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The influence of apathy and depression on cognitive functioning in Parkinson's disease

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The Influence of Apathy and Depression on Cognitive Functioning in Parkinson's Disease

by

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ABSTRACT

Depression and apathy are two of the most common psychiatric symptoms in Parkinson's disease (PD) with prevalence estimates at higher rates than in medical populations with similar levels of disability. Several studies have provided evidence to suggest that apathy and depression are independent clinical phenomena that may differentially affect cognition. Recent research suggests that apathy may account for cognitive deficits over and above that of depression, especially in the domain of executive functioning. However, few studies have examined the independent influence of depression and apathy on cognitive abilities in patients diagnosed with PD using sensitive measures of *specific* cognitive domains. In addition, many have used measures of apathy and/or depression with symptom overlap, which may not adequately measure symptoms *unique* to the target construct.

The purpose of this study was to examine the *independent* influences of symptoms of depression and apathy on memory and executive functioning in patients diagnosed with PD using severity scales specifically designed to provide greater discrimination between symptoms. Depression severity was assessed using items that do not overlap with *apathy* symptoms or with *somatic* symptoms of PD itself. Apathy was

measured using a scale previously shown to have little overlap with depressive symptoms.

Results revealed that apathy, but not depression, was significantly associated with executive functioning. In contrast, immediate memory was significantly associated with both apathy and depression. However, apathy accounted for added variance in memory scores when controlling for depression with marginal significance. When controlling for age, although less clear, these patterns remained.

Differentiation of apathy and depression and understanding their independent effects on cognitive functioning have several implications both for clinical intervention and for scientific investigation. Apathy not only has a negative impact on cognitive functioning, but also on daily functioning and caregiver burden/distress. Secondly, it has been associated with increased mortality as it may interfere with medication compliance. If appropriately identified, preliminary research suggests that symptoms of apathy may be medically treated independently of depressive symptoms. Distinguishing apathy and depression has robust implications for the advancement of psychological science, patient care, and for enhancing quality of life in patients and caregivers.

1. Introduction

Parkinson's Disease (PD), a chronic and degenerative neurological disorder, affects approximately one million people over the age of fifty in the United States alone. While motor dysfunction is most apparent in PD, psychiatric symptoms have been reported to occur in as many as 90% of PD patients (Starkstein, Mayberg, Leiguarda, Preziosi, and Robinson, 1992b), with depression being the most common symptom. Prevalence estimates of clinically elevated depression average at around 40% in this population (Cummings, 1992), compared to 4-6% of older adults in the general population (Steffens et al., 2000). Apathy, a symptom related to motivational and self-initiation impairment, is also elevated in PD and other disorders involving the basal ganglia, with an average estimated prevalence of 40.6% (van Reekum, Stuss, and Ostrander, 2005). Again, this is higher than found in the general population, where the prevalence of clinically elevated apathy is estimated at 6.8% in older adults (Onyike et al., 2007). Psychiatric symptoms may negatively impact several patient variables, including daily functioning, cognitive functioning, and quality of life and may additionally impact caregiver burden and distress (Shrag, Jahanshahi, and Quinn, 2000; Chen, 2004; Keranen et al., 2003; Gote, 1999).

Several studies suggest that apathy and depression are independent clinical phenomena that negatively affect memory, language, and executive functioning (Starkstein et al., 1992a; Pluck and Brown, 2002; Isella et al, 2002; Feil, Razani, Boone,

and Lesser, 2003). Recent research suggests that apathy may account for cognitive deficits over and above that of depression. Few studies have investigated the independent influence of depression and apathy on cognitive abilities in patients diagnosed with PD. Further, the few studies that have examined these relationships have used simple screening measures of global cognitive ability that are insensitive to specific cognitive domains.

