Other scales derived from the AES include the Apathy scale, which consists of 14 questions read by the examiner with the patient as responder (Starkstein et al., 1992). The authors felt the AES might be too demanding for Parkinson's patients and therefore shortened the inventory. Scores range from 0 to 42 with higher scores indicating greater apathy. The Apathy Scale (AS) has been found to have good inter-rater and test-retest reliability, as well as high internal consistency. Scores demonstrate a bimodal distribution and a cutoff of 14 points was identified (Starkstein et al., 1992). The AS has been validated in studies of several populations including Parkinson's disease, Alzheimer's disease, and major depressive disorder with and without dementia (Starkstein et al., 1992, 2001). It has also been suggested that the development of a semi-structured clinical interview would be helpful in identifying apathy symptoms (Starkstein et al., 2001).

Several measures examine apathy in the context of neuropsychiatric disturbances and devote a smaller number of items or single subscales to the detection of apathy. Examples include the Neuropsychiatric Inventory (NPI; Cummings et al., 1994), Apathy Inventory (IA; Robert et al., 2002), and the Frontal Systems Behavioral Scale (FrSBe; Grace & Malloy, 2001). The NPI was developed to assess a wide range of neuropsychiatric manifestations, based on the premise that they may be presenting features of dementing disorders with important diagnostic, prognostic, and management implications (Cummings et al., 1994). Ten domains which are commonly present in the dementias and have the potential to distinguish between

dementias producing different types of behavioral disturbance are assessed, including: Delusions, hallucinations, agitation/aggression, dysphoria, anxiety, apathy, disinhibition, irritability/lability, and aberrant motor activity. If the abnormal behavior is present, the frequency and severity are then indicated giving the scale additional sensitivity. Validation of the measure in a largely Alzheimer's sample, the authors found good content and concurrent validity, with high internal consistency, between-rater and test-retest reliability (Cummings et al., 1994). A wide range of psychopathology was present although mean scores were low. Apathy was most common followed by agitation, dysphoria, anxiety, irritability, and aberrant motor behavior. Apathy was also the only item that showed a significant relationship with age, with older patients rated as more apathetic (Cummings et al., 1994). Cutoff scores were not identified although elevation of the subscale score above that of normals indicated a behavioral change in that domain. The presence of hallucinations or delusions, a depression score above six, disinhibition above four, irritability above two, and any endorsement of agitation, euphoria, apathy, and motor behavior were therefore considered abnormal compared to controls (Cummings et al., 1994). A brief version of the NPI was also developed called the Neuropsychiatric Inventory Questionnaire (NPI-Q), which includes screening items for each of the twelve symptom domains. When a domain is positively endorsed, follow-up questions are administered regarding the severity and distress caused by the symptoms. The NPI-Q was found to have acceptable test-retest reliability and is regarded as a brief and reliable informant-based measure of neuropsychiatric symptom severity and related caregiver distress (Kaufer et al., 2000).

Modeled after the NPI (i.e., with frequency and severity likert scales), Robert et al., developed the Apathy Inventory (IA) to provide a separate assessment of the emotional, behavioral, and cognitive aspects of apathy (2002). The three dimensions were modeled after operationalizations of Marin's definition and include emotional blunting, lack of initiative, and lack of interest (Landes, Sperry, Strauss, & Geldmacher, 2001; Starkstein et al., 2001; Marin,1996; Robert et al., 2002). Both caregiver and patient self-report forms are available, and the scale covers each of the dimensions in a total of three questions (i.e., one question per dimension). The measure was validated in a study comparison of patients with Parkinson's disease, Alzheimer's disease, mild cognitive impairment, and controls, and found to have acceptable reliability and validity (Robert et al., 2002).

Finally, the Frontal Systems Behavior Scale (FrSBe)- formerly the Frontal Lobe Personality Scale (FLoPS), assesses behavior disturbances associated with damage to frontal subcortical brain circuits via three separate subscales of apathy, disinhibition, and executive dysfunction, and also a composite score. Available in both self-report and family or caregiver forms, the FrSBe allows comparison of behavior pre and post injury or illness (Grace & Malloy, 2001). Among a sample of 324 patients diagnosed with neurodegenerative disorders including Parkinson's, Alzheimer's, and Huntington's disease, a factor structure consistent with the proposed subscales was confirmed and the utility of the scale supported (Stout, Ready, Grace, Malloy, & Paulsen, 2003).

In 2006, Sockeel et al. presented the Lille Apathy Rating Scale (LARS) as a novel measure for detecting and quantifying apathy, and as a potential answer to existing psychometric and conceptual shortcomings including differences in the definition of apathy, a lack of standardization in the administration and scoring instructions of the AES, and drawbacks to single item inventories such as the NPI, AI, and FrSBe. It is a semistructured clinical interview based on Marin's original conceptualization, and provides an overall apathy score (ranging from -36 to +36) and composite subscores representing four distinct dimensions of apathy (Zahodne et al., 2009). Using a population of Parkinson's patients, Sockeel et al. (2006) compared the LARS, AES, and NPI with measures of depression (Montgomery and Asberg Depresion Rating scale; MADRS) and dementia (Mattis Dementia Rating Scale; MDRS). They aimed to enhance standardization, improve stability, and reduce subjective interpretations during scoring (Sockeel et al., 2006). The scale, developed in French, is a structured standardized interview administered by a clinician, with ratings based on the subject's own report on their thoughts, emotions, and activities over the previous four weeks. It consists of 33 items over 9 domains including everyday productivity, lack on initiative, lack of interest, motivation, extinction of novelty seeking, blunting of emotional responses, lack of concern, poor social life, and extinction of self-awareness. Factor analysis identified four primary factors explaining more than 65% of the total variance of intellectual curiosity, self-awareness, emotion and action initiation that are similar to previously suggested cognitive, emotional, and behavioral domains. Two secondary factors were apathy (self-awareness, emotion, and action initiation) and self-awareness. Internal

consistency, test-retest and interrater reliability were found to be high, and concurrent and criterion validity were excellent (Sockeel et al., 2006). The mean scores and confidence intervals demonstrated for different patient groups and the absence of interactions between apathy and depression support the scale's ability to discriminate between the two constructs. Correlations between the LARS and MDRS were mainly due to the apathy subscale of the depression inventory, consistent with findings of other measures such as the NPI (Sockeel et al., 2006; Levy et al., 1998). Initial cutoff scores were identified and set at 2.5 standard deviations below the mean of the control group. When the AES and LARS were compared using these cutoffs, the LARS was found to provide slightly more reliable validity (Sockeel., et al., 2006). A more recent validation of the scale in an English-speaking sample demonstrated convergent and divergent validity when compared to other apathy (AS) and depression (BDI-II) scales (Zahodne et al., 2009). While they identified cut-off scores higher than those proposed by Sockeel et al. using a receiver-operated characteristic analysis comparing the LARS to the AS, they support the use of the LARS as a "promising instrument" to explore apathy in Parkinson's disease (Zahodne et al., 2009).

Apathy in Neurologic Disease

There are many potential clinical causes of apathy including Alzheimer's disease, frontal lobe dysfunction (disruption of the frontal subcortical circuits and structures such as the anterior cingulate gyrus, globus pallidus, nucleus accumbens, and medial dorsal nucleus of the thalamus), basal ganglia disease (e.g., Parkinson's

disease, Huntington's disease, progressive supranuclear palsy, HIV/AIDS infection), thalamic and amygdala damage (e.g., Korsakoff's syndrome, Kluver-Bucy syndrome, tumor, stroke), right hemispheric damage- particularly the inferior parietal lobule and connections to the frontal lobe, partially treated or post-psychotic depression, Schizophrenia, drug-induced conditions, and other medical disorders such as "apathetic" hyperthyroidism, Lyme disease, and chronic fatigue syndrome (Marin, 1996; Starkstein & Marin, 1999; Marin et al., 2005; Roth et al., 2007).

Alzheimer's disease.

In those with Alzheimer's disease (AD), apathy is correlated with poor insight, cognitive deficits, and severe impairment in activities of daily living (Assal & Cummings, 2002). In fact, apathy is the most common neuropsychiatric symptom in AD and has been found to increase with disease progression (Mega, Cummings, Fiorello, & Gornbein, 1996). Studies have also shown that apathy and depression can be dissociated in this population, and confirm the relationship between apathy, executive dysfunction, and frontal lobe abnormalities (Starkstein et al., 2001; Assal & Cummings, 2002). Finally, functional neuroimaging studies of Alzheimer's patients have reinforced the role of the anterior cingulate in apathy with apathetic patients demonstrating bilateral hypoperfusion in the anterior cingulate compared to those who were nonapathetic (Migneco et al., 2001; in Assal & Cumming, 2002). While apathy occurs in dementias with both cortical and subcortical involvement, the underlying pathophysiology may be different. It could be that apathy in Parkinson's patients stems from primary basal ganglia involvement which then leads to

accompanied dysfunction in the anterior cingulate via frontal subcortical circuitry, while apathy of the Alzheimer's type may be due to direct damage of the cingulate itself or other frontal cortex involved in motivational circuitry.

Huntington's disease.

Neuropsychiatric symptoms such as apathy are also prevalent in Huntington's disease (HD), a neurologic movement disorder with similar underlying structural pathophysiology to that of Parkinson's disease. Burns et al. (1990) found no differences in apathy prevalence between AD and HD, with 48% of patients endorsing apathy for each. More recent literature using the Neuropsychiatric Inventory revealed a slightly higher rate of apathy prevalence (55.8%) (Paulsen, Ready, Hamilton, Mega, & Cummings, 2001). Dysfunction of the medial prefrontal circuit including the anterior cingulate produces apathy in Huntington's, similar to PD. Apathy in HD has been shown to increase with disease duration, consistent with the known pattern of neuronal degeneration which progresses from medial to lateral and from dorsal to ventral caudate impacting the dorsolateral and orbital circuits before the cingulate pathways (Caine & Shoulson, 1983; Paulsen et al., 1995; Levy et al., 1998).

Traumatic brain injury.

In addition to dementing disease and movement disorders, apathy is common in patients with traumatic brain injury (TBI). In one study, Kant et al. (2002) found 10.84% of TBI patients reported apathy and 60% endorsed both apathy and

depression. In addition, effects of apathy in TBI may not be confined to the immediate post-injury period. For example, 21% of patients surveyed six months following injury reported "difficulty in becoming interested", another study found 23% of patients reported decreased initiative two years after injury, and still another reported that 28% of patients cited "difficulty in becoming interested" seven years following the time of injury (Van Zomeren & Can den Burg, 1985; Oddy, Humphrey, & Uttley, 1978; Oddy, Coughlan, Tyerman, & Jenkins, 1985). Apathy may significantly interefere with progress in a rehabilitation setting as the unmotivated patient is often assumed to be depressed or dubbed "lazy", in effect underestimating their potential for recovery (Kant et al., 2006). The lack of emotional reactivity may also hinder the patient's ability to become properly engaged in therapeutic activities (Andersson et al., 1999). In relation to apathy and cognitive function in TBI patients, Andersson & Bergedalen (2002) found apathy scores to be associated with deficits in acqusition and memory, executive function, and psychomotor speed, and that these domains clustered with the cognitive dimension of apathy (but not behavioral or emotional aspects).

Cerebrovascular disease and stroke.

Finally, apathy has been reported as a frequent consequence of stroke (i.e., cerebrovascular) lesions. In a study of 80 patients, 9 were apathetic only, 9 were apathetic and depressed, 18 were depressed only, and 44 reported no signs of either apathy or depression (Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1993). An increased frequency of apathy was associated with major depression, and apathy was

also significantly correlated with increasing age, decline in independence in activities of daily living, and cognitive impairments. Structurally, apathy was found to be associated with lesions in the posterior limb of the internal capsule (Starkstein et al., 1993). It is evident that apathy occurs in a number of neurologic diseases, and the similarities and differences between the presentation of apathy in these various populations is still being explored. Ideally, it may be possible to use past findings in other areas to illuminate the presence of apathy in Parkinson's disease. Likewise, findings regarding apathy in PD may also be applicable to several different populations.

Neurocircuitry

Apathy and motivation are linked not only conceptually as described above, but also through underlying neural systems. This review will first examine the putative circuitry of motivation and then address the more specific neural processes involved in apathy focusing on common neurocircuitry and specific frontal subcortical circuits.

Neurocircuitry of motivation.

A motivational circuitry model described by Kalivas, Churchill & Klitenick (1993) consists of a "core" circuit whose activity is representative of the current motivational state and includes the anterior cingulate, nucleus accumbens, ventral pallidum, medial dorsal nucleus of the thalamus, and the ventral tegmental area. The flow of information through this circuit permits the translation of motivation into

action (Marin & Wilkosz, 2005). Additional structures include the amygdala and hippocampus which provide limbic input, and output structures including the motor cortex, basal ganglia, reticulospinal tract, and pedunculopontine nucleus (Marin & Wilkosz, 2005). While the core circuit is responsible for establishing and maintaining motivational state, modifying it on the basis of reward value of the current environment involves additional structures- in particular the amygdala, hippocampus, prefrontal cortex and greater limbic lobe (Kalivas et al., 1993; Heimer, 2003; in Marin & Wilkosz, 2005). Thus far, the structures mentioned in motivational circuitry have made reference to the detection of rewarding stimuli, and establishing, maintaining, and modifying an internal motivational state. However, these signals must also be communicated and transduced into outward actions and behaviors- ones that are used in research to objectively and quantitatively define motivation or a lack thereof. In general, it is the internal organization of the core circuit that allows for the communication of information regarding the individual's motivational state to be transformed into the cognitive, motor, emotional, and autonomic events which comprise goal-directed behavior. In particular, medial regions tend to receive limbic input, and more lateral regions are responsible for output (Mogenson, Jones, & Yim, 1980; Marin, 1996). Output from the motivational circuit is then managed by several structures and systems.

Traditional views implicate the motor cortex, caudate nucleus, globus pallidus, substantia nigra, and subthalamic nucleus. Other evidence also suggests that the motivational output of the core circuit has connections to locomotor and autonomic centers of the brainstem (i.e., locomotor region of the mesencephalon and

the pedunculopontine nucleus contained within) (Skinner & Garcia-Rill, 1993; Marin, 1996). There are also multiple routes for transferring signals representing goal choice to motor outputs of the core circuit including direct pathways between motor and limbic structures of the core circuit, and also indirect pathways involving regions such as the prefrontal cortex which receives information from the medial limbic components and returns information to the lateral motor output structures (Kalivas et al., 1993). Finally, the anterior cingulate (receiving limbic input from the amygdala) has been found to be extensively involved in response selection and the organization of autonomic, endocrine, vocalization, emotional and skeletal motor responses (Devinsky, Morrell, & Vogt, 1995; Marin 1996). Damage to the cingulate or the amygdala may produce the syndrome of "pure" or affective apathy in which there is a failure to initiate and sustain goal-directed behaviors despite intact cognitive, corticosensory, and extrapyramidal function (Marin, 1996).

In concordance with the above literature, clinical arguments for the inclusion of the anterior cingulate in the "core circuit" is supported by experimental evidence suggesting that the AC plays an essential role in motivational aspects of decision-making (Marin, 1996; Damasio, 1996; Bush, Luu, & Posner, 2000; Phan, Wager, Taylor, & Liberzon, 2002). Indeed, the anterior cingulate has received much attention in relation to motivation and apathy. The anterior cingulate cortex is part of a circuit involved in a form of attention which serves to regulate both emotional and cognitive processing (Whalen et al, 1998; Bush et al., 2000). Lesions to this area may therefore produce symptoms including apathy, inattention, emotional instability, akinetic mutism, and dysregulation of autonomic functions (Bush et al., 2000). The

anterior part of the cingulate cortex can be distinguished from posterior portions by both cytoarchitecture and projection patterns as well as function. For example, the anterior cingulate is thought to control the expression of emotion (acting as an effector or in an executive capacity) via skeletal, endocrine, and visceral systems, while the posterior cingulate is more evaluative in nature (i.e., monitoring sensory events and behaviors) (Vogt, Finch, & Olson, 1992). Within the anterior cingulate, cognitive and emotional information is processed separately. The cognitive division appears to be a part of a distributed attentional network with connections to the lateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas. Functions include modulation of attention and executive function by influencing sensory or response selection, complex motor control, motivation, novelty, and error detection and working memory (as reviewed in Bush et al., 2000). The more rostral and ventral affective division of the anterior cingulate is primarily responsible for assessing the salience of emotional and motivational information and regulating corresponding emotional output. Interconnections include the amygdala, periaqueductal gray matter, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and orbitofrontal cortex, with output to autonomic, visceromotor, and endocrine systems (Vogt, Finch, & Olson, 1992; Devinsky et al., 1995; Drevets & Raichle, 1998; Whalen et al., 1998; as reviewed in Bush, 2000).

Additional models of reward-related circuitry implicate similar structures to those found in motivational literature. In regards to reward detection and perception (a critical aspect of the motivational process), Schultz (2000) found dopamine neurons in the substantia nigra pars compacta and medially adjoining ventral

tegmental area to be particularly sensitive to rewarding events as opposed to neutral events. This information is particularly relevant to the current study as motor, cognitive, and motivational processes that are disrupted in Parkinson's disease are also mediated by central dopamine systems. However, neurons that respond to the delivery of rewards are also found in other brain structures besides dopamine systems including the striatum (caudate, putamen, ventral striatum including the nucleus accumbens), substantia nigra pars compacta, dorsolateral premotor and orbitofrontal cortex, anterior cingulate, amygdala, and lateral hypothalamus (as reviewed in Schultz, 2000). Animals studies have also found the amygdala and orbitofrontal cortex to be implicated in the detection, perception and expectation of rewards (Schultz, 2000), in addition to reinforcement associated learning, sensitivity to reward flexibility, and impulse control (Czernecki et al., 2002). The dorsolateral premotor areas may use reward information to prepare, plan, sequence, and execute behavior directed towards goal acquisition (as reviewed in Schultz, 2000). In sum, the ventral striatum connects the limbic and frontal executive systems via orbitofrontal and cingulate loops which are in turn modulated by mesolimbic and nigrostriatal dopaminergic systems.

Frontal-subcortical circuitry.

After having reviewed the neural underpinnings and overlapping systems of motivation and apathy, it is necessary to place these findings within the neuroanatomic context of frontal subcortical dementias and disease. Although the neural circuitry underlying apathy and PD is not a focus of the current study, it

provides a theoretical foundation for the exploration of cognitive, behavioral, and emotional domains of apathy, as well as sheds light on possible neuropsychological correlates of each domain.

Elaborating on previous seminal research by Alexander and Strick (1986), Mega & Cummings clearly describe five parallel anatomic circuits linking the regions of the frontal cortex to more subcortical structures such as the striatum (i.e., caudate and putamen), globus pallidus, substantia nigra, and thalamus (1994). Disruption of these circuits may lead to a variety of cognitive and neuropsychiatric disorders (Cummings, 1993; in Mega and Cummings). The five circuits include the supplementary motor circuit which originates in the supplementary motor area, and the oculomotor circuit originating in the frontal eye fields. Both of these were thought to be dedicated to motor function while the remaining three circuits were implicated in behavior and linked to a number of neuropsychiatric syndromes (Mega & Cummings, 1994). The dorsolateral prefrontal circuit projects from the dorsolateral prefrontal cortex to the dorsolateral portion of the caudate and underlies cognitive executive functions including complex problem solving, shifting and maintaining behavioral sets, generating motor programs, copying complicated figures, and self-direction, monitoring, and independence from environmental cues. Dysfunction may result in poor planning and organizational strategies, fluency deficits, and perseveration, etc.. Secondly, the lateral orbitofrontal circuit projects to the ventral caudate and is thought to govern empathic, civil, and socially appropriate behavior (i.e., personality and mood). Emotional lability, irritability, inappropriate affect and emotional expression, tactlessness and behavioral disinhibition have been

ascribed to lesions of this areas. And finally, the anterior cingulate circuit connects to the medial striatal/nucleus accumbens region and facilitates the intentional selection of environmental stimuli based on internal relevance (i.e., motivation) (Mega & Cummings, 1994; Tekin & Cummings, 2002). Apathy is prominent in patients with disorders affecting the subcortical structures of the anterior cingulate circuit which include thalamic lesions, Huntington's disease, and Parkinson's disease (Burns, Folstein, Brandt, & Folstein, 1990; Starkstein et al., 1992; Mega & Cummings, 1994). In addition, psychiatric disorders associated with frontal-subcortical dysfunction include obsessive-compulsive disorder, schizophrenia, major depressive disorder, and substance abuse and dependence (Tekin & Cummings, 2002).

All of the circuits have a shared common organization, with an origin in the frontal lobes and excitatory glutaminergic fibers extending to the striatum. In turn, striatal cells project inhibitory GABA fibers to both the globus pallidus interna/substantia nigra pars reticulata and the globus pallidus externa in direct and indirect pathways (Mega & Cummings, 1994; Tekin & Cummings, 2002). Each loop is a closed circuit with dedicated neurons remaining anatomically separated from parallel circuits, however, there are also open elements in each circuit where input from outside regions may influence the circuits' activity. In general, circuits mediating limbic function make outside connections with other limbic areas of the brain and those governing executive functions interact predominantly with regions controlling cognitive function. The circuits therefore integrate information from anatomically diffuse but functionally related areas (Mega & Cummings, 1994). Modulatory neurotransmitters include choline, serotonin, glutamate (excitatory),

GABA (inhibitory), and dopamine- which as the neurons project from the substantia nigra to the striatum effect all frontal-subcortical functions (Tekin & Cummings, 2002). Despite the fact that direct and indirect loops between the striatum and globus pallidus/ substantia nigra repeat in each circuit, the dopamine balance in each may differ by disease. For example, it has been found that patients with PD associated with dementia and depression have increased degeneration in the ventral tegmentum than patients without dementia or depression. Due to the fact that the ventral tegmentum provides dopaminergic input to the anterior cingulate, these demented patients have more thalamocortical deactivation than nondemented patients which likely contributes to apathy and anhedonia (Torak & Morris, 1988; Mega & Cummings, 1994). In addition, the orbitofrontal and entorhinal regions provide information to the anterior cingulate circuit regarding the internal and external environment allowing the organism to initiate motor activity based on environmental stimuli and emotional relevance. Damage to this circuit therefore disrupts the integration of external and internal information sources and produces unmotivated and apathetic behavior (Mega & Cummings, 1994).

Over time, thoughts on the delineation and function of frontal-subcortical circuits have been refined and their connections to neuropsychiatric symptoms such as apathy more deeply explored. Consensus remains regarding frontal subcortical systems mediating motivation (anterior cingulate and medial orbitofrontal cortex), socially responsive and empathic behavior (lateral orbitofrontal cortex), and executive function (dorsolateral prefrontal cortex (Bonelli & Cummings, 2008). Several authors have also nicely summarized and advanced ideas regarding the specific role

of the basal ganglia in the production of apathy (in addition to lesions of other structures of the frontal-subcortical circuits). As mentioned above, the basal ganglia is a key structure affected by dopamine depletion in Parkinson's disease. Under normal conditions, the prefrontal cortex is responsible for the initial processing of information from the external and internal environments regarding decisions about potential actions to be performed. This information is then sent to the basal ganglia which is responsible for selecting the relevant signal from background noise via temporal-spatial focalization made possible by the parallel nature of the circuits. In addition, convergence between circuits is necessary to amplify the signal. The extracted signals are then transferred to the back to the prefrontal cortex where a clear signal can be detected and contribute to decision-making and maintaining and modifying behaviors. However, in the case of focal destruction within the basal ganglia, selection and extraction of the relevant signal does not occur, the clarity of the signal emerging from the basal ganglia is diminished, ongoing behavior is not validated at the level of the prefrontal cortex and is difficult to maintain, and upcoming behaviors may not be activated at all (Levy & Dubois, 2006; Levy & Czernecki, 2006). In short, the basal ganglia is no longer able to generate the relevant neural signal at the level of its output targets in prefrontal cognitive and limbic regions, resulting in an ultimate lack of signal transfer to the prefrontal cortex and corresponding deficits in cognitive, behavioral, and emotional domains (as reviewed in: Levy & Dubois, 2006; Levy & Czernecki, 2006). Studies of apathy in other neurodegenerative disorders such as progressive supranuclear palsy have also described severe neuronal loss in the basal ganglia with a smaller degree of prefrontal

pathology suggesting that apathy is indeed a sequelae of a "prefrontal-like" syndrome due to lesions mainly affecting the basal ganglia (Hauw et al., 1994; Litvan et al., 1996; Levy & Czernecki, 2006).

Possible etiology of apathy.

Given the structural, functional and neurochemical complexity of frontal-subcortical circuits, there are a number of different sites that, if damaged, could potentially result in apathy behaviors. Significant differences in the severity of apathy have been demonstrated between "on" and "off" medication stages, and there is preliminary evidence for apathy improving following deep-brain stimulation of the subthalamic nucleus suggesting that apathy in Parkinson's disease is atleast partly a dopamine-dependent system (Czernecki et al., 2002). However, more recent evidence regarding subthalamic stimulation in Parkinson's disease (a growing treatment trend) and the development of apathy presents conflicting evidence to earlier works. A summary of relevant literature by Kirsch-Darrow et al. found that out of seven studies, four reported increases in apathy from pre to post surgery, two found no change, and one reported a reduction (2008). Perhaps the most well-controlled study which used a matched-groups design found that while apathy scores in the control group did not change, those who underwent subthalamic stimulation demonstrated increases in apathy from pre-surgery to 3 and 6 months post-surgery (Czernecki et al., 2005). Proposed mechanisms include the stimulation of nonmotor basal ganglia circuits via electrode placement and current spread, in addition to suggestions for downstream metabolic change in the cerebral cortex following

surgical subthalamic stimulation. Finally, a reduction in dopaminergic medications following surgery may be another possible mechanism for observed increases in apathy (Kirsch-Darrow et al., 2008).

Regardless of conflicting evidence regarding the role of deep brain stimulation in the etiology of apathy, it is agreed that dopaminergic frontal-subcortical systems play a vital role. Dopamine is generally thought of as relating to reward-processing mechanisms and therefore may act through associated structures and pathways (e.g., orbitomedial prefrontal cortex, ventral striatum, and meso-cortico-limbic circuit). Due to the involvement of these structures it would then be easy for one to think that apathy in Parkinson's patients falls into the subtype of emotional-affective mechanism mentioned above. However, apathy has been found in PD patients at times when dopamine pathways are generally spared, e.g., in early stages and in those without dementia (Aarsland et al., 1999, 2001; Czernecki et al., 2002, 2005; Isella et al., 2002; Pluck & Brown, 2002; Robert et al., 2002; Starkstein et al., 1989; Levy & Czernecki, 2006). PD patients have also been shown to have little impairment in reward-processing tasks (Bechara et al., 1994; Czernecki et al., 2002; Freedman & Oscar-Berman, 1986). Therefore, it has been hypothesized that apathy in PD may actually result from the disruption of cognitive processing at a global level. Basal ganglia damage leading to loss of spatial focalization results in a failure of the output structures (frontal cortex) to extract a signal's meaning. Because they cannot decipher the transmission there are related deficits in decision-making causing delayed and aborted responses, which in turn manifests as cognitive dysfunction resembling that of patients with direct dorsolateral prefrontal cortex lesions (Pillon et

al., 2002; Levy & Czernecki, 2006). This hypothesis also lays the foundation for investigation into executive function as a cognitive domain within apathy, and also exploration of its potential influence on the construct of apathy itself and emotional and behavioral manifestations.

Neuroanatomic support for apathy domains.

The concept of apathy has also been expanded as three potential mechanisms responsible producing cognitive, emotional, and behavioral apathy have been identified and linked to dysfunction within the prefrontal cortex and basal ganglia (Levy & Dubois, 2006; Levy & Czernecki, 2006). To begin, an "emotional-affective" type of apathy may result from damage and lesions to the connections between the orbital-medial prefrontal cortex and ventral striatum, resulting in an inability to establish necessary associations between emotional-affective signals and ongoing or forthcoming behaviors. Emotional blunting is a signature feature of orbital-medial prefrontal cortex dysfunction and provides insight into this type of apathy. As emotion and affect indicate motivational value of a given behavior and guide the decision making process, decreased reactivity to emotion and diminished sensitivity to reward lead to decision-making deficits resulting in a related decrease in goal-directed behaviors (Calder et al., 1994; Mendez et al,. 1989; Butters & Rosvold, 1968; Andersson, Gundersen, & Finset, 1999; Haber et al., 1995; Hollerman et al., 1998; Lough et al., 2001; Rosen et al., 2002; Selemon & Goldman-Rakic, 1985; Schultz et al., 1992; as reviewed in Levy & Dubois, 2006).

Secondly, the expression of apathy related to executive dysfunction has been termed "cognitive inertia" and is associated with difficulty elaborating a plan of action necessary to maintain or generate behavior resulting in executive deficits in working memory, rule-finding, set-shifting, and planning needed to carry out goal-directed behaviors. Apathy of this type is thought to result from lesions to the dorsolateral prefrontal cortex which projects to the dorsal caudate, and cognitive associative areas of the basal ganglia (i.e., dorsal caudate and dorsal pallidum) (Mendez et al., 1989; Owen et al., 1996; Levy & Dubois, 2006; Levy & Czernecki, 2006).

The role of the basal ganglia is particularly relevant in relation to a third more intense form of apathy referred to as "auto-activation", which describes an inability to self-activate and self-initiate thoughts and actions in the presence of spared ability to generate externally driven behavior (Ali-Cherif et al., 1984; Laplane et al., 1989; Starkstein et al., 1989). This most severe form of apathy may be due to impairments in autonomic function devoted to auto-activation, i.e., at the very base level of organismal functioning with patients tending to remain quietly in the same position or place for many hours without speaking or taking any form of self-initiative ("mental emptiness") (Levy & Dubois; 2006). This type of apathy may be the result of specific lesion sites in the basal ganglia including bilateral portions of the internal pallidum, uni- or bilateral lesions of the head of the caudate nucleus, deep frontal white matter, and lesions of the anterior and medial dorsal nuclei of the thalamus (as reviewed by Levy & Czernecki, 2006). Lesions in these areas most likely affect both limbic and cognitive territories which helps to explain the absence of extrapyramidal motor signs

(Levy & Czernecki, 2006). As described above, the failure to activate output structures in the frontal lobes when behavior depends on internal guidance is likely associated with the inability of the basal ganglia to select, extract, and amplify the relevant incoming signal from background noise, thus making the transmission of the extracted signal back to the prefrontal cortex in order to maintain ongoing and generate new behaviors impossible. Interestingly, these three proposed mechanisms (i.e, emotional-affective apathy, cognitive apathy, and auto-activation) appear to provide a platform for the three domains of apathy (i.e., cognitive, emotional, and behavioral) suggested by earlier works. Literature regarding the neuronal underpinnings of apathy, and continued psychometric and clinical studies have begun to converge lending credence to the construct of apathy and drawing attention to its importance and potential implications.

The similarities between the cognitive, emotional, and behavioral targets of the aforementioned psychometric methods, and the domains suggested and supported by neurocircuitry literature are striking. However, the need remains for further evidence of how collections of apathetic symptoms and neuropsychological correlates may group or collect in these three domains. One of the aims of this study is to elucidate these relationships and address similar shortcomings in the existing literature.

Chapter 4: Parkinson's Disease and Apathy

Overview

Apathy in Parkinson's disease is relatively prevalent with estimates ranging from 16.5-44% depending on the measures used and population sampled (Starkstein et al., 1992; Aarsland et al, 1999, 2001; Sockeel et al., 2006; Zgaljardic et al., 2007). To review, apathy refers to a set of behavioral, emotional and cognitive features- the diagnosis of which requires the presence of at least one symptom from each of the three domains of diminished goal-directed behavior, diminished goal-directed cognition, and diminished emotional reactivity (Starkstein et al., 2001). Some have also proposed a fourth dimension of self-awareness or "social apathy" (Stuss & Alexander, 2000; Dujardin, 2007). Apathy is considered to be a true feature of the Parkinson's disease process and is not a psychological response to physical impairment and associated disability, as apathy was found to be only weakly related or unrelated to disease duration, stage, or disability (Pluck & Brown, 2002). The inability to experience pleasure, or anhedonia, is closely associated with both apathy and depression and involvement of reward pathways including the ventral tegmental area and nucleus accumbens are likely. This dopamine pathway is impaired in PD therefore hindering the processing of reward which may manifest as reduced hedonic tone and contribute to the phenomenology of apathy in Parkinson's patients (Fibiger, 1984; Goerendt, Lawrence, & Brooks, 1999). In addition, apathy in PD can be dissociated from other psychiatric symptoms including depression, and is more

closely related to global cognitive impairment (particularly executive function) than severity of motor deficits (Pluck & Brown, 2002; Dujardin et al., 2007; Starkstein et al., 1992; Zgaljardic et a., 2007).

While apathy may be linked to decline in one or more cognitive domains, the strongest associations exist between apathy and executive function. Numerous studies support the link between apathy severity and executive difficulties in PD (Isella, 2002; Pluck & Brown, 2002; Starkstein et al., 1992; Zgaljardic et al., 2007). Executive functions may be defined as those involved in complex cognitions such as novel problem-solving, behavior modification following feedback and receipt of new information, strategy generation, and sequencing of complex actions (Elliott, 2003). It is the flexible coordination of multiple subprocesses to achieve a specific goal (Elliott, 2003). Research has suggested that both frontal and subcortical structures are implicated in executive function, with the likely involvement of distributed circuitry rather than distinct structures. For example, it has long been documented that patients with prefrontal damage show impairments in organization and planning, judgment, decision-making, inhibition, set-shifting, and fluency (Stuss & Benson, 1984; Milner, 1963; Shallice, 1982). However, beyond the prefrontal cortex, there is evidence from neuropsychological studies of neurologic disorders that striatal structures are also important in executive functions (Elliott, 2003). Studies of Huntington's disease, multiple systems atrophy, and progressive supranuclear palsy have all demonstrated executive function deficits. In addition, many investigations have shown Parkinson's disease to be characterized by executive dysfunction which is present early in the disease process at a time when pathology is confined to basal ganglia regions

(Robbins et al., 1994; Lawrence et al., 1995; Taylor et al., 1986; Owen et al., 1995; as reviewed by Elliott, 2003). Therefore, executive function deficits appear to be genuine concomitants of basal ganglia damage (Elliott, 2003). These findings support the suggestion that executive functioning does not depend on the prefrontal cortex in isolation, but rather on the intact functioning of frontal subcortical circuitry mediated by dopaminergic transmission. And although the prefrontal cortex is a vital component underlying executive function, posterior cortical regions and subcortical structures must collaborate with the prefrontal cortex to allow for successful executive processing (Elliott, 2003). As the presence of both apathy and executive dysfunction in PD may result from similar structural and functional underpinnings (i.e., compromised frontal subcortical circuitry), it is not difficult for one to expect that they may co-occur. Accordingly, neuropsychological findings in Parkinson's disease have supported this relationship.

Starkstein et al. reported apathetic patients performed more poorly on tasks of verbal fluency (Controlled Oral Word Association Test- FAS; Benton, 1976) and an executive task requiring set shifting (Trail Making Test- B; Reitan, 1955) under time constraints, where the apathetic patients' performance was slow yet accurate (1992). High apathy patients have also been found to perform below the level of low apathy groups on various measures of executive function including verbal fluency tests, the Stroop task (Bush et al., 1998), and the Wisconsin Card Sort Test (Nelson, 1976), all of which require set-shifting and maintenance (Pluck & Brown, 2002). More general cognitive impairment in the apathetic patients was also revealed, possibly due to memory deficits secondary to executive dysfunction (Pluck & Brown, 2002).

Zgaljardic and colleagues found a significant relationship between apathy symptoms for all PD patients and self-report depression (BDI-II; Beck et al., 1993) and executive dysfunction (FrSBe; Grace & Malloy, 2001), and also that increasing apathy was best predicted by cognitive measures of verbal fluency, verbal working memory, and verbal abstraction (2007). Given the strong association between apathy and executive function, several authors have begun to suggest and explore the existence of a distinct subgroup of nondemented PD patients with significant levels of apathy and associated executive dysfunction. In short, apathetic individuals with PD may have a distinct profile of cognitive decline involving executive dysfunction from early in the disease process (Zgaljardic et al., 2007; Pluck & Brown, 2002; Starkstein, 2001).

It is apparent that apathy is a prevalent syndrome in Parkinson's disease and may have a different genesis and presentation than that found in cortical disorders such as Alzheimer's disease. In addition, the relationship between apathy and executive function has only recently been identified and begun to be explored. It is possible that executive function may be wholly responsible for what is viewed as "cognitive" apathy, or perhaps it exists as a separate outside entity influencing the apathy construct in its entirety. It is therefore the hope of the author that this study will advance the understanding of these constructs and further elucidate the complex nature of their relationship as they occur in Parkinson's disease.

Clinical Implications

The importance of accurate identification and treatment of apathy in neurologic patients should not be ignored. Apathetic patients are difficult to manage clinically due to missed appointments and lack of medication adherence. Motivational loss may undermine physical rehabilitation and coping skills and these patients are overall at greater risk for treatment failure (Marin, 1996). In regards to psychosocial well being, the individual may seem depressed, disengaged and indifferent, may withdraw from family and friends, and vocational loss is common. The individual may also experience a loss of social autonomy and contribute to family burden (Marin & Wilkosz, 2005). Neuropsychiatric symptoms in general (e.g., apathy, depression, or psychosis) contribute to patient distress, increase the need for medical care and associated costs, add to caregiver burden, and often precede placement in assisted living facilities (Assal & Cummings, 2002). Proper identification of neuropsychiatric symptoms is also essential as there is growing evidence that they may serve as early markers of disease and developing dementia (Assal & Cummings, 2002).

Evaluation and Assessment

Accurate diagnosis of apathetic syndromes has crucial implications for assessment and treatment (Silva & Marin, 1999). If overdiagnosed, reversible and more readily treated causes of diminished motivation and reductions in goal-directed behaviors may be overlooked (e.g., stupor, delirium), while underdiagnosis may lead to premature attempts at physical rehabilitation or other forms of intervention whose

success depends on strong motivation (Marin & Wilkosz, 2005). Assessment of syndromes of diminished motivation such as apathy, "depends on the etiology and the interactions of multiple biological, psychosocial, and socio-environmental factors that control motivated behavior," thereby necessitating the assessment of each individually (Marin & Wilkosz, 2005). A comprehensive evaluation might include a review of the patient's medical history, making sure to rule out neurologic or psychiatric conditions that may cause apathy (e.g., neurologic disease, psychiatric disturbances such as major depressive disorder, schizophrenia, substance abuse, and personality disorders characterized by passivity or social withdrawal; Marin et al., 1995).

In addition, a systematic psychosocial evaluation including assessment of the patient's social and physical environment may be required (Marin & Wilkosz, 2005). It is important to establish whether apathy has been present throughout the patient's childhood or adult life, whether it represents a change in personality, is diminished in relation to others of their cohort, and is severe enough to interfere with psychosocial functioning (Silva & Marin, 1999). Experiences of psychological trauma, personal loss, and phase-of-life events may also diminish motivation and should be considered.

As elderly patients often have multiple clinical difficulties, it is important to assess possible interactions between medical, psychological and neurologic variables. In particular, medications and medication interactions may alter levels of motivation. While dopaminergic agents are usually thought of as mediators of motivational change, one must also consider serotonergic, adrenergic and cholinergic agents due to their interaction with dopamine systems (Marin & Wilkosz, 2005). For example,

there is some evidence suggesting that selective serotonin reuptake inhibitors (SSRI's) may induce apathy directly or through interaction with antipsychotics such as haloperidol (Hoehn-Saric, Lipsy, & McLeod, 1990).

Treatment

Treatment for apathy may involve both pharmacologic and psychotherapeutic intervention. Catecholaminergic systems and particularly the mesolimbic dopamine system play a critical role in the reward system and in modulating motivated behaviors. Therefore it is not surprising that catecholaminergic agents such as methylphenidate, dopaminergic agonists, and atypical antipsychotics have received a great deal of attention and are thought to be especially effective (McAllister, 2000; Roth et al., 2007). Several open-label case studies reporting methylphenidate to be effective at reducing apathy in patients diagnosed with major depressive disorder (Padala et al., 2005, 2007). Atypical antipsychotics have also shown beneficial effects for negative symptoms associated with schizophrenia, and when added to a regimen including SSRI's have been found to reduce apathy in major depressive disorder patients (Alvarez et al., 2006; Marangell et al., 2002). Dopamine agonists (i.e., agents that increase dopamine release or delay dopamine reuptake) appear promising and findings are consistent with the suggested frontal subcortical circuitry in apathy etiology. Levodopa, a common drug used to treat motor symptoms of Parkinson's disease, was reported to reduce apathy as assessed by the Apathy Scale, in a study of 23 depressed and nondepressed PD patients matched with healthy controls. This improvement was noted irrespective of whether patients were evaluated first in the

"off" or "on" medication state (Czernecki et al., 2002). However, even with levodopa as a first-line agent for treating motor symptoms, the evidence is inconsistent regarding its effectiveness in reducing cognitive or emotional dysfunction in Parkinson's disease. Other catecholamine agonists such as selegiline, amantadine, and bromocriptine have shown some success in reducing apathy in case studies of those with traumatic brain injury, cerebral infarction and hematoma (Van Reekum et al., 1995; Kraus & Maki, 1997; Marin et al., 1995; Debette et al., 2002; Newburn & Newburn, 2005). Further, acetylcholinesterase inhibitors such as donepezil, galantamine, and rivastigmine have also been shown to reduce apathy in patients with Alzheimer's disease and dementia with lewy bodies (as reviewed in Roth et al., 2007). While these studies offer a firm starting point, it is clear that there is a need for further investigation and controlled clinical trials of pharmacologic agents for treating apathy, particularly within the Parkinson's population.

The preservation of cognitive abilities and communications skills in patients with apathy (compared to more severe forms of diminished motivation) may also allow for greater use of psychological and social interventions (Marin & Wilkosz, 2005). The general goal of psychosocial interventions is to define the patient's deficits and also identify residual abilities in order to design compensatory programs. This may include increasing the reward potential of the environment and increasing opportunities for socialization, with the intervention always being introduced methodically and the goals defined collaboratively (Marin & Wilkosz, 2005). While many interventions have been suggested including discussion groups, activity therapy, cognitive-communication therapy, validation/integrated emotion-oriented

care, multisensory stimulation, and psychomotor therapy, only a few have shown reductions in apathy (Roth et al., 2007). It is also likely that apathy occurring in neurodegenerative disorders such as Parkinson's disease is more difficult to treat than that acquired through traumatic brain injury or other means, due to the progressive nature of the disease and accompanying cognitive decline.

Overall, it is evident that early detection, accurate identification, and thorough medical, psychiatric, and psychosocial evaluations are crucial in successfully treating apathetic syndromes. In turn, proper assessment can aid in developing individualized treatments and optimizing patient management and care.

Chapter 5: Rationale

Apathy is recognized as an important neuropsychiatric symptom in Parkinson's disease. Apathy in PD is believed to result from insult or degradation of frontal-subcortical circuits and structures, similar to those involved in the generation of motor symptoms. The prevalence of PD-related apathy ranges from 16-53% and individuals with apathy may exhibit decreased treatment compliance and responsiveness, and experience a loss of social autonomy and reduction in quality of life. The caregiver may also experience increased distress and burden (Marin, Biedrzycki, & Firinciogullari, 1991; Pluck & Brown, 2002; Zgaljardic et al., 2007; Kirsch-Darrow, Mikos, & Bowers, 2008).

Apathy has been formally defined as a lack of motivation not otherwise attributable to intellectual impairment, emotional distress, or diminished level of consciousness. Specifically, the lack of motivation must manifest in three areas including diminished goal-directed overt behaviors, diminished goal directed cognition, and diminished emotional concomitants of goal-directed behavior (Marin et al., 1991). The construct of apathy has proven to be valid and reliable across various populations, and one that is distinct from depression. Silva and Marin (1999) have stated, "The essential difference between apathy and depression is that apathy is a syndrome of diminished motivation, whereas depression is defined by disturbances in mood". Indeed, a lack of interest or apathy may be a symptom of depression, and depression and apathy may co-occur, but they have also been found time and again to exist as separate entities. Studies have also shown that while an apathetic patient may

be aware of the emotional valence of a stimuli or event, they do not *feel* it physiologically, nor does this absence of emotion arouse concern (Bowers et al., 2006; Tranel & Damasio, 1994).

The purpose of this study is three-fold. First, the reliability and validity of the AES-S will be confirmed in the present PD sample. In addition, the cognitive, behavioral, and emotional apathy domains suggested in the literature and supported by neurocircuitry models will be explored using items from the Apathy Evaluation Scale as defined by Marin et al. (1991). Second, the relationship between individual apathy domains and cognitive function will be investigated and specific neuropsychological correlates identified. Finally, contributing and protective factors in the development of apathy or individual domains will be explored, as well as potential outcomes for the individual.