The present study will attempt to enhance our understanding of the independent influences of depression and apathy on memory and executive functioning in patients diagnosed with PD using sensitive and more specific cognitive measures. Hierarchical regression will allow for examination of the influence of depression on cognitive performance while controlling for the independent influence of apathy, and vice versa. Before providing a detailed account of the methodological plan for the present study, an introduction to PD and a review of the literature that has examined the relationships between depression, apathy, and cognition in this population is provided.

Parkinson's Disease

First described as the "shaking palsy" by James Parkinson in 1817 (Parkinson, 1817), Parkinson's Disease (PD) has since become prevalent worldwide, occurring in an estimated 1% of people over the age of fifty, or about one million people, in the United States alone (Stern, 1993). Most cases of PD present after the age of 50, with a mean age of onset at 55 to 60 years (Mackin, 2000; Stern, 1993). Few cases, if any, appear after the age of 80 (Mackin, 2000). Although the exact cause of PD remains unknown, there are

several theorized causes of the disorder. These include toxic exposures (environmental, occupational, or drug induced), oxidative stress, and genetics. Most cases of PD are considered idiopathic, or of unknown cause.

PD is a chronic, progressive neurodegenerative disorder marked by slow degeneration of dopaminergic neurons primarily in the substantia nigra. The depletion of dopamine interferes largely with the nigrostriatal pathway of the basal ganglia, a system largely implicated in the production of movement and coordinated muscle control (Gibb, 1992). PD patients have lost at least 60-70% of their dopamine-producing cells by the time motor symptoms appear (Fearnley and Lees, 1991). Although dopamine and the nigrostriatal pathway are primarily affected, there is evidence of disruption to other brain regions (e.g. locus ceoruleus, specific reticular nuclei) and circuits (e.g., mesolimbic pathway) as well, resulting in noradrenergic, serotonergic, and cholinergic abnormalities of the basal ganglia (Lang and Lozano, 1998, Mackin, 2000). Decreased dopamine in the mesolimbic pathway, a system related to reward sensitivity, may contribute to psychiatric symptoms of depression and apathy (Lieberman, 2006; Fibiger, 1984).

The classic triad of motor signs in PD include resting tremor, rigidity, and bradykinesia/akinesia (Lang and Lozano, 1998). Resting tremor is the most common and identifiable sign of disease, being the initial complaint in approximately 70% to 75% of cases (Stern, 1993). Tremors often occur in the hands, fingers, forearms, foot, mouth, or chin, and take place when the limbs are at rest. When the patient voluntarily initiates movement, however, the tremor subsides. Rigidity refers to muscle stiffness that occurs, also called cogwheeling, which can result in muscle pain or discomfort during movement.

Bradykinesia refers to the slowness of voluntary movement, such as standing up, walking, and sitting down, that occurs because of delayed transmission signals from the brain to the muscles. Parkinson's gait, characterized by a shortened stride, and shuffling steps, is a common feature. Other primary motor symptoms include postural instability, or poor balance, and other coordination impairment. In later stages of the disease, akinesia (lack of voluntary movement), festination (more severe and abnormal gait pattern), hypophonia (voice weakness), dysarthria (speech impairment), chewing and swallowing difficulties, as well as drooling can occur (Mackin, 2000).

Symptom progression varies by individual but typically progresses over a period of 10 to 20 years (Langston, 1990). Progression can be divided into three states: early, nonfluctuating, and fluctuating (Bradley, 1996). Patients in the early stage of disease may be monosymptomatic or have multiple mild symptoms that do not need medication management, with symptoms typically presenting unilaterally. In the nonfluctuating stage, symptoms become disabling and may not respond to first-line therapy. Once patients have reached the fluctuating stage of disease, continual progression of symptoms has occurred and control over symptoms fluctuates. Postural instability and gait disturbance is increased and function has become more impaired despite therapy.