Apathy is one of many neuropsychiatric symptoms of injury, illness, and disease which are often overlooked and whose impact can be underestimated. However, literature regarding the importance of identification and possible implications of such symptoms has begun to demand appropriate attention. While symptoms such as apathy that may go unrecognized can negatively impact the patient and their prognosis, they also provide an opportunity for clinical advancement. This study aims to not only confirm existing findings regarding apathy in PD, but also to investigate proposed cognitive, emotional, and behavioral domains, and associations between apathy and cognitive function. In addition, through investigation of the relationship between apathy and multiple predictors and outcomes, the understanding of the construct as it occurs in Parkinson's disease will

be greatly improved. This in turn may allow clinicians to more accurately assess and identify apathy, providing more individualized treatments and ideally improving prognoses and quality of life for patients of neurodegenerative disease.

Chapter 6: Specific Aims

Aim 1

To further define the presentation of apathy in Parkinson's disease using the Apathy Evaluation Scale- Self-Report version (AES).

Aim 1a

To confirm the construct validity of the AES in a sample of PD patients.

Hypothesis.

Convergent validity will be established with other measures of apathy (i.e., apathy scales and items from the NPI-Q and FrSBe).

Rationale.

Marin et al. (1991) found satisfactory internal consistency, test-retest reliability, and interrater reliability of the AES, which was also confirmed by several authors in a Parkinson's sample (Starkstein et al., 1992; Pluck & Brown 2008).

Subscales of the NPI-Q and FrSBe questionnaires have also been proven valid and reliable measures of apathy (Cummings et al., 1994; Grace & Malloy, 2001). While convergence of the AES with other apathy measures has been examined in dementia groups (e.g., Alzheimer's dementia and frontotemporal dementia; Clarke et al., 2007) less is known regarding their convergence in a Parkinson's sample. In this study, the AES is expected to converge with other validated measures of apathy, in congruence with previous findings.

There is preliminary evidence to support the notion of apathy and anxiety as divergent constructs (Marin et al., 1991). However, more recent publications have noted comorbid apathy and anxiety in PD patients (Pluck & Brown, 2002). The current study recognizes these syndromes may co-occur, but since the constructs are inherently different they should also demonstrate sufficient divergence. Self-report measures of anxiety will be used to examine the association with apathy.

It is expected that the AES will be significantly correlated with other apathy measures, but no relationship will be found with anxiety.

Aim 1b

To establish a factor structure of the AES confirming cognitive, emotional, and behavioral domains.

Hypothesis.

A factor structure of the AES will be identified, consistent with Marin et al.'s (1996) classification of cognitive, emotional, and behavioral items.

Rationale.

Previous studies have identified several factor structures of the AES (e.g., Marin et al., 1991: Apathy, Curiosity/Novelty Seeking, and Insight/Lack of Concern/Need for ADL Structure; Clarke et al., 2007: Apathy, Interest, and Other factors). Despite these findings, little attention has been paid to the presence of theoretical cognitive, emotional, and behavioral domains within apathy. In their initial publication of the AES, Marin et al. (1991) described cognitive, emotional, and behavioral factors and categorized individual items based on these subtypes.

However, the methodology for this classification was not well described and the factors have not been psychometrically tested. In order to address this, an item analyses of the AES will be used to identify which individual items support test reliability, and then confirmatory factor analysis will be employed to impose a factor structure based on Marin's classification. These factors are expected to be sufficiently independent of one another and demonstrate good model fit.

Aim 2

To define the relationship between neuropsychological function and the three apathy domains.

Hypothesis 1

Measures of executive function will significantly correlate with the cognitive apathy factor.

Rationale.

The most common neuropsychological impairment in PD is executive dysfunction. Executive functions include a number of complex mental processes such as working memory, rule-finding, set-shifting, and planning needed to carry out goal-directed behaviors. Parkinson's patients with apathy have been found in multiple studies to perform more poorly on tasks of executive function while those without apathy do not. Until now, no studies have examined the relationship between executive function and cognitive apathy. In the current study several neuropsychological measures of executive function (e.g., Wisconsin Card Sorting

Test, Wechsler Adult Intelligence Scale- Digit Span, Longest Span Backwards, etc.) are expected to be significantly associated with the cognitive apathy construct.

Hypothesis 2

Measures of psychomotor speed will correlate with the behavioral apathy factor in accordance with the concepts of bradyphrenia and 'auto-activation.'

Rationale.

Apathy has been shown to be related to the concept of bradyphrenia, defined as a "slowing of cognitive processing associated with impairments in concentration and attention" (Rogers, Lees, Smith, Trimble, & Stern, 1987; Mayeux, Stern, Williams, Cote, Frantz, & Dyrenfurth, 1986). In addition, Levy and Dubois (2006) discussed a severe form of apathy referred to as "auto-activation," defined as an inability to self-activate and self-initiate thoughts and actions (Ali-Cherif et al., 1984; Laplane et al., 1989; Starkstein et al., 1989). We will use several measures (i.e., Oral Trails Making Test- trials A and B, and the Symbol Digit Modalities Test) to explore the relationship between psychomotor speed and behavioral apathy.

Hypothesis 3

Mood will be highly correlated with the emotional apathy factor.

Rationale.

The relationship between apathy and depression has been well-studied. It is generally accepted that while related, each entity has distinct individual features (Marin et al., 1993, 1994; Starkstein et al., 1992, 2001; Pluck & Brown, 2002; Levy

et al., 1998; Kirsch-Darrow et al., 2006; Levy & Dubois, 2006). This study employs self-report measures of depressive and dysphoric symptomotology (i.e., BDI-II and NPI-Q-Dysphoria items), which are expected to be significantly associated with emotional apathy.

Aim 3

To identify demographic, disease, and psychosocial factors linked to the overall apathy construct.

Hypothesis 1

Left-sided motor onset, non-tremor onset, older age of disease onset, and lower education level will predict increased apathy.

Rationale.

Left-side onset, non-tremor symptom onset, older age of disease onset, and less education have all been associated with greater cognitive impairment in PD (Katzen et al., 1998, 2006; Cohen et al., 2007; Dufouil et al., 2003). However, their relationship with apathy has not been well studied in PD. In this study, the relationship between demographic and disease information (side onset, symptom onset, age of disease onset, and education level) and the novel apathy construct as derived from the CFA of the AES will be examined.

Hypothesis 2

Advanced disease stage and longer disease duration will not significantly predict greater apathy.

Rationale.

Findings regarding the relationship of apathy and disease stage and duration are unclear. Although neuroanatomic studies have linked neurodegeneration in PD to the development of apathy, several studies have found no relationship between apathy and the disease process (Pluck & Brown, 2002). In this study, the relationship between apathy and measures of disease stage (Hoehn & Yahr rating) and disease duration (years from disease onset to exam) will be studied to clarify this complex relationship.

Hypothesis 3

Apathy will predict poorer quality of life, less independence in activities of daily living, and greater caregiver burden.

Rationale.

Individuals with apathy exhibit decreased treatment responsiveness, decreased compliance, loss of social autonomy, reduction in patient quality of life, and increased caregiver distress and burden (Marin, 1996; Assal & Cummings, 2002; Marin & Wilkosz, 2005). Self-report measures of quality of life, basic and complex activities of daily living, and caregiver burden will be used to confirm the relationship between apathy and these psychosocial factors.

Chapter 7: Methods

Participants

Patients in this study were diagnosed with idiopathic Parkinson's disease at the University of Miami Movement Disorders Clinic by specialists based on U.K. PD Brain Bank criteria. All were between the ages of 40-85 and were either primarily English or Spanish-language speakers. Exclusion criteria consisted of a diagnosis of non-idiopathic PD, less than 8th grade education, previous neurosurgical procedure (e.g., pallidotomy, deep-brain stimulation, tumor resection, radiation to the brain, gamma knife, chemotherapy in the last 10 years), neurologic illness or insult other than PD (e.g., Alzheimer's disease, seizures, Tourette's syndrome, stroke/TIA, meningitis/encephalitis, head trauma with loss of consciousness, coma, brain tumor), and major psychiatric conditions requiring longstanding treatment (e.g., addiction [alcohol, drug abuse, or gambling], psychosis, major depression, anxiety, or bipolar disorder). Given the focus of the current study on apathy, only patients who completed the Apathy Evaluation Scale (AES) were included.

Written informed consent was obtained from each patient according to a University of Miami IRB approved protocol.

Procedures

Data Collection

Data for this study was aggregated from two separate databases. A participant inclusion flow chart can be found in Figure 1. The "Initial" dataset was collected

from 1984 to the mid 1990's and includes cognitive, affective, and neurologic data. The second "Recent" dataset was started in 2000 and data collection is ongoing. These two studies contain cross-sectional information including demographic, disease, and neuropsychological data.

The initial sample included 613 PD patients (Initial, $n = 309$; Recent, $n = 304$). Five hundred and six participants met inclusion criteria (Initial, $n = 309$; Recent, $n = 197$). Of the 506 individuals meeting inclusion criteria, participants from the Initial database were more likely to be Non-Hispanic ($X^2(1, N = 459) = 134.54$, $p < .001$), older at the time of diagnosis ($t(493) = 5.726$, $p < .001$), older at the time of exam ($t(498) = 3.514$, $p < .001$), had more advanced disease stage ($t(187.4) = 2.014$, $p = .045$), shorter disease duration ($t(459) = -6.334$, $p < .001$), endorsed fewer depressive symptoms (BDI: $t(426) = -2.337$, $p = .020$) and performed more poorly on a test of global mental status (MMSE: $t(219.1) = -3.691$, $p < .001$), compared to participants from the Recent dataset. Both groups were more apt to endorse tremor versus non-tremor symptom onset ($X^2(1, N = 297) = 4.812$, $p = .028$). Participants from each database were similar on all other demographic and disease measures. In regard to neuropsychological performance, participants from the Initial database performed more poorly on tasks of semantic verbal fluency (Animals: $t(449) = -3.406$, $p = .001$), visual recognition (BVRT: $t(319) = -2.754$, $p = .006$), visual discrimination (Ghent: $t(205.8) = -4.751$, $p < .001$), visual orientation and integration (HVOT: $t(344.0) = -2.582$, $p = .010$), line orientation judgment (JLO: $t(329.0) = -1.966$, $p = .050$), and naming (BNT: $t(403) = -2.205$, $p = .028$), compared to participants from the Recent

dataset. In contrast, Initial participants demonstrated better performance on a task of verbal abstraction than their Recent counterparts (WAIS Similarities: $t(436) = 2.709$, $p = .007$). Additional data regarding this comparison can be found in Table 1.

The disparity between databases on demographic and disease factors is likely a reflection of advancements in medical diagnosis and patient identification, and increasing variation in treatment strategies over time. These initial disparities between databases were not perceived as interfering with or confounding data analysis. Further, closer inspection of differences between groups based on neuropsychological performance reveals that some of the mean differences that are statistically significant, may not be clinically meaningful, i.e., the actual differences in performance scores are quite small and do not translate to clinically significant changes in cognition.

Of the 506 participants who met inclusion criteria, one hundred and forty-one participants completed the AES (Initial, $n = 67$; Recent, $n = 74$), while three hundred and sixty-five participants did not. The group that did not complete the AES performed more poorly on a global screening measure of mental status (MMSE: $t(287.1) = -2.987$, $p = .003$), and endorsed greater levodopa equivalent daily dose (LEDD: $t(119.6) = 2.005$, $p = .047$), than those who completed the questionnaire. The groups were similar on all other demographic and disease measures. In regard to neuropsychological performance, the group who did not complete the AES performed more poorly than those who completed the questionnaire on measures of semantic fluency (BNT: $t(403) = -2.140$, $p = .033$), visual recognition (BVRT: $t(319) = -4.531$, $p < .001$), visual discrimination (Ghent: $t(277.0) = -6.615$, $p < .001$), visual

orientation and integration (HVOT: $t(203.7) = -3.375$, $p = .001$), line orientation judgment (JLO: $t(215.3) = -3.242$, $p = .001$), naming (BNT: $t(403) = -2.140$, $p = .033$), auditory attention and working memory (WAIS Digits Backwards: $t(449) = -2.091$, $p = .037$), verbal abstraction (WAIS Similarities: $t(148.2) = -3.028$, $p = .003$), verbal recall for listed material (CVLT Total: $t(163) = -2.012$, $p = .046$), and long delay free recall (CVLT Long delay: $t(416) = -2.896$, $p = .004$). As mentioned previously, inspection of group means reveals that these statistically significant differences between groups based on neuropsychological performance may not be clinically meaningful. However, there is some indication that individuals who did not complete an AES and were excluded from further analyses comprise a more impaired sample. This is addressed in the *Limitations* section, but did not have a significantly adverse effect on the present findings. Additional information including group means can be found in Table 2.

Some measures differed between datasets. Only the Recent dataset contained medication information, tasks of psychomotor speed (Symbol Digit Modalities Test, Oral Trail Making Test), and psychosocial outcome measures (Parkinson's Disease Questionnaire, Lawton Instrumental Activities of Daily Living Scale, Katz Index of Independence in Activities of Daily Living, Caregiver Burden Scale). Therefore, for measures only contained in one of the two databases, distinctly smaller sample sizes were available for analysis (*see* Table I). In addition, the Initial dataset used the Zung Self-Report Anxiety Inventory to measure anxious symptomotology while the

Recent dataset used the Beck Anxiety Inventory. More information regarding these measures and the statistical precautions taken to address these differences are provided below (*see* Statistical Analyses).

The 141 subjects having met inclusion criteria and completed an AES were used in further analyses to investigate the formal aims of this study.

Neurologic Exam

Patients were evaluated by specialists at the University of Miami Movement Disorders Clinic and met criteria for idiopathic Parkinson's disease based on U.K. PD Brain Bank criteria (Hughes et al., 1993). Disease stage and severity as indicated by the Hoehn & Yahr scale (Hoehn & Yahr, 1967) was collected from neurologic reports of the referring physician.

Clinical Interview

All participants underwent a comprehensive interview and neuropsychological evaluation in the Division of Neuropsychology at the University of Miami. The clinical interview was conducted with each subject prior to testing in order to gather information regarding patient demographics (i.e., date of birth, age, gender, handedness, language), psychosocial history (e.g., education and employment), current cognitive, emotional and physical complaints, personal medical and psychiatric history, family medical and psychiatric history, substance use, medications, possible toxic exposures, and activities of daily living.

Information about disease course (i.e., date of symptom onset, date of formal diagnosis, symptom at onset, side of onset, and a description of current symptoms) was also collected via self-report.

Neuropsychological Examination

The neuropsychological evaluation consisted of a battery of tests shown to be clinically and empirically sensitive to the spectrum of cognitive functions often compromised in Parkinson's disease. The selected measures are standardized, published instruments that are commonly used for neuropsychological evaluations. They have been found to be valid and reliable (as reviewed in Strauss, Sherman, & Spreen, 2006) and are sensitive to neuropsychological decline in areas including language, memory, visuospatial skills, abstract reasoning, attention and executive function, mood and affect, quality of life, and disease and disability. The individual measures are described below by domain (also see *Figure 2*):

Language.

Boston Naming Test (BNT; Kaplan et al., 1983): A test of confrontational naming and word finding abilities in which the patient names objects in presented pictures. Semantic and phonemic cues may be provided to assess the severity of dysnomia. The number of spontaneously correct answers (including those with stimulus cues) on odd-numbered questions was used for analysis (odds administration- 30 points possible).

Wechsler Adult Intelligence Scale- Third Edition, Similarities subtest (WAIS-III-Similarities; Wechsler, 1997): This subtest of the WAIS-III evaluates verbal abstract reasoning, as defined by the ability to ascribe general commonalities between objects. Scaled scores for the measure were used for analysis.

Wechsler Adult Intelligence Scale- Third Edition, Digit Span- Longest Span Forward (WAIS-III Digits Forward; Wechsler, 1997): This subtest of the WAIS-III evaluates immediate auditory attention, as the subject must recite strings of numbers. For this measure, the greatest number of digits (length of span) successfully recalled in a forward manner is thought to be a reflection of general language skill, and was used for analysis as an indicator of the language construct.

Memory.

California Verbal Learning Test- Second Edition (Delis et al., 2000): A test of verbal learning, immediate and delayed recall, and recognition of verbal material. Variables used in the current study included total words recalled (CVLT-Total; sum of items correct on trials 1-5), and the number of correct items recalled on short and long delay free recall (CVLT-II-Short Free Recall; CVLT-Long Free Recall; respectively).

Benton Visual Retention Test (BVRT; Benton, 1974): A measure of visual memory, spatial perception, and visuoconstruction abilities in which the patient correctly identifies a previously presented figure out of four similar choices. Total number of items correct (out of 16) was used for analysis.

Visuospatial abilities.

Ghent Embedded Figures Test (Ghent, 1956): A task of visual discrimination; the stimuli include overlapping outlines of various pictures which the subject must identify. Total number of items correct (out of 36) was used for analysis.

Hooper Visual Orientation Test (HVOT; Hooper, 1983): In this test of visual rotation and integration, pictures are presented that have been cut into pieces and re-arranged on paper. The subject must mentally reorganize and identify the object as a whole. The number of items correct (out of 30) was used for this analysis.

Judgment of Line Orientation (JLO; Benton et al., 1978): A task of visual judgment and discrimination. Total score on odd-numbered questions was used for analysis (15 points possible).

Abstract Reasoning and Executive function.

Wechsler Adult Intelligence Scale- Third Edition, Digit Span- Longest Span Backward (WAIS-III Digits Backward; Wechsler, 1997): As mentioned previously, this subtest of the WAIS-III evaluates immediate auditory attention as the subject must recite strings of numbers. For this domain, the greatest number of digits (length of span) successfully recalled in a backward manner is a reflection of working memory, and was used for analysis as an indicator of the attention and executive function construct.

Controlled Oral Word Association Test (FAS/Animals; Benton & Hamsher, 1976): This test of verbal fluency and set maintenance asks the participant to name as many words as possible in a given phonemic or semantic category under a time constraint (1 minute). The total number of words given by the participant for the F-A-S trials and also the total number of words given for the semantic category of "animals" (not including repetitions and intrusions) were used for analysis.

Proverb Interpretation (Proverb; Gorham, 1956): A measure requiring the patient to identify the correct interpretation of common proverbs, e.g., "Never judge a book by its cover" given several possible construals. The subject receives two points for a correct answer which is abstract in nature, one point for a correct but concrete response, and zero points for incorrect answers. The total number of points earned (out of 20) was used for analysis.

Wisconsin Card Sorting Test- modified version (mWCST; Nelson, 1976, as modified from Grant & Berg, 1948, 1981; Manual- Heaton, 1993): In this test of mental flexibility, rule-finding, set maintenance and shifting, the subject must match cards to targets based on color, form (shape), or number given little prior instruction. The number of categories completed consisting of six consecutive correct responses was used for analysis (out of 6).

Processing & Psychomotor Speed

Symbol Digit Modalities Test (SDMT; Smith, 1973): A test of psychomotor speed administered in a written format where the participant matches numbers to specific symbols as if decoding a sequence. The number of correct responses in 90 seconds was used for analysis.

Oral Trail Making Test (as derived from Trail Making Test; Reitan, 1955; Ricker & Axelrod, 1994): A measure of cognitive speed and executive function in which the patient recites the alphabet and counts to 26 under timed conditions (Trails A), and then must alternate between letters and numbers in a similar fashion (Trails B). The time to complete each individual task (OTMT-A, OTMT-B) was used as an indicator of processing and psychomotor speed.

Self-report measures.

Additional measures included self-report inventories of depressive and anxious symptomotology (BDI-II: Beck Depression Inventory- Second Edition, Beck et al., 1996; Beck Anxiety Inventory, Beck et al., 1993; Zung Self-Rating Anxiety Scale, Zung, W., 1971), subjective cognitive dysfunction (FrSBe: Frontal Systems Behavior Scale, Grace & Malloy, 2002), neuropsychiatric symptoms (NPI-Q: Neuropsychiatric Inventory Questionnaire: Cummings et al., 1994), quality of life (PDQ: Parkinson's Disease Questionnaire, Jenkinson, C., Fitzpatrick, R., Peto, V., Greenhall, R., & Hyman, N., 1997), caregiver burden (CBS: Caregiver Burden Scale, Zarit, Reever, & Bach-Peterson, 1980), and independence in activities of daily living

(IADL: Lawton Instrumental Activities of Daily Living Scale, Lawton & Brody, 1969; KADL: Katz Index of Independence in Activities of Daily Living, Katz et al., 1970). Subjects received a total score for each questionnaire.

Apathy.

As previously stated, this study used the Apathy Evaluation Scale- Self-Report version (AES; see Appendix for questionnaire), developed by Marin et al. (1991). The questionnaire features 18 items with likert scale responses. Associations between each item and cognitive, behavioral, or emotional-type apathy have been proposed, and several factor structures have been identified (Marin et al., 1991; Clarke et al, 2007). The measure has been proven a valid and reliable measure and is regarded as the gold standard in apathy measurement (Marin et al., 1991, 1993; Clarke et al., 2007; Starkstein et al., 1992, 2001; Kirsch-Darrow et al., 2008).

Subscales of other measures were also used to assess apathy. These included the FrSBE Apathy- Before Illness and FrSBe Apathy- After Illness scales, and the NPI-Q Apathy item.

Medication data.

In the Recent database, information regarding prescribed medications was gathered from patient medical records. Calculations for levodopa-equivalent daily dose (LEDD) were derived from equations suggested by Hobson et al., (2002) and resulted in the following formula: levodopa = 1 (+ levodopa x .25 if taking tolcapone or entacapone); levodopa (continuous release) = .75 (+ levodopa x .25 if taking

tolcapone or entacapone); pramipexole = 67; ropinirole = 16.67; pergolide = 100; bromocriptine = 10; apomorphine = 10. This detailed formula allows for the estimation of levodopa dose across various medications with different mechanisms of action (e.g., levodopa, dopamine agonist, NMDA receptor agonist, etc.). Levodopa information was not available from the Initial dataset, therefore analyses conducted regarding LEDD reflect the Recent dataset only.

Statistical Analysis

This study includes multiple aims and hypotheses. Prior to analysis all variables were evaluated for normality and homoscedascity of residuals, and appropriate corrections (e.g., natural log transformation) made for skewness (> 3) and kurtosis (> 10) as suggested by Kline (1998). Descriptive characteristics of all variables were provided using Statistical Package for the Social Sciences© (SPSS) version 16.0.

In addition, some analyses were designed using structural equation modeling (SEM) and conducted using statistical program M*plus*© version 5.1 and demo version 5.2 (Muthén & Muthén, 2007). Within M*plus*, analyses included confirmatory factor analysis, and correlation and regression analysis. Model fit was assessed using Chi-Square Test of Model Fit ($p \geq .05$), CFI/TLI indices ($\geq .95$), Root Mean Square Error of Approximation (RMSEA; $\leq .06$) and the Standardized Root Mean Squared Residual ($\leq .09$). Proper post-hoc procedures will also be taken to further elucidate

findings. **Please note, caution should be taken when inferring directionality from results of regression analyses, as the data sample is cross-sectional in nature.**

In order to address *Aim 1*, "To further define the presentation of apathy in PD using the AES," several analyses were conducted. First, the validity of the AES total score was explored through correlational analyses, using other apathy measures as indicators of convergent validity (FrSBe- Apathy- After Illness scale; NPI-Q Apathy item).

To further demonstrate the validity and generalizability of the data, an attempt was made to replicate exisiting findings with the present sample. A cutoff for clinical apathy was determined based on previous findings in the literature. Marin et al., 1991, reported a cutoff of 37.5 which was two standard deviations above the mean, while a more recent study found a cutoff of 36.5 for the AES- Self Report version (Clark et al., 2007). For this study, the latter cutoff was selected. Patients with a total score greater than or equal to 36.5 were deemed to have clinical apathy (AP). An independent samples *t*-test was then used to compare those with apathy (AP) to those without (NoAP) on demographic, disease, and neuropsychological measures to document a profile of cognitive impairment in Parkinson's individuals.

Before moving forward to establish a factor structure of the AES consistent with Marin's classification and suggested by other literature, (*Aim 1b)*, an item analysis was conducted to establish internal consistency, using Cronbach's alpha coefficient as an indicator. Results informed which individual items would be included in further analyses; those that increased reliability if deleted were excluded. Next, using structural equation modeling and confirmatory factory analysis, a factor

structure was imposed on the AES. The scale was divided into Cognitive, Behavioral, Emotional, and Other latent domains, as suggested by item coding included in Marin et al., 1991, with individual items as indicators. Tentatively (i.e., pending results of the item analysis), the cognitive latent would be indicated by item # 1, 3, 4, 5, 8, 11, 13, and 16; the behavioral domain would be indicated by item # 2, 6, 9, 10, and 12; the emotional domain would be indicated by item # 7, and 14; and the other domain would be indicated by item # 15, 17, and 18. As stated previously, model fit was assessed using Chi-Square Test of Model Fit, CFI/TLI indices, Root Mean Square Error of Approximation, and the Standardized Root Mean Squared Residual. Modification indices that were compatible with, and supported by, current thinking and theory were employed.

The purpose of *Aim 2* was to define the relationship between domains of neuropsychological function and the three apathy subtypes. First, each domain was modeled as a latent variable with specific cognitive measures as indicators:

Cognitive Latent	**Neuropsychological Indicators**
Language	Boston Naming Test (BNT) WAIS-III- Similarities (WAIS- Similarities) WAIS-III-Digit Span, Longest Span Forward (WAIS-Digits Forward)
Memory	California Verbal Learning Test-II Total (CVLT-Total) California Verbal Learning Test- Short delay free recall (CVLT-Short Free Recall) California Verbal Learning Test- Long delay free recall (CVLT-Long Free Recall) Benton Visual Retention Test (BVRT)
Visuospatial Skills	Judgment of Line Orientation (JLO) Ghent Embedded Figures Test (Ghent) Hooper Visual Orientation Test (HVOT)
Attention and Executive Function	WAIS-III- Digit Span, Longest Span Backward (WAIS-Digits Backward) Modified Wisconsin Card Sorting Test (mWCST) Proverb Interpretation (Proverb) Controlled Oral Word Association Test (FAS, Animals)
Processing and Psychomotor Speed	Oral Trail Making Test- Trails A time (OTMT-A) Oral Trail Making Test- Trails B time (OTMT-B) Symbol Digit Modalities Test (SDMT)
Mood	Beck Depression Inventory- Second Edition- total score (BDI) Neuropsychiatric Inventory- Dysphoria subscale total score (NPI-Q-Dys)

Measures that were part of a single overarching test (i.e., CVLT total, short delay free recall, long delay free recall, and FAS and Animals) were correlated. In the event of a saturated model (in which the number of free parameters exactly equals the number of known values; three or less indicators), then the strengths of the individual indicator loadings were assessed rather than model fit.

Next, the relationship between the second-order CFA of apathy confirmed in *Aim 1* and the latent models of neuropsychological domains in *Aim 2* above, were explored through regression analysis. However, as previously mentioned, due to the cross-sectional nature of the current data, it is difficult to infer directionality and interpretations should be guarded accordingly. The results from *Aim 1* informed this analysis. If the cognitive, behavioral, and emotional apathy domains were found to be highly correlated, then the domains of neuropsychological functioning would be examined in relations to the second-order AES latent. However, if they were sufficiently independent, then the relationship between neuropsychological function and the *individual* domains of apathy would be explored.

Finally, as part of *Aim 3,* several additional regressions were carried out within the SEM framework. First, demographic and disease variables including gender, education level, side onset, symptom at onset, disease duration, disease stage, and LEDD were examined as predictors of the apathy latent. In addition, the influence of apathy on psychosocial factors such as quality of life, caregiver burden, and activities of daily living (as measured by the Parkinson's Disease Questionnaire, Caregiver Burden Scale, Katz Index of Independence in Activities of Daily Living,

and Lawton Instrumental Activities of Daily Living Scale, respectively) were explored through individual regression analyses. Due to a smaller amount of available data regarding these outcomes (only individuals in the Recent database were administered these measures), model estimates including loadings, variances, residuals, intercepts, and correlations were fixed according to the final model confirmed in *Aim* 1. Therefore, the regression equation was evaluated instead of model fit.

In sum, the analyses as outlined above are expected to confirm and extend prior research on apathy in PD. This study will address key issues related to the reliability and validity of the AES, and identify the theoretical cognitive, emotional, and behavioral subtypes of apathy. In addition, neuropsychological correlates of apathy and the proposed subtypes will be explored. Finally, this study will examine the relationship between apathy and disease, demographic and psychosocial variables.

Chapter 8: Results

Revisions

Given that findings from earlier analyses directly influenced later methodology, it was necessary to make the following revisions to the original aims:

Aim 1a

The NPI-Q- Apathy item did not sufficiently correlate with the AES or other apathy measures. After discussion with the statistician it was decided that single items did not have appropriate power to be included in analyses. Therefore, single item measures from the NPI-Q were dropped from further exploration.

Aim 1b

Results of the confirmatory factor analysis revealed three highly correlated factors (Cognitive/Emotional with Behavioral, $r = .813$; Cognitive/Emotional with Other, $r = .853$; Behavioral with Other, $r = .833$). Therefore, further examination of the relationship between disease, demographic, neuropsychological variables and the apathy construct were conducted in relation to the second-order apathy latent, instead of individual apathy factors.

Aim 2- Hypothesis 2

Indicators of the Processing and Psychomotor Speed domain (Proc/Psych Speed) initially included subscores from the Oral Trail Making Test (OTMT-A and

OTMT-B) and performance on the Symbol-Digit Modalities test. However due to sample size limitations and poor fit of the measurement model (only two of the three indicators loaded significantly), this hypothesis could not be examined.

Aim 2- Hypothesis 3

The proposed Mood domain was to be indicated by the Beck Depression Inventory and the dysphoria item from the Neuropsychiatric Inventory Questionnaire (NPI-Q). As described above, single item measures from the NPI-Q were dropped from further exploration. This left the BDI measure as the only indicator of the mood latent. Therefore, the BDI was instead handled as an observed variable, and not as an indicator of a latent. Apathy was examined as a predictor of the BDI to address this aim.

Aim 3

The contents of *Aim 3* remain unchanged. However, *Aim 3 Hypothesis 1* and *Hypothesis 2* will be discussed earlier in the text since they address predictors of apathy that will be controlled for in later analyses. **The organization of the results section reflects this logical progression of findings.**

Results

Sample Characteristics

One hundred and forty-one participants met inclusion criteria and completed the AES (Initial, $n = 67$; Recent, $n = 74$). Of those 141 subjects, participants from the Initial database were significantly older at the time of exam ($t(139) = -3.906$, $p < .001$) and at the age of diagnosis ($t(138) = -3.896$, $p < .001$), and more likely to be non-Hispanic ($X^2(2, N = 130) = 19.791$, $p < .001$) compared to those from the Recent dataset. The groups were similar on all other disease and demographic factors. There were no significant differences in global mental status, levels of apathy, or depression.

In regard to neuropsychological measures, controlling for age at exam, subjects from the Initial dataset demonstrated significantly stronger performance on tasks of verbal abstraction (WAIS- Similarities: $F(1, 102) = 27.067$, $p < .001$), immediate auditory attention (WAIS- Digits Forward: $F(1, 110) = 5.454$, $p = .021$), working memory (WAIS- Digits Backward: $F(1, 110) = 5.983$, $p = .016$), and verbal fluency (FAS: $F(1, 90) = 4.726$, $p = .032$) compared to those from the Recent dataset (see Table 3).

As previously addressed, the disparities between databases on demographic and disease factors are likely due to advancements in medical diagnosis and patient identification, and increasing variation in treatment strategies over time. Despite these differences, the combined sample of 141 individuals from both the Initial and Recent dataset comprise a well-rounded and representative sample of individuals throughout the spectrum of Parkinson's disease and related symptomatology (demographic and

disease characteristics are provided in Table 4), therefore initial disparities between databases were not perceived as interfering with or confounding data analysis. Closer inspection of differences between groups based on neuropsychological performance also reveals that some of the mean differences that are statistically significant, may not be clinically meaningful or represent significant functional differences.

Several additional analyses were conducted to more fully characterize the present sample. Using established cutoff scores of 36.5 for the AES (Clarke et al., 2007), and 13.0 for the BDI-II (Beck et al., 1996), the total sample was comprised of 50 individuals (47.2%) with no apathy or depression, 12 with apathy but no depression (11.3%), 26 with depression but no apathy (24.5%), and 18 subjects with both apathy and depression (17.0%). Next, an additional analysis explored the relationship between ethnicity and apathy. For those individuals with ethnicity data (n = 127, 90.1% of the total sample), it was found that 19 Hispanic patients completed the AES in addition to 108 Non-Hispanic patients (ethnicity was restricted to these two majority groups for this analysis). In general, there was a trend for Hispanic patients to have higher mean scores on the AES ($t(20.825) = 1.928$, $p = .068$), and they were also significantly more likely to meet cutoff criteria for clinical apathy compared to Non-Hispanic patients (Hispanic: 52.6% met criteria for clinical apathy; Non-Hispanic: 27.8% met criteria for clinical apathy; $X^2(1, N = 127) = 4.626$, $p = .031$). The Hispanic patients were significantly younger at the age of exam ($t(125) = -1.779$, $p = .078$) and demonstrated a trend for having a younger age of disease onset ($t(30.805) = -1.999$, $p = .055$). Hispanic patients also performed more poorly than the Non-Hispanic group on cognitive measures of language including confrontation

naming (BNT: $t(99) = -3.502$, $p = .001$), verbal abstraction (WAIS-Sim: $t(97) = -2.393$, $p = .019$), verbal learning (CVLT-Total: $t(99) = -2.153$, $p = .034$) and phonemic fluency (FAS: $t(83) = -1.977$, $p = .051$), in addition to measures of immediate auditory attention (WAIS-DS-Forward: $t(102) = -2.488$, $p = .014$) and working memory (WAIS-DS- Backward: $t(102) = -3.086$, $p = .003$). While ethnic differences between groups in the presentation of apathy is not the primary focus of the current study, these findings warrant future attention and more comprehensive research. Given that Hispanic patients comprised only a minority of the current sample these findings were not thought to considerably impact or alter the interpretation of the current findings.

Preliminary Analyses: Validity of the AES in a Parkinson's sample (Aim 1a)

Correlational analyses indicated that AES total scores were significantly positively correlated with the FrSBe Apathy-After Illness scale ($r(38) = .358$, $p = .023$), but not with the FrSBe Apathy- Before Illness scale ($r(40) = .024$, $p = .879$).

In order to replicate existing findings with the present sample, a cutoff for clinical apathy using the AES was assigned at a total score of 36.5 based on previous findings (Marin et al., 1991; Clarke et al., 2001). An independent sample *t*-test of individuals with clinical apathy (AP, $n = 43$) and those not meeting this threshold (NoAP, $n = 98$) revealed no differences between groups based on disease, demographic, or medication variables, except for a statistical trend indicating that subjects without apathy were likely to have greater education than individuals with apathy ($t(113) = 1.938$, $p = .055$). Controlling for education, the AP group was found

to perform more poorly on tests of visual rotation and integration (HVOT: $F(2,94) = 4.689$, $p = .033$) and verbal phonemic fluency (FAS: $F(2,91) = 3.929$, $p = .051$), compared to the NoAP group. The AP group also endorsed greater depression (BDI: $F(2,103) = 7.794$, $p = .006$), and there was a trend for caregivers of the AP group to report greater caregiver burden (CBS: $F(2,23) = 3.961$, $p = .060$) than caregivers of the NoAP group (see Table 5).

Medication data was available for patients from the Recent dataset. Table 6 provides this information for those with and without apathy. Using a rigorous formula derived from previous research (see Methods), levodopa-equivalent daily dose (LEDD) was calculated. There was no difference in LEDD between NoAP and AP groups. In addition, no differences were observed when NoAP and Ap groups were compared on other parkinsonian medications (i.e, L-dopa, dopamine agonists, NMDA receptor agonists, anticholinergics, COMT-inhibitors, MAO-B inhibitors, cholinesterase inhibitors) and other psychotropics (e.g., selective seratonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, etc.).

Item Analysis (Aim 1b)

An item analysis of the AES produced a Cronbach's alpha coefficient ($r = .901$) that indicated a high degree of internal consistency among the 18 items. There was evidence for low item variability and strong item correlations with the total score. However, results also indicated that removal of three items resulted in an increase in scale reliability in this population. These three items, #6, 10, and 11, use more

syntactically complex language and grammar (i.e., double-negatives) and are reverse-coded by the clinician for scoring. These items were removed from further analyses. Complete data for the item analysis can be found in Table 7.

Confirmatory Factor Analysis (Aim 1b)

A confirmatory factor analysis was conducted using Marin et al.'s (1991) classification of "Cognitive", "Behavioral", "Emotional", and "Other" items. Latent variables were created for each domain (e.g., Cognitive, Behavioral, Emotional, and Other) with individual scale items as indicators. The three reverse-coded items that decreased scale reliability (item # 6, 10, 11) were excluded. This beginning model is illustrated in Figure 2. The chi-square test suggested poor model fit ($\chi^2 = 227.096$, $df = 86$, $p < .001$, RMSEA = 0.198, SRMR = 0.059), therefore several revisions to the model were made using modification indices with theoretical support. In particular, several correlations were specified between indicators (e.g., "I have friends" and "Getting together with friends is important to me"). Modification indices also suggested that questionnaire item #1 could indicate Behavioral and Emotional latents in addition to the Cognitive factor, therefore it was dropped from the analysis due to cross-loading. Finally, statistical warnings indicated very high correlations between latent variables (Emotional with Cognitive, $r = 1.011$; Cognitive with Other, $r = .866$; Emotional with Other, $r = .834$; Behavioral with Other, $r = .832$; Cognitive with Behavioral, r = .828; Emotional with Behavioral, $r = .785$). Since the Cognitive and Emotional latent variables demonstrated the greatest association, they were combined. The final model, using Marin's descriptors, then had three factors-

Cognitive/Emotional, Behavioral, and Other. All indices demonstrated that the proposed final model fit the empirical data well ($\chi^2 = 72.751$, $df = 70$, $p = .3876$; CFI/TLI = .997/.997; RMSEA = .017; SRMR = .036). Variance explained (R^2) by the Cognitive/Emotional, Behavioral, and Other latent variables were 83.3%, 79.3%, and 87.4%, respectively. The final model is illustrated in Figure 3. While factors remained highly correlated (Cognitive/Emotional with Behavioral, $r = .813$; Cognitive/Emotional with Other, $r = .853$; Behavioral with Other, $r = .833$), this model was superior in fit relative to the combination of other domains, or the loading of all indicators onto one latent ($\chi^2 = 144.681$, $df = 86$, $p < .001$, CFI/TLI = .949/.937, RMSEA = .070, SRMR = .047). The final model represents three correlated but distinct factors of apathy in our Parkinson's sample. **Given that this second-order model represented a revised or modified version of the AES, it will be referred to as R-Apathy from this point forward.**

The association between R-Apathy and other apathy measures was explored. There was a trend for R-Apathy to predict the FrSBe Apathy- After Illness scale ($\beta = 2.918$, S.E. = 1.653, $z = 1.766$). R-Apathy did not predict the FrSBe Apathy -Before Illness scale ($\beta = -0.257$, S.E. = 1.154, $z = -0.222$), which would be expected to diverge.

Demographic and disease correlates of R-Apathy (Aim 3, Hypothesis 1 and 2)

Demographic and disease factors including gender, education (years), side of PD symptom onset, symptom at PD onset (tremor vs. non-tremor), disease duration, disease stage (Hoehn & Yahr), and levodopa-equivalent daily dose (LEDD) were

examined as predictors of R-Apathy (Reminder: data is cross-sectional, use caution when inferring directionality). When all measures were entered together, there was a significant association between education and R-Apathy (β = -0.100, S.E. = 0.044, z = -2.245), with individuals with lower education demonstrating increased apathy. Therefore, education was held as a covariate for further analyses. Aspects of hypothesis 1 were not upheld, i.e., side of symptom onset, symptom at onset, and current disease stage (H&Y) were not significantly associated with R-Apathy. See Figure 4 and Table 8 for full regression model and results, respectively.

Modeling Neuropsychological Domains (Aim 2)

Each neuropsychological domain was modeled as a latent variable with specific cognitive measures as indicators. The Language domain was indicated by performance scores on the Boston Naming Test (BNT), the WAIS- Similarities subtest, and the WAIS- Digit Span digits forward measure. The model was saturated (i.e., just-identifed; in SEM a model in which the number of free parameters exactly equals the number of known values, resulting in zero degrees of freedom) and could not be evaluated for model fit, however each indicator loaded significantly onto the Language latent (BNT: λ = .582; WAIS-Sim: λ = .615; WAIS-DS-LSF: λ = .492; for all values, $p < .001$).

The Memory domain was indicated by performance scores on tests of verbal and visual memory (i.e., CVLT-II-tot, CVLT-II-sf, CVLT-II-lf, BVRT). Correlations

were specified between the three CVLT scores. Each indicator loaded significantly onto the Memory latent (CVLT-II-Tot: $\lambda = .938$; CVLT-II-sf: $\lambda = .921$; CVLT-II-lf: $\lambda = .926$; BVRT: $\lambda = .548$; for all values, $p < .001$). The chi-square test and other indices demonstrated good model fit ($\chi^2 = 5.002$, $df = 2$, $p = .082$; CFI/TLI = .992/.975; RMSEA= .116 ; SRMR = .020).

Tests of line orientation judgment (JLO), visual discrimination (Ghent) and visual rotation and integration (HVOT) were used as indicators of the Visuospatial domain. Again, the model was saturated and could not be evaluated for model fit, however each indicator significantly loaded onto the Visuospatial latent (JLO: $\lambda = .486$; Ghent: $\lambda = .784$; HVOT: $\lambda = .878$; for all values, $p < .001$).

The cognitive domain of Attention and Executive Function (Att/Exe) was indicated by several tests including WAIS-DS backwards (WAIS-DS-LSB), the Wisconsin Card Sort Test (mWCST), Proverb Interpretation (Proverb), and verbal fluency tasks (FAS, Animals). A correlation was specified between FAS and Animals as they are from the same test (COWAT). Each indicator loaded significantly onto the Att/Exe latent (WAIS-DS-LSB: $\lambda = .429$; mWCST: $\lambda = .681$; Proverb: $\lambda = .614$; FAS: $\lambda = .756$; Animals: $\lambda = .637$, for all values, $p < .001$) and the overall model demonstrated good fit ($\chi^2 = 5.397$, $df = 5$, $p = .3693$; CFI/TLI = .996/.992; RMSEA = .026; SRMR = .032).

Full illustration of the four cognitive domains successfully modeled as latent constructs (i.e., Language, Memory, Attention and Executive Function, and Visuospatial Skills) can be found in Figure 5. When latent variables for all neuropsychological domains were examined together, a high correlation was found

between the Attt/Exe domain and other cognitive latents (Language: (r = .870); Memory: (r = .932); Visuospatial: (r = .813) underscoring some contribution of executive function to skills in many domains. In order to isolate the domains we have outlined, each latent was examined individually in relation to R-Apathy.

Relationship Between Neuropsychological Domains and R-Apathy (Aim 2)

To study the association between domains of neuropsychological function and the apathy construct, R-Apathy was examined as a predictor of each individual cognitive domain. Education was included as a covariate in all models.

Using a regression model within the SEM framework, R-Apathy was not significantly associated with performance on tasks of Language (β = -0.084, S.E. = 0.149, z = -0.564) or Memory (β = -0.126, S.E. = 0.109, z = -1.151) (see Figures 6 and 7).

R-Apathy was found to significantly and negatively predict the Attention and Executive Function latent (β = -0.277, S.E. = 0.124, z = -2.224). The overall model demonstrated excellent fit (χ^2 = 173.463, df = 160, p = .2208; CFI/TLI = .988/.986; RMSEA = .024; SRMR = .062). A diagram illustrating all parameters can be found in Figure 8.

The Visuospatial latent was also significantly negatively associated with R-Apathy. The model indicated good fit (χ^2 = 150.295, df = 126, p = .0690; CFI/TLI = .979/.974; RMSEA = .037; SRMR = .061) and the regression of R-Apathy predicting Visuospatial was significant (β = -0.243, S.E. = 0.118, z = -2.061; see Figure 9).

Finally, the models that illustrated significant associations between R-Apathy, i.e., Att/Exe and Visuospatial skills, were combined (see Figure 10). R-Apathy was significantly related to Atte/Exe (β = -0.251, S.E. = 0.127, z = -1.979), and there was a trend for an association with Visuospatial skills (β = -0.219, S.E. = 0.124, z = -1.760). All indicator loadings were also significant (All λ values > .400, p < .001) and the overall model demonstrated sufficient fit on multiple indices (χ^2 = 260.652, df = 217, p = .0227; CFI/TLI = .967/.962; RMSEA = .038; SRMR = .073).

Apathy and Depression (Aim 2 Hypothesis 3)

In the current sample, depression (total BDI score) and apathy (total AES score) were highly and significantly positively correlated (r(106) = .499, p < .001). Several analyses were conducted to further define the relationship of depression to R-Apathy and neuropsychological correlates. First, it was found that R-Apathy significantly predicted depression controlling for education (β = 4.116, S.E. = 0.786, z = 5.236, r = .505), and the overall model demonstrated good fit (χ^2 = 112.558, df = 96, p = .1190; CFI/TLI = .985/.981; RMSEA = .035; SRMR = .048; see Figure 11).