While motor dysfunction is typically the most apparent in PD, psychiatric symptoms are also prevalent and have been reported to occur in as many as 90% of PD patients (Starkstein et al., 1992b). Depression is the most common psychiatric symptom with apathy, anxiety, sleep disturbance, and hallucinations occurring at high rates as well. Hallucinations are commonly attributable to anti-Parkinson's medications and are

typically visual and benign in nature (Mackin, 2000). Psychiatric symptoms have a significant negative impact on daily functioning, quality of life, cognitive functioning and caregiver burden and distress (Shrag, Jahanshahi, and Quinn, 2000; Chen, 2004; Keranen et al., 2003).

Mental decline affects up to 90% of patients (Pirozzolo, Hansch, Mortimer, Webster, and Kuskowski, 1982). In contrast, *severe* cognitive impairment is less frequent, affecting approximately 25% of patients, as most symptoms are subtle and do not interfere significantly with everyday activities (Mayeux et al., 1990; Stocchi and Brusa, 2000). Characteristic cognitive changes in PD include impairment in attention, abstraction and reasoning, visuospatial abilities, executive functions, and memory (Stocchi and Brusa, 2000).

The greatest area of difficulty for PD patients involves executive functions. These mental operations are involved in adapting to novel situations, problem solving, planning, generating new concepts and elaborating cognitive and behavioral responses to environmental situations (Stocchi and Brusa, 2000). Tests commonly used to evaluate executive functions include Trail Making Test, Stroop test, letter fluency (e.g., FAS), Tower of London for problem solving, and Wisconsin Card Sorting Test (WCST).

Regarding memory disturbance, impairment may be found in working memory, immediate recall, and delayed recall. Research has shown that PD patients have more pronounced impairments on immediate memory tasks compared to delayed memory tasks (Sagar, Cohen, Sullivan, Corkin, and Growdon, 1988). The ability to register, store, and consolidate data appears preserved; however, the recall deficit is due to impairment in the

ability to activate processes that are associated with the functional use of memory stores (Stocchi and Brusa, 2000). Long-term memory is impaired due to a decrease in attentional resources rather than decreased storage (Pillon, Dubois, and Agid, 1996). This decreased attentional capacity interferes with organizing material to be remembered, temporal ordering, and memory retrieval strategies (Harrington, Haaland, Yeo, and Marder, 1990).

Visuospatial disturbance may also be present in PD, but results from a decrease in processing resources rather than from a specific visuospatial dysfunction (Brown and Marsden, 1986).

Depression in PD

Depression is the most common psychiatric symptom in PD, and is found at higher rates in this population than in medical populations with similar levels of disability, such as rheumatoid arthritis (Brown and Jahanshahi, 1995; Cummings and Masterman, 1999; Zesiewicz and Hauser, 2000). Prevalence estimates of depression in PD range from 3 to 70% (Cummings, 1992; Burn, 2002), although most estimates are closer to 40%, with just over half meeting criteria for major depression and just under half meeting criteria for dysthymia or minor depression (Cummings, 1992). The variability reported across studies is partially dependent upon heterogeneous samples used (e.g., hospitalized, community-based) as well as the research tools used to measure depression, with lower rates generally reported in studies that include diagnostic criteria and scripted interviews (e.g., Structure Clinical Interview for the DSM-IV, SCID)

compared to studies using rating scales (e.g., Beck Depression Inventory, BDI; Beck et al., 1961, 1996) (Edwards et al., 2002).

Symptom overlap also contributes to the variability in prevalence estimates. Symptoms of depression, primarily somatic [e.g., psychomotor retardation, flat affect, "masked facies" (reduced facial expression of emotion), anergia], often overlap with core features of PD (Edwards et al., 2002), and may lead to an over-estimation of depression in patient samples. Most prevalence studies in research centers find depression in 40% to 50% of PD patients (Edwards et al., 2002; Mayeux, Stern, Williams, Sano, and Cote, 1986; der Gotham, Brown, and Marsden, 1986), with half meeting criteria for major depressive disorder (MDD) and half meeting criteria for dysthymia or minor depression (Starkstein, Preziosi, Bolduc, and Robinson, 1990b; Brown and MacCarthy, 1990).