Because of the significant relationship between apathy and depression, earlier analyses were repeated with depression as a covariate, in addition to education. With both variables as covariates, similar findings were observed; R-Apathy significantly predicted the domains of Att/Exe (β = -0.297, S.E. = 0.129, z = -2.305; χ^2 = 202.335, df = 177, p = .0931; CFI/TLI = .979/.975; RMSEA = .032; SRMR = .066) and Visuospatial skills (β = -0.245, S.E. = 0.119, z = -2.065; χ^2 = 171.072, df = 141,

p = .0430; CFI/TLI = .975/.969; RMSEA = .039; SRMR = .064) (see Figure 12 and 13*)*. Further, a combined model (see Figure 14) with R-Apathy predicting both Att/Exe and Visuospatial skills while covarying education and depression, revealed a significant association between R-Apathy and Att/Exe (β = -0.253, S.E. = 0.131, z = -1.938) and a trend for R-Apathy predicting Visuospatial skills (β = -0.202, S.E. = 0.126, z = -1.602). While the Chi-Square test of model fit indicated suboptimal fit, several other indices suggested a more cohesive model (χ^2 = 292.833, df = 236, p = .0068; CFI/TLI = .958/.951; RMSEA = .041; SRMR = .074). It is possible that with a larger sample size the relationship between variable and overall model fit might be improved.

Psychosocial Measures and R-Apathy (Aim 3, Hypothesis 3)

The association of apathy with variables such as quality of life (PDQ), activities of daily living (KADL and IADL), and caregiver burden (CBS) was explored. In these regression models, all loadings, variances, residuals, intercepts, and correlations of the second-order latent model of R-Apathy were constrained due to small sample size for the outcome measures. Only the regression path was tested, and model fit could not be examined. Education was included as a covariate and each outcome was entered individually.

Greater R-Apathy significantly predicted decreased quality of life as measured by the PDQ, where a higher score indicates increased impairment (β = 11.675, S.E. = 4.859, z = 2.403; see Figure 15). However, when depression is also a covariate, R-Apathy is no longer associated with quality of life, likely due to the high correlation

between depression and the quality of life measure (β = 1.546, S.E. = 4.248, z = 0.364; BDI and PDQ: r = .709; see Figure 14). R-Apathy was not significantly associated with basic or complex activities of daily living (KADL: β = 0.060, S.E. = 0.290, z = 0.207; IADL: β = -0.395, S.E. = 0.447, z = -0.884; respectively), or caregiver burden (CBS: β = 4.589, S.E. = 3.207, z = 1.431). Therefore, when controlling for both education and depression, Aim 3 Hypothesis 3 is not supported. Full regression results are summarized in Table 9.

Chapter 9: Discussion

The first step of this investigation was to show that the AES is a valid and reliable measure of apathy in PD. This study confirmed convergent and discriminant validity by demonstrating a significant association with a measure of self-report apathy following PD diagnosis, and no observed relationship with a measure of apathy before illness, respectively. These findings provided support for the use of the AES in the current study.

Investigation of Theoretical Apathy Factors

This study established a factor structure for apathy in PD, which includes Cognitive/Emotional, Behavioral, and Other domains (R-Apathy). The questionnaire items within each factor may be interpreted as reflecting internally generated mental engagement, active initiation and participation directed into the external environment, and self-perception, respectively (see Table 10). While the factors are highly correlated, the findings, nevertheless, are important. The final model demonstrated good statistical fit and was significantly better than other model variants. These findings represent distinct, albeit correlated, factors of apathy in a PD sample. This revised model that includes the removal of confounding questionnaire items and introduction of novel factors (Cognitive/Emotional, Behavioral, and Other), demonstrated sufficient validity.

In contrast, the original hypothesis that the AES could be divided into independent Cognitive, Behavioral, Emotional, and Other domains, as suggested in previous research was not supported. There are several possible explanations. First,

it may be that there is not a clear-cut distinction between cognitive, behavioral, and emotional manifestations of apathy in PD as suggested by prior authors (Marin et al., 1991; Levy & Dubois, 2006; Levy & Czernecki, 2006) or that exists in other disorders (e.g., Alzheimer's disease, TBI, Frontotemporal dementia). Rather, apathy in PD (as measured by the AES) may present or be defined as a combination of cognitive and emotional items that together reflect internally generated forms of mental engagement, and behavioral items representing active initiation and participation that are directed into the external environment. In other words, the cognitive/emotional factor of apathy may correspond to cognitive processes such as slowing (bradyphrenia) and mental disengagement, while motor difficulties such as tremor that interfere with outward physical functioning may comprise the behavioral apathy presentation.

The confirmation of a factor structure of apathy in PD including cognitive/emotional and behavioral factors also has implications for understanding its etiological basis. It is possible that the current delineation of apathy subtypes mirrors the contribution of different neurotransmitter systems. It may be that internally generated forms of engagement are partly mediated by non-dopaminergic pathways such as cholinergic networks, a finding reported in literature linking apathy and cognitive dysfunction. Likewise, behavioral apathy may be influenced by tremor-dominant motor symptoms associated with dopaminergic networks. As a caveat, some motor symptoms that are non-dopaminergic in nature (bradykinesia, postural instability) have also been associated with greater cognitive decline. Further projects mapping these apathy groups onto motor subtypes and neurotransmitter systems are

needed, and may yield enlightening results. Given the above neurotransmitter hypothesis, we would predict that the cognitive/emotional apathy factor would be most highly correlated with non-dopaminergic-based cognitive dysfunction and non-tremor dominant presentations, while the behavioral factor would be associated with tremor-dominant (dopaminergic) subtypes.

An additional hypothesis of the current study was that the observed apathy (i.e., AES) factors could be linked to cognitive inertia, emotional-affective apathy, and auto-activation, concepts proposed by Pluck & Brown (2002). Upon close inspection, the concept of cognitive inertia appears compatible with our Cognitive/Emotional factor and its association with cognitive impairment in executive and visuospatial functioning. Emotional-affective apathy may also reflect a form of mental disengagement and reduced reactivity to emotional stimuli represented by items in the Cognitive/Emotional factor. Both cognitive inertia and emotional affective apathy involve prefrontal cortical areas, implicated in higher-order cognitive functions. The concept of auto-activation could not be fully assessed in the current study due to a lack of measures for basic reactivity and autonomic function. Further, the present sample may not be ideal for examining this hypothesis since auto-activation refers to a severe form of apathy characterized by mental emptiness and a complete lack of self-initiated cognition and movement, features that were clearly not present in our sample.

In the process of establishing a factor structure for the AES in the present sample, this study was the first to identify three questionnaire items (i.e., item # 6, 10, 11) that represent potential sources of confound when the AES is implemented in a

PD sample. These items are syntactically more complex and therefore more difficult for those with cognitive impairments. For example, question #6 states "I put little effort into anything," and the patient must endorse "not at all," "slightly," "somewhat", or "a lot." If they are experiencing apathy they should choose the response "a lot," although this is opposite to the response pattern from all other items. These items are also reverse-coded, leaving the opportunity for clinician errors in the scoring process if they are not familiar with the protocol. Given these results, it is recommended that clinicians use caution when administering the protocol and consider highlighting the ambiguous items for the patient/participant in order to prevent misinterpretation.

Psychosocial and Neuropsychological Correlates of Apathy

Having established a novel and valid factor structure for apathy in PD, referred to as R-Apathy, neuropsychological correlates of the model could be further examined using SEM. The SEM model is a novel statistical tool for the study of apathy as it allows the researcher to model apathy as a continuous variable, and to remove measurement error from apathy and neuropsychological constructs. SEM permitted for the exploration of a number of demographic and disease variables which could potentially contribute to an apathy presentation.

Education was found to be significantly associated with the R-Apathy construct. Existing studies have demonstrated the protective nature of educational attainment against cognitive impairment, and have also demonstrated a relationship between lower education and greater prevalence of hallucinations, depression,

delusions, and sleep disturbances (Cohen et al., 2007; Stern, 2009). However, this study is the first to find a significant association between education and apathy presentation. It is possible that this relationship exists due to the high correlation between apathy and cognitive impairment. Another explanation may be that there is such thing as "motivational reserve", a term related to its "cognitive reserve" counterpart (Katzman et al., 1988; Stern, Gurland, Tatemichi, Tang, Wilder, & Mayeux, 1994; Stern, 2009). An individual with greater educational attainment may be more able to recruit cognitive, emotional, and behavioral systems allowing the individual to remain engaged and compensate for increasing amotivational factors, in turn masking the presence of apathy.

The relationship of apathy and depression as highly correlated but also distinct constructs is well documented in the literature (Kirsch-Darrow et al., 2006; Levy et al., 1998; Levy & Dubois, 2006; Marin, 1993; Starkstein et al., 1992, 2001). This study confirmed a high association between apathy and depression, but also demonstrated differentiation between groups. In the present sample, of those individuals completing both apathy and depression questionnaires, 50 did not endorse apathy or depression (47.2%), 12 had apathy but no depression (11.3%), 26 had depression but no apathy (24.5%), and 18 met criteria for both depression and apathy (17.0%).

R-Apathy was found to be significantly and negatively associated with performance on tasks of attention and executive function, and visuospatial skills. More specifically, apathy was associated with skills of executive function including verbal fluency (FAS), problem-solving, set-maintenance and shifting (WCST), verbal

abstraction (Proverbs), and working memory (WAIS-III Digit Span Backwards). These findings are consistent with previous research documenting executive dysfunction in apathetic patients in a variety of neurodegenerative disorders (Dujardin, Sockeel, Delliaux, Destee, & Defebvre, 2009; Pluck & Brown, 2002; Zgaljardic, 2007; Starkstein, 1002, 2001). It is clear that those with apathy have more difficulty on tasks requiring rapid retrieval, problem-solving, working memory, and higher order processing. They may need additional assistance in making health care decisions, require greater supervision, and may be more dependent on others for completing basic and instrumental activities of daily living. Given the strong association between apathy and executive function, several authors have previously suggested the existence of a subgroup of nondemented PD patients with significant levels of apathy and associated executive dysfunction. In short, apathetic individuals with PD may have a distinct profile of cognitive decline involving executive dysfunction from early in the disease process (Zgaljardic et al., 2007; Pluck & Brown, 2002; Starkstein, 2001). The present findings support this concept.

Furthermore, apathy was associated with visuospatial abilities. This finding is not completely unexpected, given that most visuospatial tasks also have a large executive component, requiring mental manipulation and higher-order processing. Visuospatial skills are integral for a variety of everyday activities including mental imagery, navigation, distance and depth perception, and visuospatial construction. Without these faculties, one might become easily disoriented, have difficulty driving, and make visual misperceptions. Together, these results suggest that the presence of apathy is a marker for possible impairment in executive function and visuospatial

skills- both of which are important to an individual's global functioning. Each is also common in early PD and plays a role in later expression of Parkinson's disease dementia (Levin & Katzen, 1995; Mohr, Mendis, & Grimes, 1995; Muslimovic, Post, Speelman, & Schmand, 2005; Muslimovic et al., 2007; Brown & Marsden, 1986; Cooper, Sagar, Tidswell, & Jordan, 1994; Lees & Smith, 1983; Taylor et al., 1990). Further, recent studies have found apathy to be a predictor and possible early marker of the dementing process (Dujardin et al., 2009). The role of apathy as a catalyst in progression towards dementia is also an area of interest. While the individual measures used to tap into specific cognitive domains varies between studies, these findings confirm previous research regarding the general relationship between apathy, executive function and visuospatial skills, and provides information on additional measures that may be sensitive to the presence of apathy. It is important to note that although these analyses controlled for both education and depression, associations between apathy and areas of cognitive impairment remained. Hence, apathy was associated with specific areas of cognitive impairment not explained by depressive symptomatology. Given the above findings, clinicians should remain vigilant for signs of cognitive impairment in patients with apathy, and provide recommendations accordingly.

In contrast, no relationship was observed between R-Apathy and language and memory domains, suggesting that apathy is selectively associated with executive and visuospatial functioning. There are also several alternative explanations. First, language and memory difficulties are generally thought to occur later in the disease process and secondary to executive dysfunction. The average disease stage of the

present sample was a moderate 2.45 (H&Y); therefore deficits in language and memory may not yet be evident in this group. Second, executive deficits are thought to be the predominant cognitive dysfunction in PD and therefore they may have masked or minimized the appearance of other relationships. Finally, the measures selected to represent the language and memory domains may have been less sensitive to impairment or prompted the recruitment of additional faculties to complete. For example, it has been qualitatively observed that the CVLT (verbal memory measure) appears more difficult to the patient at face value, and they therefore may recruit additional strategies, focus, and motivation for the test, ultimately improving performance. This in turn may have masked more minimal deficits.

While apathy and education were found to be highly related, the hypothesis that other demographic and disease factors such as left-sided motor onset, non-tremor onset, and older age of disease onset would be associated with apathy, was not supported. Further investigation of each of these variables as independent predictors of apathy, and possible interaction between measures is warranted. With regard to symptom onset, and in accordance with the above proposed hypotheses (i.e., that cognitive impairment may be associated with non-tremor (non-dopaminergic-dominant) symptom presentation), one might have expected a greater relationship between non-tremor onset and apathy. In addition, previous research has shown that those patients with left-side, non-tremor symptom onset (i.e., bradykinesia and rigidity) demonstrate greater cognitive decline (Katzen et al., 2006) . However, it is important to note that PD symptoms may migrate and evolve over time, so that the symptom at onset may not be the pre-eminent symptom presentation at a later point in

time. Further, this study utilized patient's self-report of their first symptom experienced and these recollections may be subject to inaccuracies. Next, existing literature on the relationship between disease course/stage and apathy is mixed. Disease stage as measured by the Hoehn and Yahr scale is largely based on observation of the patient's motor symptoms. These outward physical manifestations may not be an accurate representation of the underlying progression of pathophysiological mechanisms that also contribute to the apathy presentation. Therefore, more accurate quantitative markers are needed to better assess the relationship between apathy and disease stage.

Finally, R-Apathy was found to be significantly associated with decreased quality of life in our PD sample, but further exploration revealed that this relationship was not significant in the presence of depression, likely due to the high correlation between depression and quality of life. This result suggests that decrements in quality of life may be more attributable to depressogenic mood features than an apathetic amotivational syndrome. In addition, no significant associations were found between R-Apathy and psychosocial outcomes such as independence in basic and instrumental activities of daily living, and caregiver burden, after controlling for education and depression. It is possible that apathy may not have a direct effect on impairments in daily living, but rather have an indirect effect mediated by cognitive impairment (which was not examined in the current study). Regardless of the exact mechanism, it remains likely that apathy is associated with functional activities of daily living. Psychosocial outcomes such as caregiver burden also remain an important aspect of non-motor PD symptom presentation and should continue to be studied. Several

studies of PD and other neurodegenerative disease have found that caregivers for those with apathy experience greater caregiver burden, and that aside from the more rare neuropsychiatric symptoms (e.g., delusions, agitation/aggression), apathy was the symptom that most frequently caused caregiver distress, followed by depression, anxiety, and irritability (Marin, 1996; Assal & Cummings, 2002; Marin & Wilkosz, 2005; Leiknes, Tysnes, Aarsland, & Larsen, 2010). These findings are not surprising as caregivers must address the physical and cognitive difficulties of their loved one (i.e., tremor, bradyphrenia, bradykinesia) in addition to the presence of emotional flattening and amotivation which can be particularly taxing. The lack of findings between apathy and psychosocial outcomes is believed to be an artifact of sample size, as only a portion of the subjects completed these psychosocial outcome measures. Further testing with larger sample sizes is needed to more accurately define these relationships.

Additional Findings

Analysis of medication data revealed no differences in the level of LEDD or non-parkinsonian medications between subjects with clinical apathy, and those not meeting criteria for clinical apathy. Due to the cross-sectional nature of the data, it remains unclear whether levodopa or other medications impact the presentation of apathy. However, the current findings do not support this relationship and rather suggest that apathy is independent of levodopa dose or non-parkinsonian medications.

In regards to levodopa, it is possible that the dopaminergic pathways have already sustained such damage that the administration of excess dopamine is ineffective in modifying the apathy presentation.

In general, these findings highlight the fact that apathy should not only be thought of as a dopamine-dependent syndrome (Pedersen, Larsen, Alves, & Aarsland, 2009; Starkstein, Merello, Jorge, Brockman, Bruce, & Power, 2009). Apathy has also been increasingly linked to non-tremor dominant motor presentations (e.g., bradykinesia, postural instability, gait difficulty), more rapid decline in speech and axial impairment, and dementia, all of which are predominately associated with dysfunction in non-dopaminergic subcortical pathways. In fact, while the biological basis of apathy remains somewhat unclear, a number of neurotransmitter deficits have been implicated in the presentation of apathy including dopaminergic, cholinergic, noradrenergic, and serotonergic systems, in addition to the presence of Lewy body pathology in more advanced disease stages (van Reekum, 2005; Emre, 2003). Additionally, there has been evidence in PD for extensive cell loss in the basal forebrain nuclei, which is the main source of cholinergic pathways to the cortex. This loss of cholinergic neurons is believed to be the biologic basis for cognitive decline and specific neuropsychiatric symptoms, including apathy, in Alzheimer's disease and related dementias (Dujardin, 2009; Jellinger, 1991; Figiel & Sadowsky, 2008; Wynn & Cummings, 2004).

Limitations

There are several potential limitations of the current study. First, further research is needed on the influence of ethnicity in the presentation of apathy. In this study, 19 Hispanic patients completed the AES, and were found to have a significantly greater risk of meeting criteria for clinical apathy, compared to a Non-Hispanic group. While the AES was forward and back-translated to Spanish, it was not empirically validated with this population. It remains to be seen whether Hispanic patients interpret AES questionnaire items in a different way, or subjectively perceive apathy in a different manner, compared to Non-Hispanic individuals. In general, it is not clear that the construct of apathy is equivalent for Hispanic and Non-Hispanic populations. Further research is needed to clarify these relationships.

Next, there is a possibility of selection bias. Patients were pre-surgical candidates and therefore may have been more motivated for evaluation but also more impaired than a natural community sample. Individuals who did not complete the AES endorsed greater LEDD and performed more poorly a global screening measure and multiple measures of neuropsychological function. Level of impairment may have influenced their ability to complete all measures. For example, self-report questionnaires such as the AES are often given towards the end of the neuropsychological evaluation and in time-limited cases may be omitted. Omitted or incomplete questionnaires often result from patient fatigue and/or cognitive impairment. Regardless, this study identified a number of patients with significant apathy and associated neuropsychological correlates, even in the context of more mild PD profiles. Second, medication data was available for only a portion of the

participants. However, this is not thought to have impacted the current findings. As summarized above, apathy is regarded to be independent of levodopa daily dose. In addition, investigation of our patients *with* medication data revealed no differences in non-parkinsonian medication between those with and without clinical apathy.

In regard to statistical limitations, there are potential weaknesses inherent to the use of structural equation modeling. Perhaps one of the biggest limitations of SEM is the need for a substantial sample size to calculate stable estimates of covariances, correlations, and other parameters. A minimum of ten subjects per estimated parameter is recommended (Nunnally, 1967; Westland, 2010). Sample size of the current study (n = 141) prohibited the use of a more complex model to explore apathy (e.g., modeling the relationship of R-Apathy and all neuropsychological domains simultaneously or all psychosocial measures simultaneously). Further, only a portion of the sample completed psychosocial outcome measures (i.e., PDQ, CBS, IADL, KADL). Larger sample sizes are needed to confirm the present findings. Secondly, SEM is a confirmatory approach. The investigator imposes a model based on empirical theory and findings, however the possibility remains of alternative successful models. One must also be sure not to omit extraneous variables that may potentially confound findings. In the current study care was taken to include as many variables as possible that may contribute to the apathy presentation. Preliminary findings were incorporated into later analyses and appropriate modifications based on those results were implemented. The delegation of neurocognitive measures to specific domains of neuropsychological function was made based on empirical evidence and clinical experience. However, the definition of these domains does tend

to vary between studies and there were also correlations between domains. Specifically, the Attt/Exe domain was highly correlated with other cognitive latents (Language, Memory, and Visuospatial). This is not surprising due to the contribution of executive function to skills in many domains. Further, most higher-order measures rely on executive skills because they are embedded in the complexity of the task. For example, verbal memory for listed material requires the use of semantic grouping strategies or the generation of a contextual story by which to memorize and organize the information. Retrieval of information is also a frontal-executive skill. Recruitment of strategy, use of mental organization, and retrieval skills are decidedly executive in nature. The results of this study are thought to be an accurate reflection of the relationship between apathy and neuropsychological correlates.

Finally, the Apathy Evaluation Scale was the only apathy measure used in the current study. While the AES has been proven a valid and reliable measure of apathy, it may possess limited sensitivity to differentiate between apathy subtypes in a Parkinson's sample. These limitations should be considered when interpreting results. Further study of large PD samples with a greater range of Parkinson's-related impairment, more variability in apathy severity, with detailed medication data, and that employ multiple measures of apathy, will be helpful to confirm the present findings and more fully elucidate the relationship between apathy, neuropsychological correlates, and psychosocial outcomes.

Implications and Future Directions

Apathy remains an important dimension in understanding nonmotor changes in PD. As a whole, apathy correlated with specific areas of neuropsychological dysfunction apart from the influence of depression. Manifestations of apathy such as mental disengagement and behavioral withdrawal are key features of the disease presentation. The importance of evaluating apathy as a contributing factor to patients' neurocognitive status, mood, and psychosocial functioning should not be underestimated. An apathy evaluation should also be included as a standard part of a Parkinson's evaluation. Future study of large PD samples with a greater range of Parkinson's-related impairment, more variability in apathy severity, with detailed medication data, and that employ multiple measures of apathy, will be helpful to confirm the present findings and more fully elucidate the relationship between apathy, neuropsychological correlates, and psychosocial outcomes.

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Tables

Table 1.
Comparison of PD patients from the Initial and Recent Databases

		Group Means (SD)		
	n	Initial (*n* = 309)	Recent (*n* = 197)	*p*
Demographic and Disease Characteristics				
Age at Exam	500	68.0 (9.94)	64.91 (9.08)	<.001*
Gender (M/F)	463	172/94	130/167	.767
Education (yrs)	460	14.08 (2.84)	14.52 (3.12)	.114
Ethnicity (NH/H//O)	506	293/7/9	87/72/38	<.001*
Handedness (R/L/A)	461	237/26/1	177/15/5	.097
Age at Disease Onset	495	60.21 (11.06)	54.64 (9.82)	<.001*
Disease Duration	461	7.06 (5.34)	10.33 (5.65)	<.001*
Disease Stage (H&Y)	306	2.45 (1.00)	2.22 (0.88)	.045*
Side Onset (R/L/U)	345	71/61/19	99/75/20	.694
Predominant Symptom (T/NT)	297	117/45	112/23	.028*
MMSE	332	25.65 (3.90)	27.05 (2.56)	<.001*
AES	141	34.21 (8.51)	32.45 (10.90)	.290
BDI	428	10.81 (7.82)	12.60 (7.94)	.020*
Neuropsychological Test Performance				
Boston Naming Test	405	24.15 (4.48)	25.20 (4.69)	.028*
WAIS- Similarities	438	10.98 (2.70)	10.22 (3.10)	.007*
WAIS- Digits Forward	451	6.19 (1.19)	6.21 (1.51)	.877
WAIS- Digits Backward	451	4.38 (1.24)	4.32 (1.40)	.628
CVLT-Total	205	39.05 (14.43)	35.73 (12.14)	.137
CVLT-Short free recall	491	6.03 (3.64)	6.34 (3.35)	.377
CVLT-Long free recall	481	6.61 (3.78)	6.88 (3.56)	.464
BVRT	321	8.47 (3.28)	9.63 (3.23)	.006*
WCST- Categories completed	300	3.66 (1.98)	3.42 (2.30)	.478
Proverbs	323	15.89 (3.84)	16.11 (3.95)	.661
FAS	365	34.49 (14.67)	33.16 (12.36)	.376
Animals	451	13.60 (5.29)	15.32 (5.40)	.001*
JLO- Odds	390	9.28 (3.80)	9.99 (3.18)	.050*
Ghent	332	30.35 (5.77)	33.02 (3.88)	<.001*
HVOT	386	17.86 (7.60)	19.58 (5.32)	.010*

Note. Categorical variables Gender, Ethnicity, Handedness, Side Onset, and Predominant Symptom are Chi-Square analyses; values are frequencies. Gender: M/F = Male/Female; Handedness: R/L/A = Right/Left/Ambidextrous; Side Onset: R/L/U = Right/Left/Unknown; Ethnicity: NH/H/O = Non-Hispanic/Hispanic/Other; Predominant Symptom: T/NT= Tremor/Non-Tremor. Education is measured in years, high school graduate = 12.
* $p \leq .05$

Table 2.
Comparison of PD patients who completed the AES, and those who did not complete the AES

		Group Means (SD)		
	Total *n*	No AES (*n* = 365)	Completed AES (*n* = 141)	*p*
Demographic and Disease Characteristics				
Age at Exam	500	66.45 (9.77)	67.62 (9.57)	.225
Gender (M/F)	463	233/113	69/48	.100
Education (yrs)	460	14.26 (3.05)	14.27 (2.69)	.971
Ethnicity (NH/H//O)	506	272/60/33	108/19/14	.699
Handedness (R/L/A)	461	308/33/4	106/8/2	.622
Age at Disease Onset	495	58.15 (10.84)	57.64 (11.16)	.644
Disease Duration	461	8.27 (5.41)	8.98 (6.49)	.248
Disease Stage (H&Y)	306	2.34 (0.95)	2.60 (1.09)	.124
Side Onset (R/L/U)	345	120/102/28	50/34/11	.688
Predominant Symptom (T/NT)	297	168/51	61/17	.788
LEDD	143	1054.98 (783.13)	843.33 (455.78)	.047*
MMSE	332	26.13 (3.50)	27.14 (2.59)	.003*
BDI	428	11.3 (7.72)	12.25 (8.46)	.320
Neuropsychological Test Performance				
Boston Naming Test	405	24.24 (4.50)	25.36 (4.72)	.033*
WAIS- Similarities	438	10.41 (2.66)	11.50 (3.40)	.003*
WAIS- Digits Forward	451	6.20 (1.37)	6.20 (1.23)	.987
WAIS- Digits Backward	451	4.28 (1.28)	4.58 (1.40)	.037*
CVLT-Total	205	34.14 (10.99)	38.36 (13.70)	.015*
CVLT-Short free recall	419	5.97 (3.43)	6.67 (3.73)	.072
CVLT-Long free recall	418	6.40 (3.64)	7.58 (3.73)	.004*
BVRT	321	8.24 (3.20)	10.03 (3.23)	<.001*
WCST- Categories completed	300	3.55 (2.01)	3.77 (2.15)	.425
Proverbs	323	15.82 (3.96)	16.26 (3.57)	.369
FAS	365	33.57 (13.91)	35.65 (14.32)	.219
Animals	451	14.08 (5.55)	15.09 (4.88)	.085
JLO- Odds	390	9.21 (3.72)	10.43 (3.13)	.001*
Ghent	332	30.07 (5.84)	33.48 (3.36)	<.001*
HVOT	386	17.83 (7.24)	20.27 (5.72)	.001*
OTMT-A	72	18.22 (31.67)	9.61 (4.98)	.208
OTMT-B	65	39.37 (13.43)	34.92 (17.68)	.329
Symbol Digit Modalities	181	25.74 (12.18)	31.14 (12.23)	.004*
CBS	33	23.11 (13.53)	27.96 (15.71)	.420
IADL	43	9.00 (2.97)	10.72 (2.87)	.096
KADL	47	14.45 (3.24)	16.56 (1.75)	.062
NPIQ- Total	42	3.70 (2.06)	3.50 (2.34)	.810
FrSBe Apathy- Before Illness	47	70.88 (19.95)	84.64 (19.25)	.074
FrSBe Apathy- After Illness	43	82.25 (14.63)	94.17 (24.20)	.191

Note. Categorical variables Gender, Ethnicity, Handedness, Side Onset, and Predominant Symptom are Chi-Square analyses; values are frequencies. Gender: M/F = Male/Female; Handedness: R/L/A = Right/Left/Ambidextrous; Side Onset: R/L/U = Right/Left/Unknown; Ethnicity: NH/H/O = Non-Hispanic/Hispanic/Other; Predominant Symptom: T/NT= Tremor/Non-Tremor. Education is measured in years, high school graduate = 12.
* $p \leq .05$

Table 3.
Comparison of PD patients from the Initial and Recent Databases, having completed the AES

		Group Means (SD)		
	n	Initial (*n* = 67)	Recent (*n* = 74)	*p*
Demographic and Disease Characteristics				
Age at Exam	141	70.78 (9.45)	64.77 (8.80)	<.001*
Gender (M/F)	117	26/17	43/31	.803
Education (yrs)	115	14.02 (2.47)	14.42 (2.82)	.443
Ethnicity (NH/H//O)	133	61/1/0	47/18/3	<.001*
Handedness (R/L/A)	116	38/4/0	68/4/2	.407
Age at Disease Onset	140	61.35 (11.21)	54.32 (10.12)	<.001*
Disease Duration	116	10.24 (6.05)	10.38 (7.03)	.914
Disease Stage (H&Y)	55	2.82 (0.87)	2.36 (1.04)	.187
Side Onset (R/L/U)	95	12/8/2	38/26/9	.916
Predom. Symptom (T/NT)	78	19/4	42/13	.542
MMSE	114	26.75 (2.87)	27.38 (2.34)	.210
AES	141	34.21 (8.51)	32.45 (10.90)	.290
BDI	106	12.21 (8.28)	12.28 (8.58)	.963
Neuropsychological Test Performance				
Boston Naming Test	109	25.67 (3.60)	25.09 (3.90)	.156
WAIS- Similarities	105	13.33 (2.95)	10.29 (3.14)	<.001*
WAIS- Digits Forward	113	6.55 (1.19)	6.00 (1.21)	.021*
WAIS- Digits Backward	113	4.95 (1.45)	4.35 (1.33)	.016*
CVLT-Total	110	38.98 (14.26)	37.96 (13.35)	.077
CVLT-Short free recall	110	6.90 (4.02)	6.54 (3.58)	.093
CVLT-Long free recall	110	7.71 (4.00)	7.51 (3.60)	.114
BVRT	92	9.28 (3.19)	10.62 (3.16)	.721
WCST- Categories completed	80	3.53 (2.17)	3.98 (2.13)	.602
Proverbs	86	16.12 (3.25)	16.39 (3.88)	.522
FAS	93	37.52 (16.16)	34.10 (12.55)	.032*
Animals	115	14.55 (5.08)	15.40 (4.78)	.707
JLO- Odds	104	10.48 (3.39)	10.40 (2.96)	.198
Ghent	91	32.85 (4.26)	33.98 (2.37)	.652
HVOT	96	19.64 (6.92)	20.75 (4.58)	.501

Note. Categorical variables Gender, Ethnicity, Handedness, Side Onset, and Predominant Symptom are Chi-Square analyses; values are frequencies. Gender: M/F = Male/Female; Handedness: R/L/A = Right/Left/Ambidextrous; Side Onset: R/L/U = Right/Left/Unknown; Ethnicity: NH/H/O = Non-Hispanic/Hispanic/Other; Predominant Symptom: T/NT= Tremor/Non-Tremor. Education is measured in years, high school graduate = 12. Comparisons between apathy groups on neuropsychological measures are ANCOVA's with age at exam as covariate.
* $p \leq .05$

Table 4.
Sample Characteristics

	n	Mean ± SD	Minimum	Maximum
Demographic and Disease Factors				
Age at exam	141	67.62 ± 9.57	40.00	79.00
Age of disease onset	140	57.64 ± 11.18	27.00	80.00
Education (yrs)	115	14.27 ± 2.69	8.00	22.00
Gender (M/F)	69/48			
Handedness (R/L/A)	106/8/2			
Ethnic category (NH/H/O)	108/19/3			
Disease stage (H&Y)	55	2.45 ± 1.02	1.00	5.00
Disease duration (years)	116	10.33 ± 6.66	0.00	38.00
Side of PD onset(R/L/U)	50/34/11			
Symptom Onset (T/NT)	61/17			
MMSE	114	27.16 ± 2.55	16.00	30.00
AES	141	33.28 ± 9.84	18.00	62.00
BDI-II	106	12.25 ± 8.43	0.00	36.00
LEDD*	79	491.15 ± 530.58	0.00	2,250.00
Neuropsychological Measures				
BNT	109	25.31 ± 3.78	12.00	30.00
WAIS-III-Sim	105	11.53 ± 3.40	2.00	19.00
WAIS-DS-LSF	113	6.20 ± 1.23	3.00	9.00
WAIS-DS-LSB	113	4.58 ± 1.40	0.00	8.00
CVLT-II-Tot	110	38.34 ± 13.64	10.00	76.00
CVLT-II-sf	110	6.67 ± 3.73	0.00	16.00
CVLT-II-lf	110	7.58 ± 3.73	0.00	16.00
BVRT	92	10.03 ± 3.23	2.00	16.00
mWCST	80	3.75 ± 2.15	0.00	6.00
Proverbs	86	16.26 ± 3.57	5.00	20.00
FAS	93	35.65 ± 14.32	7.00	66.00
Animals	115	15.09 ± 4.88	3.00	29.00
JLO	104	10.43 ± 3.13	2.00	15.00
Ghent	91	33.48 ± 3.36	18.00	36.00
HVOT	96	20.27 ± 5.72	6.00	30.00
OTMT-A*	49	9.61 ± 4.98	4.95	32.00
OTMT-B*	46	34.92 ± 17.68	6.93	95.66
SDMT*	70	31.14 ± 12.23	5.00	54.00
BAI*	71	14.58 ± 10.08	0.00	41.00
Zung*	65	36.91 ± 8.56	4.00	54.00
CBS *	25	27.36 ± 15.66	2.00	69.00
PDQ*	35	50.94 ± 33.02	3.00	146.00
IADL*	33	10.67 ± 2.84	5.00	14.00
KADL*	36	16.56 ± 1.75	11.00	18.00
NPIQ- Total*	33	3.39 ± 2.38	0.00	8.00
FrSBe Apathy- Before Illness*	42	26.74 ± 6.47	14.00	40.00
FrSBe Apathy- After Illness*	40	33.63 ± 9.33	17.00	52.00

Note. Gender: M/F = Male/Female; Handedness: R/L/A = Right/Left/Ambidextrous; Side Onset: R/L/U = Right/Left/Unknown; Ethnicity: NH/H/O = Non-Hispanic/Hispanic/Other; Predominant Symptom: T/NT= Tremor/Non-Tremor. Education is measured in years, high school graduate = 12.
*Measures available from only one database, Initial or Recent.

Table 5.
Comparison of PD patients with clinical apathy and those without apathy, using the AES.

		Group Means (SD)		
	n	No Apathy (NoAP) (*n* = 98)	Clinical Apathy (AP) (*n* = 43)	*p*
Demographic and Disease Characteristics				
Age at Exam	141	67.36 (9.31)	68.23 (10.22)	.619
Gender (M/F)	117	48/36	21/12	.521
Education (yrs)	115	14.57 (2.58)	13.50 (2.86)	.055†
Ethnicity (NH/H//O)	133	78/9/2	30/10/1	.099
Handedness (R/L/A)	116	79/5/0	27/3/2	.053†
Age at Disease Onset	140	57.21 (11.01)	58.63 (11.63)	.495
Disease Duration	116	10.50 (7.01)	9.87 (5.75)	.648
Disease Stage (H&Y)	55	2.44 (.99)	2.50 (1.11)	.834
Side Onset (R/L)	95	36/24	14/10	.888
Predom. Symptom (T/NT)	78	44/12	17/5	.901
LEDD	79	535.70 (543.43)	382.69 (492.41)	.247
MMSE	114	27.25 (2.28)	26.90 (3.22)	.797
AES	141	28.09 (5.20)	45.17 (7.34)	<.001*
Neuropsychological Test Performance				
Boston Naming Test	109	25.55 (3.69)	24.71 (4.01)	.676
WAIS- Similarities	105	11.61 (3.29)	11.35 (3.69)	.799
WAIS- Digits Forward	113	6.20 (1.21)	6.23 (1.28)	.657
WAIS- Digits Backward	113	4.63 (1.41)	4.42 (1.39)	.472
CVLT-Total	110	39.34 (12.88)	35.67 (15.39)	.219
CVLT-Short free recall	110	6.79 (3.58)	6.37 (4.17)	.641
CVLT-Long free recall	110	7.73 (3.66)	7.20 (3.96)	.560
BVRT	92	10.22 (3.03)	9.59 (3.68)	.552
WCST- Categories completed	80	3.93 (2.15)	3.30 (2.14)	.261
Proverbs	86	16.39 (3.57)	15.92 (3.61)	.881
FAS	93	37.93 (14.09)	29.77 (13.43)	.051 †
Animals	115	15.67 (5.11)	13.56 (3.92)	.093
JLO- Odds	104	10.45 (2.90)	10.40 (3.69)	.713
Ghent	91	33.86 (3.34)	32.59 (3.30)	.106
HVOT	96	21.18 (5.24)	17.93 (6.29)	.003 *
OTMT-A	49	9.01 (3.89)	11.11 (6.97)	.496
OTMT-B	46	34.67 (19.04)	35.51 (14.73)	.874
Symbol Digit Modalities	70	31.32 (12.70)	30.59 (10.99)	1.00
BDI	106	10.54 (7.14)	16.60 (9.91)	.006*
BAI	71	13.47 (9.41)	17.83 (11.53)	.081
Zung	65	35.57 (9.13)	39.35 (6.95)	.510
CBS	25	23.24 (15.56)	36.13 (12.60)	.060 †
PDQ	38	44.46 (33.92)	69.67 (22.52)	.087
IADL	33	10.83 (3.12)	10.22 (1.99)	.606
KADL	36	16.52 (1.89)	16.67 (1.32)	.973
NPIQ- Total	33	3.12 (2.28)	4.25 (2.66)	.220
FrSBe Apathy- Before Illness	42	26.58 (6.70)	27.33 (5.87)	.530
FrSBe Apathy- After Illness	40	32.28 (8.74)	39.00 (10.23)	.142

Note. Cutoff for clinical apathy = 36.5. Categorical variables Gender, Ethnicity, Handedness, Side Onset, and Predominant Symptom are Chi-Square analyses; values are frequencies. Gender: M/F = Male/Female; Handedness: R/L/A = Right/Left/Ambidextrous; Side Onset: R/L/U = Right/Left/Unknown; Ethnicity: NH/H/O = Non-Hispanic/Hispanic/Other; Predominant Symptom: T/NT= Tremor/Non-Tremor. Education is measured in years, high school graduate = 12. Comparisons between apathy groups are ANCOVA's with education as covariate.
* $p \leq .05$
†Statistical trend, $p \leq .06$

Table 6.
Medication profiles.

	Group Frequencies (% group)		
	No Apathy (NoAP) (n = 55)	Clinical Apathy (AP) (n = 19)	p
Parkinson medications			
L-Dopa	29 (52.7)	13 (68.4)	.234
Dopa-agonist	22 (40.0)	9 (47.4)	.575
NMDA rec. agonist	8 (14.5)	5 (26.3)	.245
Anticholinergic	5 (9.1)	1 (5.3)	.598
COMT-inhibitor	15 (27.3)	7 (36.8)	.431
MAO-B inhibitor	7 (12.7)	5 (26.3)	.166
Cholinesterase inhibitor	1 (1.8)	0 (0.0	.554
Non-Parkinsonian medications			
Antipsychotics	3 (5.5)	1 (5.3)	.975
SSRIs	3 (5.5)	1 (5.3)	.975
Tricyclics	0 (0.0)	1 (5.3)	.087
Antidepressants	6 (10.9)	2 (10.5)	.963
Statins	5 (9.1)	2 (10.5)	.854

Note. Comparison is chi-square analysis.

Table 7.
Item Analysis of the AES

Scale Reliability: Cronbach's Alpha = .901

Item	Mean	SD	Item-Total Correlation	Cronbach's Alpha if Item Deleted
1	1.780	.871	.673	.892
2	2.056	.852	.601	.894
3	1.688	.837	.658	.893
4	1.971	.948	.687	.891
5	1.837	.938	.642	.893
6	2.362	1.064	.099	.912
7	2.050	.936	.660	.892
8	1.567	.848	.685	.892
9	1.830	.902	.713	.891
10	1.497	.875	.284	.903
11	2.170	1.055	.166	.909
12	1.816	.816	.529	.896
13	1.738	.859	.517	.897
14	1.638	.804	.601	.894
15	1.546	.732	.373	.900
16	1.738	.867	.674	.892
17	2.014	.910	.764	.889
18	1.986	.941	.755	.889

Note. Item # 6, 10, and 11 increased reliability if deleted, therefore they were removed from further analyses.

Table 8.
The Influence of Demographic and Disease Variables on R-Apathy

	Regression Estimates			
	β	S.E.	*z*	StdYX
Demographic and Disease Measures				
Gender	-0.203	0.235	-0.864	-.094
Education	-0.100	0.044	-2.245	-.252*
Side Onset (R/L/U)	-0.323	0.275	-1.176	-.150
Predominant Symptom (T/NT)	0.389	0.313	1.242	.159
Disease Duration (yrs)	0<.001	0.018	0.020	.002
Disease Disability (H&Y)	0.085	0.176	0.483	.087
LEDD	0<.001	0<.001	-0.787	-.113

Note. Data is cross-sectional, caution is needed when inferring directionality. Side Onset: R/L/U = Right/Left/Unknown; Predominant Symptom: T/NT= Tremor/Non-Tremor; H&Y = Hoehn and Yahr disease rating; LEDD = Levodopa Equivalent Daily Dose.
* $p \leq .05$

Table 9.
The Influence of R-Apathy of Psychosocial Outcomes

	Regression Estimates			
	β	S.E.	*z*	StdYX
Psychosocial Measures				
PDQ	11.675	4.859	2.403	.353*
CBS	4.589	3.207	1.431	.296
IADL	-0.395	0.447	-0.884	-.139
KADL	-0.015	0.132	-0.116	.035

Note. Education is held as covariate. Data is cross-sectional, caution is needed when inferring directionality. When depression is also controlled for, PDQ regression is no longer significant (β = 1.546, S.E. = 4.248, *z* = 0.364).
* $p \leq .05$

Table 10.
R-Apathy factors derived from CFA in SEM.

Cognitive/Emotional Items (mental engagement)

3.) Getting things started on my own is important to me.
4.) I am interested in having new experiences.
5.) I am interested in learning new things.
8.) Seeing a new job through to the end is important to me.
13.) Getting together with friends is important to me.
16.) Getting things done during the day is important to me.
7.) I approach life with intensity. (previously Emotional item)
14.) When something good happens I get excited. (previously Emotional item)

Behavioral Items (active initiation and participation)

2.) I get things done during the day.
9.) I spend time doing things that interest me.
12.) I have friends.

Other Items (self-perception)

15.) I have an accurate understanding of my problems.
17.) I have initiative.
18.) I have motivation.

Note. Each questionnaire item was assigned to a factor based on suggested categorization by Marin et al., 1991. Cognitive and emotional items were combined into a single latent as suggested by Mplus CFA statistical findings. Reverse coded items (#6,10,11) were omitted as recommended by item analysis findings; item #1 was also later omitted due to cross-loading with cognitive, emotional, and behavioral factors. The resulting factors remain correlated (.8-.89), however model fit indices suggest they do have distinct psychometric properties and represent a best-fit model.