Research studies that use diagnostic criteria in identifying levels of depression typically define major and minor depression using criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). According to the most recent edition of the DSM (i.e., DSM-IV-TR; APA, 2000) major depression is defined by the presence of five or more of the following symptoms during the same two-week period and representing a change from previous functioning, with at least one of the symptoms being (1) or (2):

(1) depressed mood
(2) markedly diminished interest or pleasure in all, or almost all, activities
(3) significant weight loss when not dieting or weight gain, or decrease in appetite
(4) insomnia or hypersomnia
(5) psychomotor agitation or retardation
(6) fatigue or loss of energy
(7) feelings of worthlessness or excessive or inappropriate guilt
(8) diminished ability to think or concentrate, or indecisiveness

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

As for minor depression, depressive symptoms must be present for at least two weeks but fewer than five symptoms are required.

Depression in PD differs from idiopathic depression in that PD patients experience relatively increased levels of dysphoria and pessimism about the future, irritability, sadness and suicidal ideation, while guilt, self-blame, feelings of failure, and completed suicide are less common (Brown, MacCarthy, Der Gotham, and Marsden, 1988; Taylor, Saint-Cyr, Lang, and Kenny, 1986). Depression in PD is an important issue to address as these patients have more rapid disease progression, increased cognitive decline, increased functional disability, and poorer quality of life than PD patients without depression (Sano et al., 1989; Starkstein et al., 1992b; Cole et al., 1996).

It remains unclear whether PD patients have a biological vulnerability to depression, or whether depression is a reaction to disability. In support of the former hypothesis, Schuurman et al. (2002) found an increased incidence of PD in patients with a prior history of depression, perhaps reflecting a biological risk factor for depression in still symptom-free, preclinical stages of PD. Other studies also support that symptoms of depression often precede motor symptoms and the diagnosis of PD (Brown and Jahanshahi, 1995; Cummings and Masterman, 1999).

Hypotheses for the etiology of depression in PD tend to favor neurodegeneration as the primary source (Tandberg, Larsen, Aarsland, Laake, and Cummings, 1997; Cummings and Masterman, 1999). Evidence exists to suggest that dopamine, serotonin,

and norepinephrine play an important role in depression (e.g., Cummings and Masterman, 1999; Zesiewicz, Gold, Chari, and Hauser, 1999). PD patients who experience the 'on-off' phenomenon (i.e., fluctuations in motor symptoms that are associated with response to medication), for instance, complain of a greater level of depression during the 'off' state, when dopamine levels are low and motor symptoms are more severe (Menza, Sage, Marshall, Cody, and Duvoisin, 1990). Several studies have found lower levels of 5-hydroxyindoleacetic acid, the principal metabolite of serotonin, in PD patients with depression as compared to PD patients without depression (e.g., Sjostrom and Ross, 1973; Ashcroft et al., 1966). In addition, norepinephrine levels are more markedly decreased in PD patients with depression as compared to those without depression (Lieberman, 2006). In PD, each of these neurotransmitter systems is disrupted and may underlie the high rates of depression as well as the cognitive impairment that is experienced.

Depression and Cognition in PD

Prior studies of PD patients indicate that depression has an adverse impact on cognitive functioning and may serve as a risk factor for cognitive decline. One epidemiologic study revealed that depression was a significant and independent predictor of incident dementia in PD (Stern, Marder, Tang, and Mayeax, 1993). In the first longitudinal study to investigate the influence of depression on cognitive decline in PD, Starkstein and colleagues (Starkstein, Bolduc, Mayberg, Preziosi, and Robinson, 1990a) found that patients who were depressed at baseline showed significantly greater decline

in global cognitive functioning (i.e., MMSE score) at a three- to four-year follow-up as compared to PD patients who were not depressed at baseline.