Figures

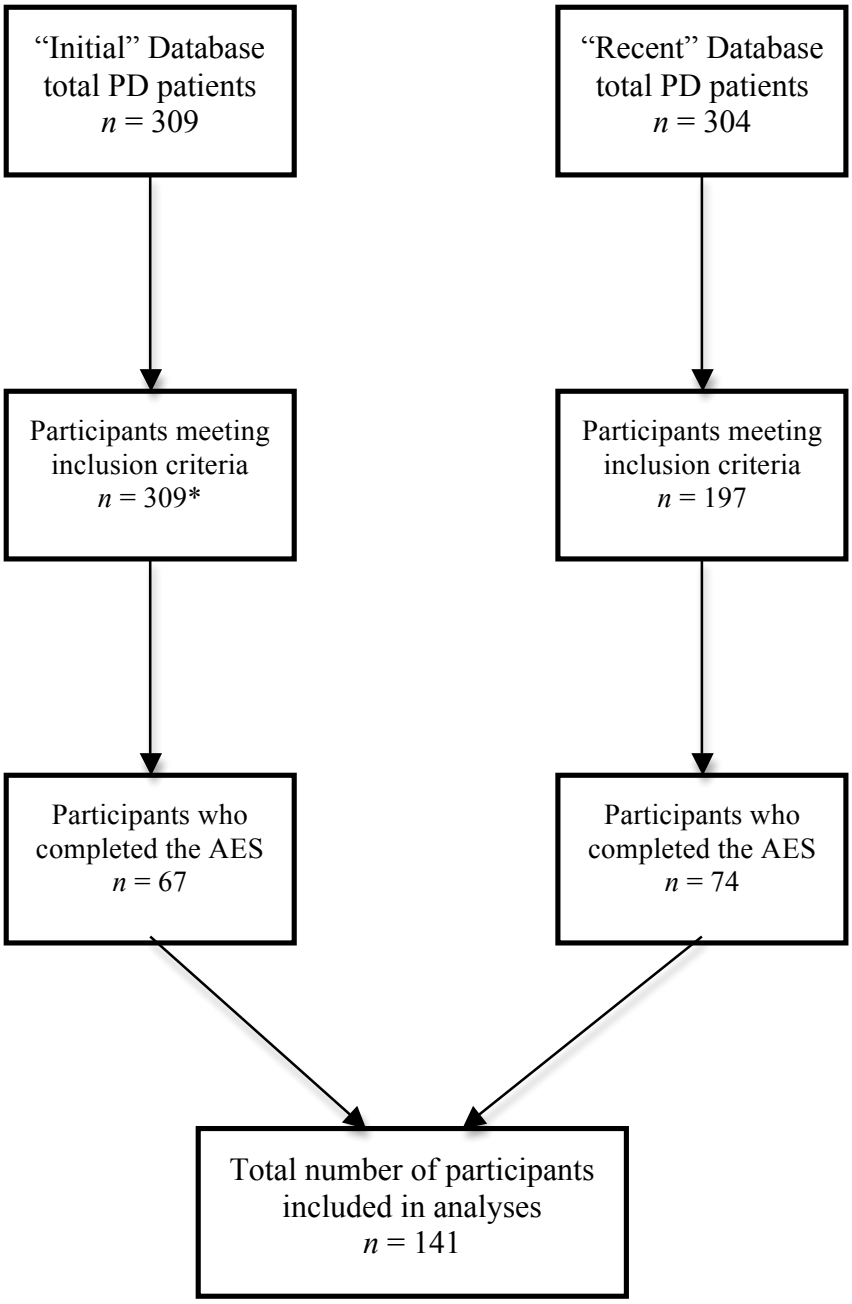

Figure 1. Participant inclusion flow chart. *Patients from the Initial database were not entered unless they met inclusion criteria.

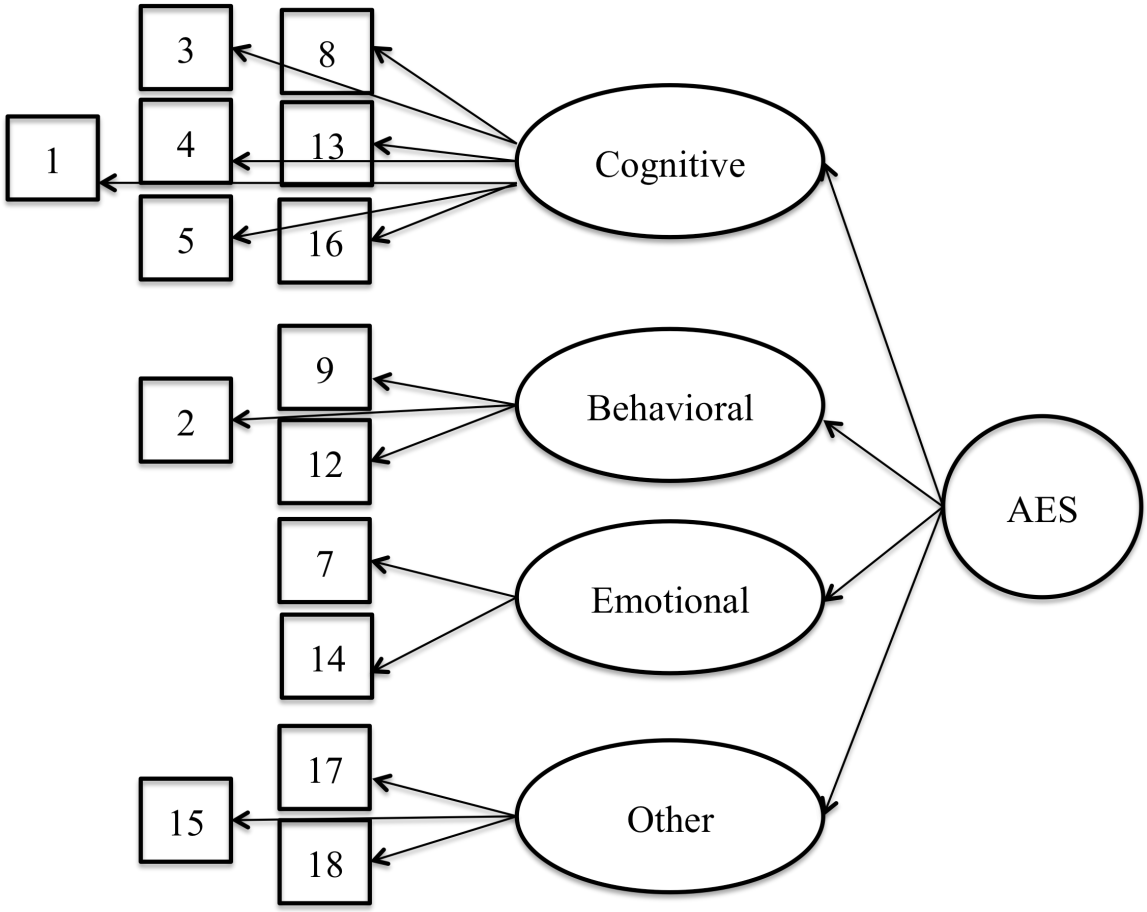

Figure 2. Original second-order CFA using Marin et. al's classification of questionnaire items. Model fit: $\chi^2 = 227.096$, $df = 86$, $p = 0<.001$; CFI/TLI= 0.877/0.849; RMSEA = 0.108; SRMR = 0.059.

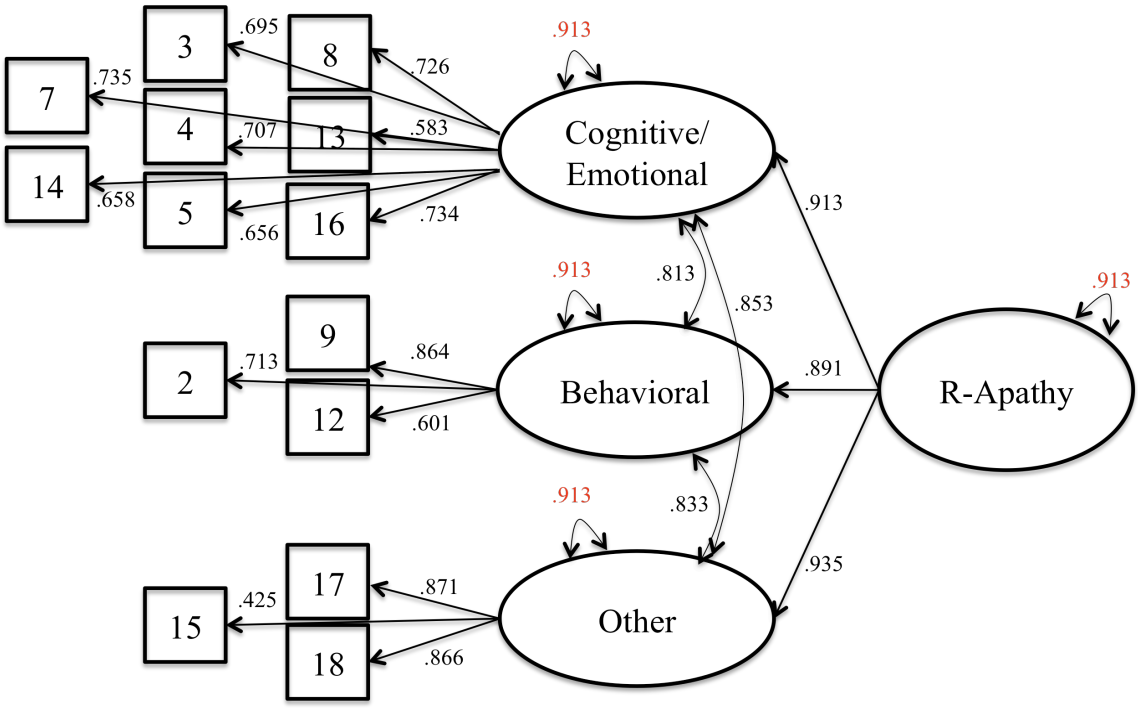

Figure 3. Final revised apathy model. Fit indices: χ^2 = 72.751, *df* = 70, *p* = .3876; CFI/TLI = .997/.997; RMSEA = .017; SRMR = .036.

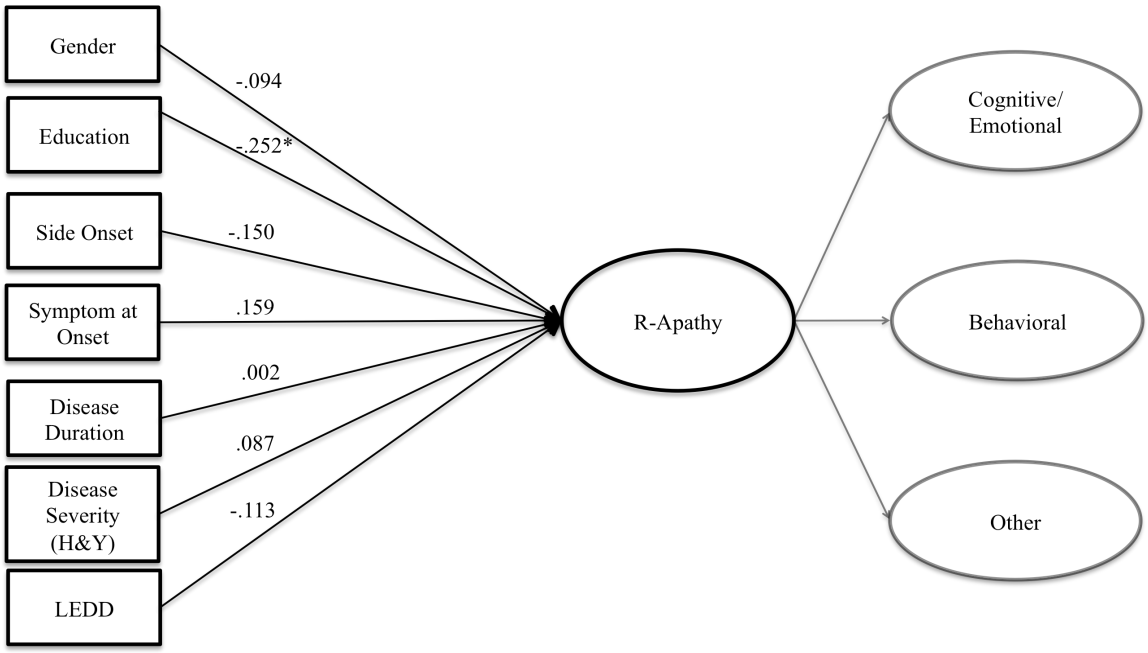

Figure 4. Association between demographic and disease factors, and R-Apathy. Values are standardized regression coefficients, however due to the cross-sectional nature of the data caution should be used when inferring directionality.

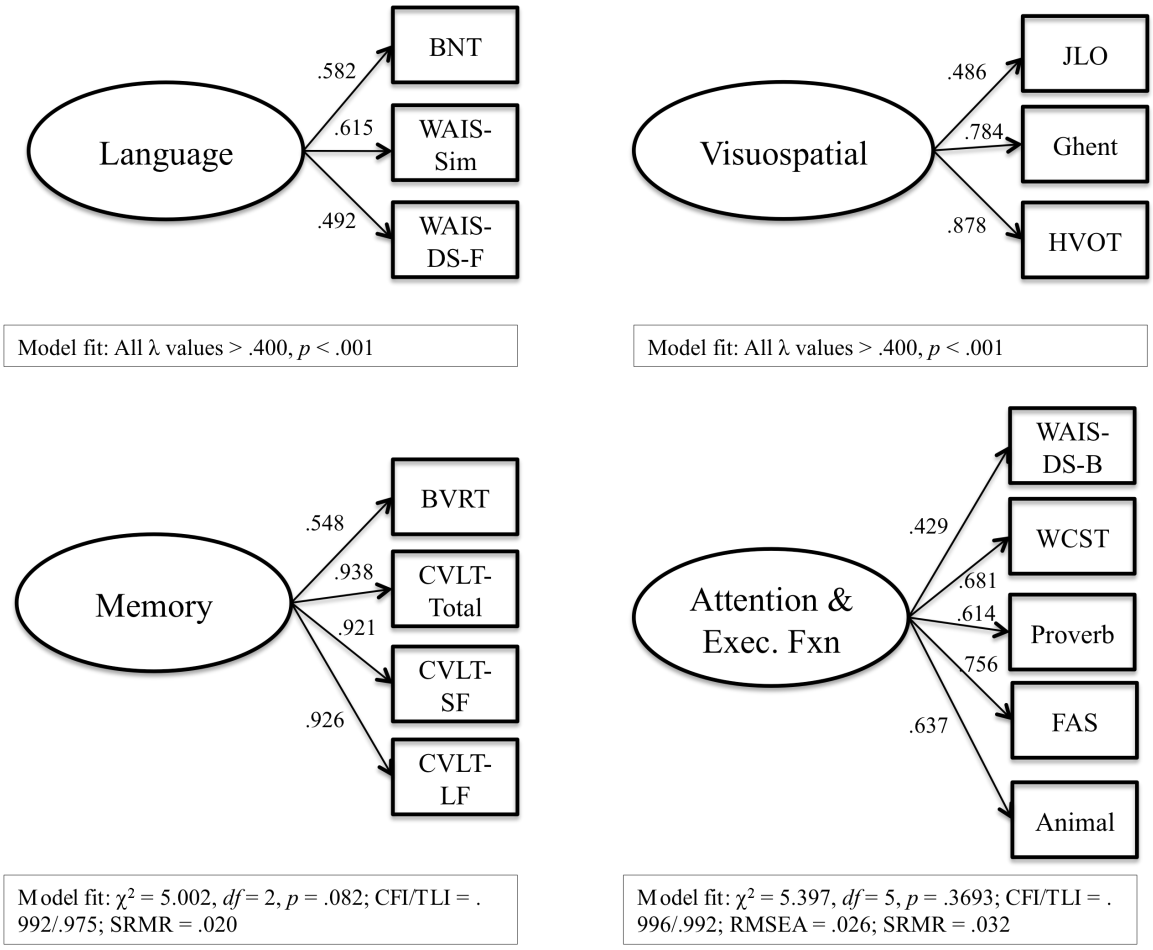

Figure 5. Latent models of neuropsychological domains.

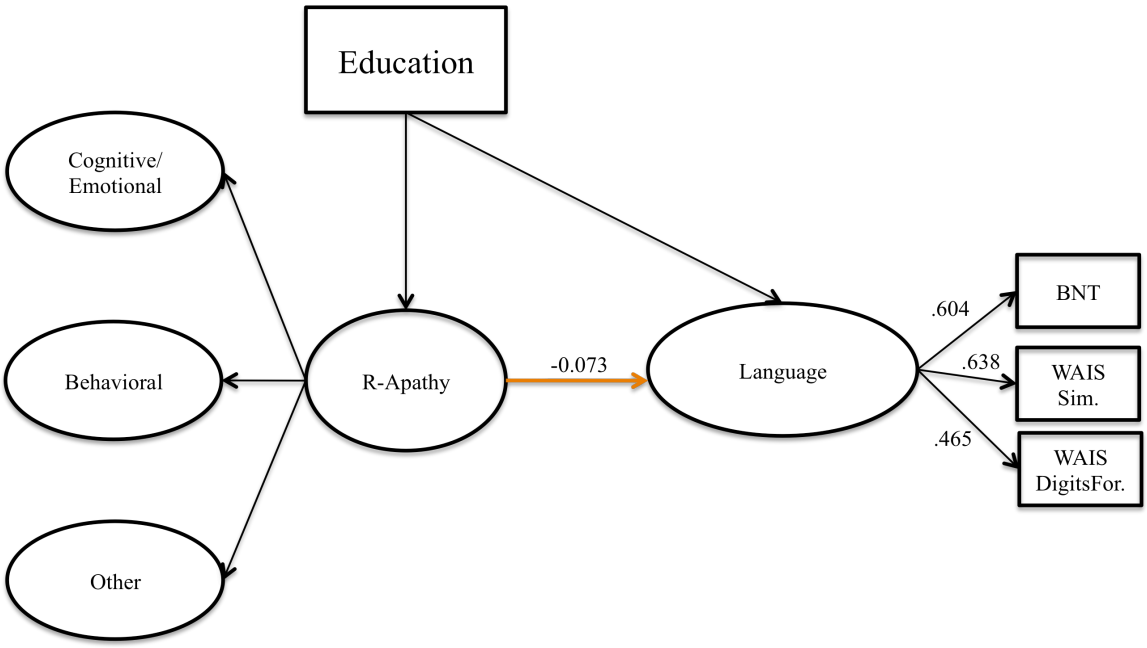

Figure 6. The association between R-Apathy and Language skills. Fit indices: χ^2 =150.764, *df* = 126, *p* = .066; CFI/TLI = .978/.973; RMSEA = .037; SRMR = .062.

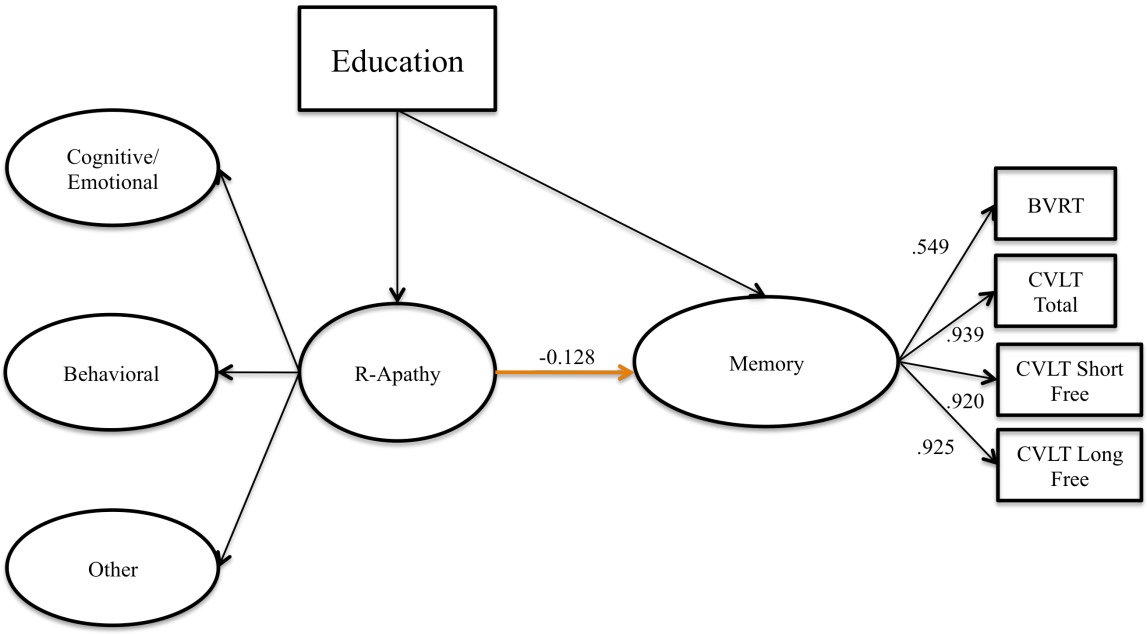

Figure 7. The association between R-Apathy and Memory skills. Fit indices: χ^2 =188.687, *df* = 143, *p* = .006; CFI/TLI = .968/.962; RMSEA = .048; SRMR = .071.

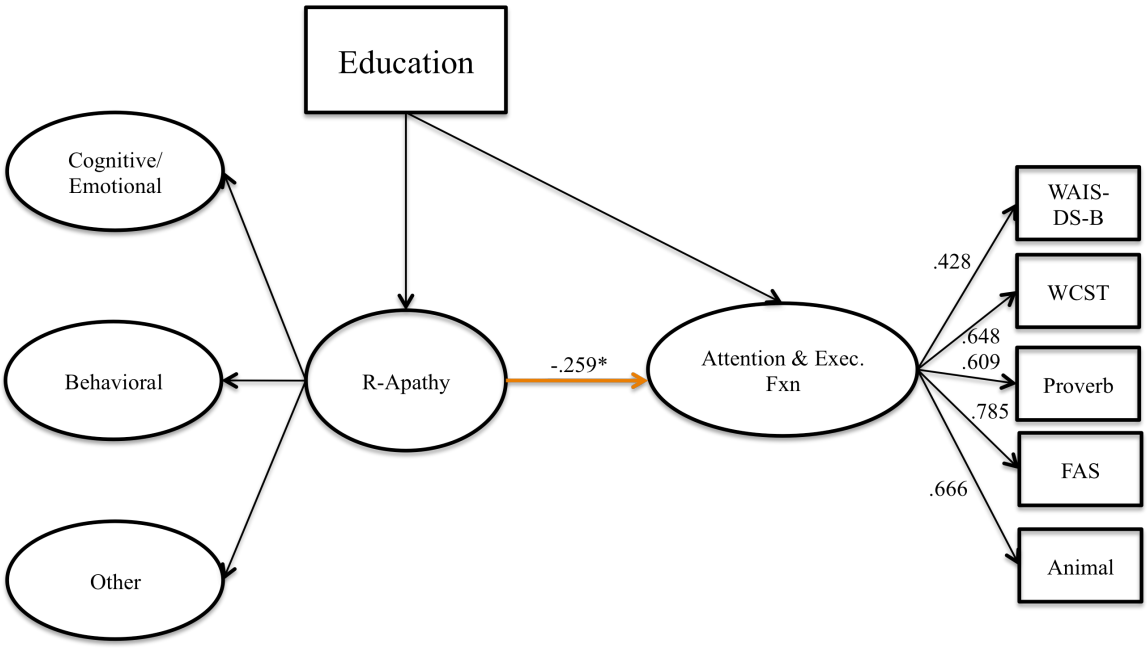

Figure 8. The influence of R-Apathy on skills of attention and executive function. Fit indices: χ^2 = 173.463, *df* = 160, *p* = .2208; CFI/TLI = .988/.986; RMSEA = .024; SRMR = .062

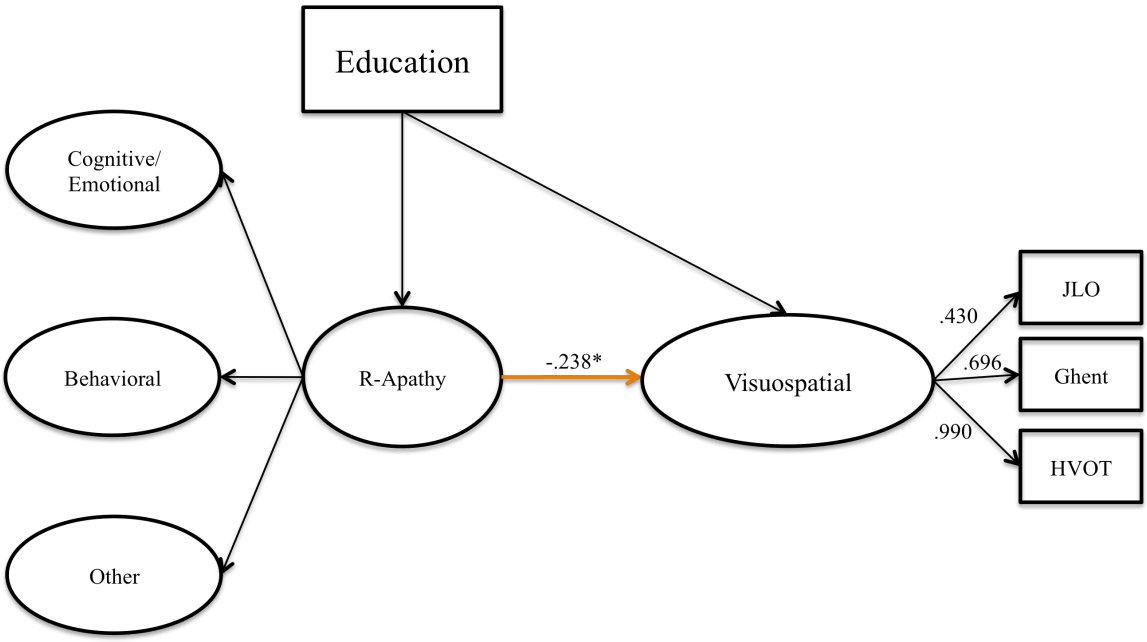

Figure 9. The influence of R-Apathy on visuospatial skills. Fit indices: χ^2 =150.295, *df* = 126, *p* = .069; CFI/TLI = .979/.974; RMSEA = .037; SRMR = .061

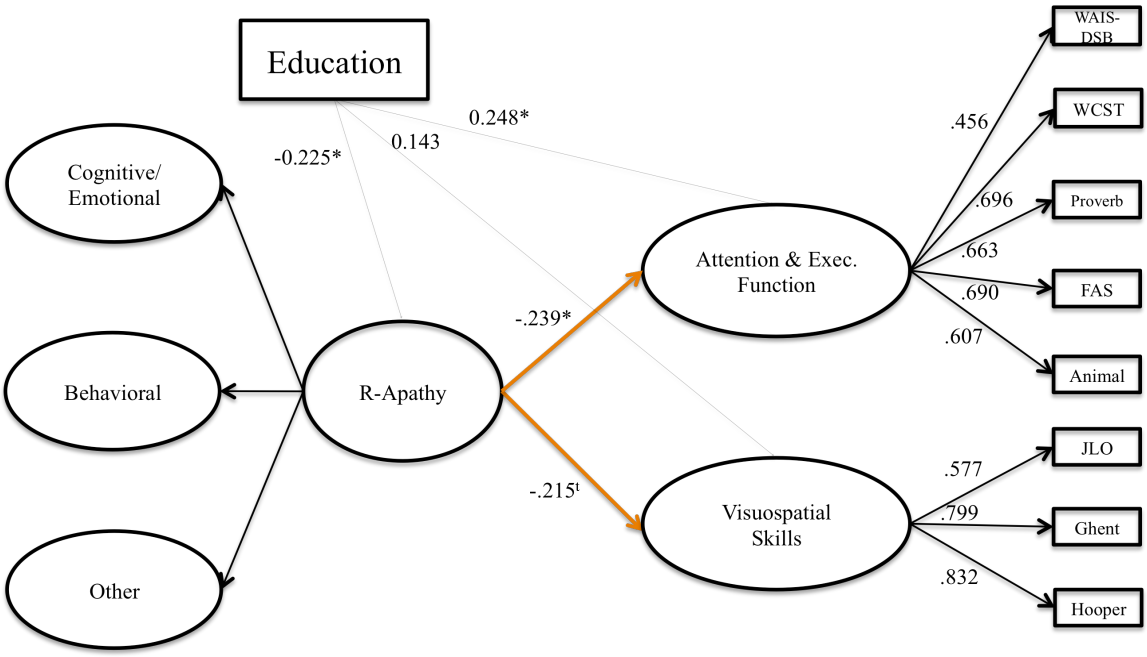

Figure 10. Model with apathy predicting both skills of attention/executive function and visuospatial skills; controlling for education. Regression coefficients shown are standardized values. Fit indices: $\chi^2 = 260.652$, $df = 217$, $p = .0227$; CFI/TLI = .967/.962; RMSEA = .038; SRMR = .073. All λ values > .400, $p < .001$.
$^{*}p < .05$ $^{t}p < .08$

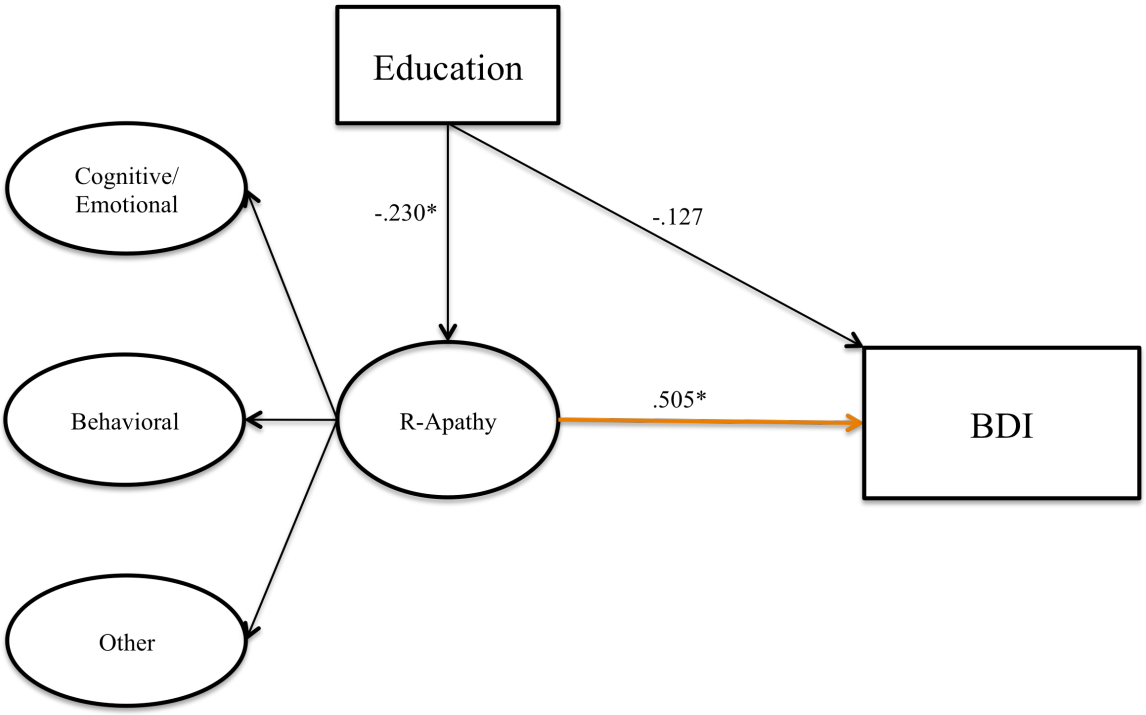

Figure 11. R-Apathy significantly predicted depression, while covarying education. Regression coefficients shown are standardized values. BDI: $\beta = 4.116$, S.E. = 0.786, $z = 5.236$; $\chi^2 = 112.558$, df = 96, p = .1190; CFI/TLI = .985/.981; RMSEA = .035; SRMR = .048.

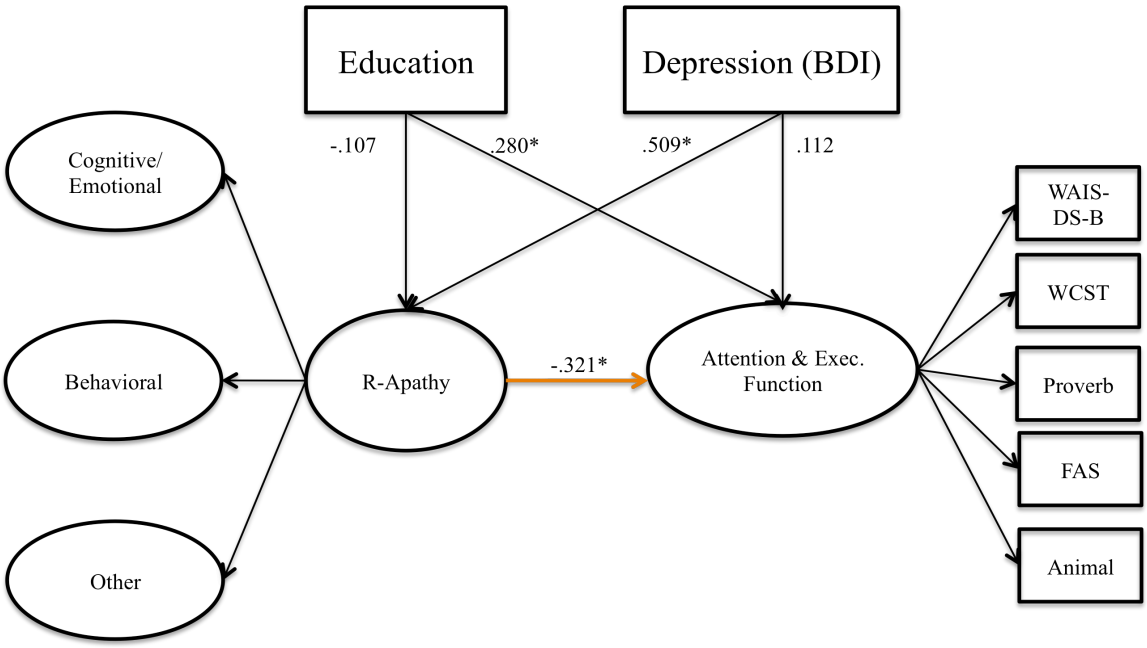

Figure 12. Regression coefficients shown are standardized values. Fit indices: χ^2 = 202.335, *df* = 177, *p* = .0931; CFI/TLI = .979/.975; RMSEA = .032; SRMR = .066. All λ values > .400, *p* < .001 .

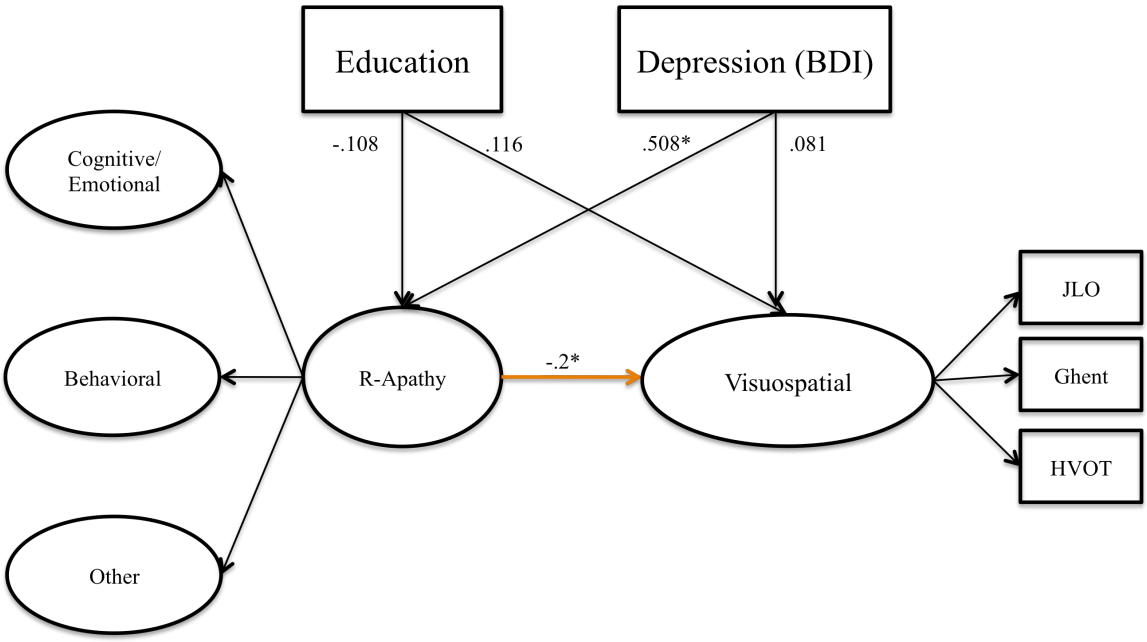

Figure 13. Regression coefficients shown are standardized values. Fit indices: $\chi^2 = 171.072$, $df = 141$, $p = .043$; CFI/TLI = .975/.969; RMSEA = .039; SRMR = .064. All λ values > .400, $p < .001$.

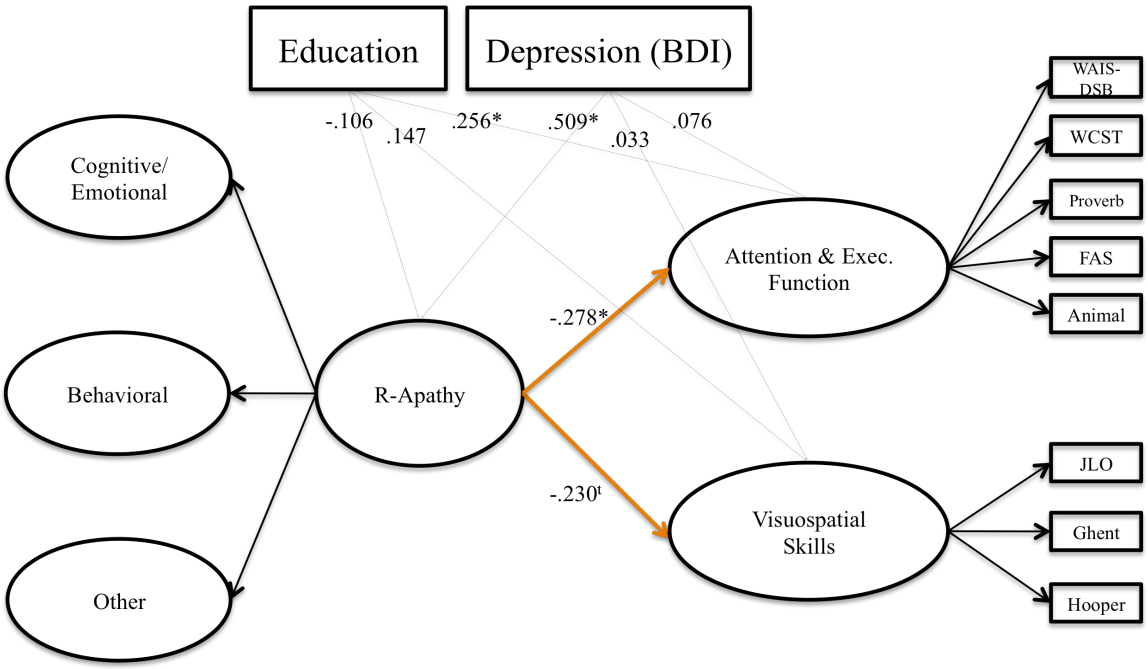

Figure 14. Final model with apathy predicting both skills of attention and executive function, and visuospatial skills; controlling for both education and depression. Regression coefficients shown are standardized values. Fit indices: $\chi^2 = 292.833$, $df = 236$, $p = .0069$; CFI/TLI = .958/.951; RMSEA = .041; SRMR = .074.
All λ values > .400, $p < .001$. $^{*}p < .05$ $^{t}p < .10$

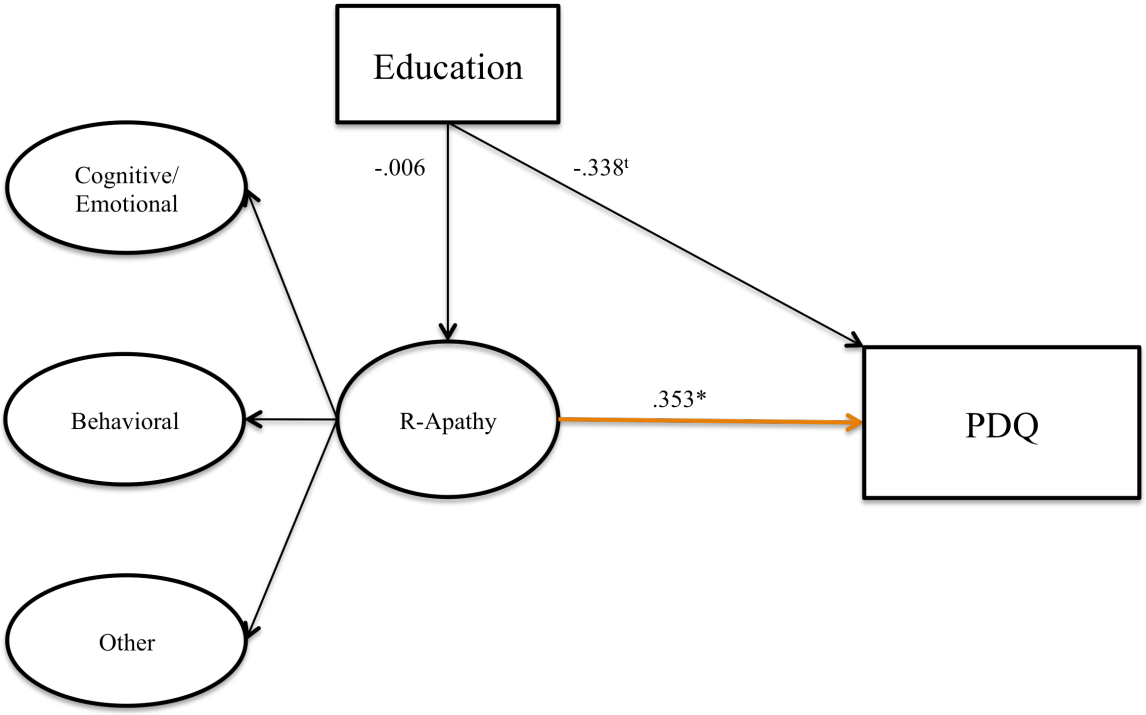

Figure 13. R-Apathy significantly predicted quality of life (β = 11.675, S.E. = 4.859, z = 2.403). Regression values are standardized values. All loadings, variances, residuals, intercepts, and correlations or R-Apathy were specified. Only regression is tested. PDQ = Parkinson's Disease Questionnaire. $^{*}p < .05$ $^{t}p < .10$

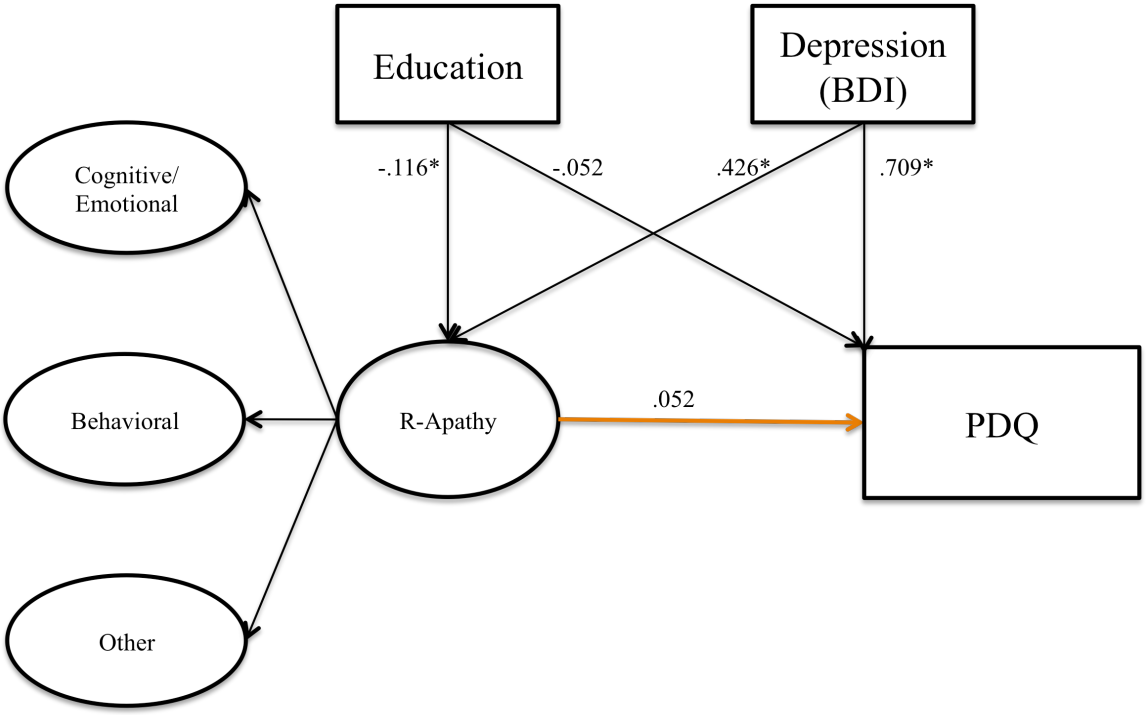

Figure 14. R-Apathy significantly predicted quality of life (β = 1.546, S.E. = 4.248, *z* = 0.364). All loadings, variances, residuals, intercepts, and correlations or R-Apathy were specified. Only regression is tested. PDQ = Parkinson's Disease Questionnaire.
$^{*}p < .05$

Appendix

Apathy Evaluation Scale (Self-Rated)

Name: _____ Date: _____

Instructions: For each statement, circle the answer that best describes your thoughts, feelings, and activity in the **past 4 weeks, including today.**

1.) I am interested in things.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

2.) I get things done during the day.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

3.) Getting things started on my own is important to me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

4.) I am interested in having new experiences.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

5.) I am interested in learning new things.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

6.) I put little effort into anything.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

7.) I approach life with intensity.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

8.) Seeing a job through to the end is important to me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

9.) I spend time doing things that interest me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

10.) Someone has to tell me what to do each day.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

11.) I am less concerned about my problems than I should be.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

12.) I have friends.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

13.) Getting together with friends is important to me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

14.) When something good happens, I get excited.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

15.) I have an accurate understanding of my problems.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

16.) Getting things done during the day is important to me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

17.) I have initiative.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

18.) I have motivation.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

The Apathy Evaluation Scale was developed by Robert S. Marin, M.D. Development and validation studies are described in RS Marin, RC Biedrzycki, S Firinciogullari: "Reliability and Validity of the Apathy Evaluation Scale," *Psychiatry Research*, 38: 143-162, 1911.