In a later study, Starkstein et al. (1992b) divided depressed PD patients into two groups: (1) those meeting DSM-III criteria for major depression, and (2) those meeting DSM-III criteria for minor depression. At one year follow-up, patients with *major* depression at baseline evaluation showed significantly greater decline in global cognitive functioning than those with *minor* depression or *no* depression at baseline. Patients were matched for duration of illness and disability severity in order to control for the possibility that these disease factors, rather than depression, were accounting for the cognitive declines.

In a series of studies, Tröster and colleagues built upon the literature to further investigate the relationship between depression and cognition in PD (i.e., Tröster, 1995a; Tröster, 1995b; Norman, Tröster, Fields, and Brooks, 2002). First, they compared PD patients with depression (PDD) and without depression (PDN) to normal control (NC) subjects matched for age, education, gender, disease duration, age of disease onset, and disease severity to find that both PD groups (PDD and PDN) showed greater impairment on a screening measure of global cognitive ability (i.e., Mattis Dementia Rating Scale, DRS), with particular impairments on Conceptualization and Initiation/Perseveration subscales, as compared to NC subjects. PDD patients performed significantly *worse* than PDN patients (Tröster, 1995a). To follow, they used a more extensive battery of neurocognitive assessments to evaluate the qualitative difference in cognitive abilities between PDD and PDN patients (Tröster, 1995b). Results suggested that depression

exacerbated some memory and language impairments previously associated with PD and that depression influences the *severity* rather than the *quality,* or pattern, of cognitive impairment in PD.

In a third study, these researchers (Norman et al., 2002) added a comparison group of subjects with depression but without PD (D) that would allow them to determine whether the previously identified cognitive impairments were due to a combined effect of PD and depression or to depression alone. This is important since the same frontal metabolic changes that may be strongly related to cognitive impairment are found in depressed individuals regardless of having a PD diagnosis (Dolan et al., 1994; Norman et al., 2002). Results revealed poorer overall cognitive functioning (i.e., DRS total) in both PD groups (PDD and PDN) as compared to non-PD groups (NC and D). Interestingly, both depressed groups (D and PDD) performed more poorly on the Memory subscale as compared to PDN patients, suggesting that the memory impairment found in PDD patients may be a result of depression alone as opposed to a combined effect of depression and PD.

In a similar study, Kuzis and colleagues (1997) found that patients with depression, with or without PD, showed significantly greater impairment on verbal executive (fluency) ability and auditory attention as compared to those who were non-depressed (PDN and NC). PDD patients were significantly more impaired than the other three groups on concept formation (i.e., Raven Progressive Matrices) and set shifting (Wisconsin Card Sorting Test), a measure of executive functioning. Further, no differences in cognitive performance were found between PDN patients and NC subjects.

In sum, the presence of depression in PD may exacerbate existing cognitive deficits on tasks such as concept formation, memory, language, and executive functioning.

Apathy in PD

In contrast to depression, apathy and abulia (a more severe form of apathy) are not characterized by anhedonia, hopelessness, or low mood; rather, they are characterized by isolated lack of motivation and self-initiative (Shrag, 2004). The study of apathy as a neuropsychiatric construct in neurological disorders has only recently begun, with its initiation in 1990 (Marin, 1990; Marin, Biedryzycki, and Firinciogullari, 1990; Burns, Folstein, Brandt, and Folstein, 1990; Robinson and Starkstein, 1990). Apathy, derived from the Greek term *pathos,* meaning passions, is conventionally defined as the absence or lack of emotion, feeling, interest, or concern (Marin, 1990, 1991). Clinically, this definition of apathy is lacking and fails to address a variety of other psychological features. Individuals with frontal lobe injury, for instance, may be experiencing apathy along with some other intense emotion, such as irritability or euphoria. Similarly, a depressed individual may appear to be "lacking emotion, interest, and concern," while s/he is indeed experiencing severe internal emotional pain.

Marin provided a more clinically appropriate definition of apathy as a primary *motivational impairment* that is, importantly, not secondary to cognitive or intellectual impairment, emotional distress, or diminished level of consciousness (drowsiness and/or diminished attention) (Marin, 1990, 1991). One who meets this definition of apathy may

be regarded as having apathy *syndrome*. Loss of motivation due to disturbance of intellect (e.g., dementia), emotion (e.g., depression), or level of consciousness (e.g., delirium) defines the *symptom* of apathy (Marin, 1991). Motivation itself refers to characteristics and determinants of goal-directed behavior (Marin, 1991).

Stuss et al. (2000) revised the definition of apathy as "an absence of responsiveness to stimuli as demonstrated by a lack of self-initiated action," suggesting that this definition would allow for objective behavioral measurement. They proposed that previous conceptualizations of apathy as a lack of motivation were flawed in that assessment of inner urges is problematic and necessitates inference based on observations of affect and behavior.

Marin (1991) proposed that symptoms of apathy can be classified into three concomitants of goal-directed behavior: "emotional" (i.e., lack of emotional responsiveness; lack of excitement or emotional intensity; unchanging affect), "cognitive" (i.e., lack of interest; lack of concern about one's personal problems; diminished importance or value attributed to various goal-related domains), and "(overt) behavioral" (i.e., lack of effort; lack of initiative or perseverance; compliance or dependence on others to structure activity).

Since apathy itself may be considered as behavioral (i.e., an observable state), Levy and Dubois (2005) refer to the third domain as an "auto-activation deficit" that is not primarily due to an "emotional" or "cognitive" deficit and can be reversed by external stimulation. They proposed that the three concomitants of apathy (i.e., emotional-affective, cognitive, and auto-activation of behavior) may each be explained by

disruption to three underlying mechanisms and their associative basal ganglia subregions: orbital-medial, dorsal-lateral, and dorsal-medial streams. Amotivational symptoms are reported in several cases of frontal impairment (i.e., stroke, degeneration, head injury) and frontal-subcortical limbic dysfunction (i.e., PD, AD, stroke) and may underlie associated executive functioning deficits (Isella et al., 2002).

PD is a classic example of a subcortical disorder in which apathy is a well-recognized feature (Isella et al., 2002; Pluck and Brown, 2002; Aarsland et al., 1999; Starkstein et al., 1993, 1995; Marsden and Parkes, 1977) and it is hypothesized that nigrostriatal dopamine depletion in PD may contribute (Levy and Dubois, 2005). Clinically significant apathetic symptoms are present in approximately 40% to 45% of PD patients (Isella et al., 2002; Starkstein et al., 1992a), compared to 6.8% in healthy older adults (Onyike et al., 2007), with apathetic *syndromes* (not secondary to depression, delirium, or dementia) present in about 12% of PD patients (Starkstein et al., 1992a).

Apathy appears to be a result of neurological disturbance rather than a result of psychosocial limitations of physical disability. Pluck and Brown (2002) showed that, while PD and osteoarthritis are similarly chronic, progressive conditions that cause significant levels of disablement, significant levels of apathy were found in PD patients, but no evidence of apathy was present in osteoarthritic patients. Isella et al. (2002) showed that groups of patients with low, moderate, and high levels of apathy did not differ from each other in PD duration or severity, suggesting that apathy unlikely represents a simple reaction to disability. These findings together have been provided as

support for the view that apathy is not a psychological response to physical disability, but rather a neurobiological feature of PD.

Some hypotheses suggest that apathy and depression are related to distinct neurological circuits, with depression being secondary to dysfunction of brainstem serotoninergic neurons (i.e., raphe nuclei) that project to limbic areas, and apathy derived from the noradrenergic deficit at the locus coeruleus (connected with cortical and subcortical structures) (Starkstein et al., 1992a; Mayeux et al., 1987). Marin (1990, 1991; also see Isella et al., 2002) suggested that a frontal-subcortical limbic circuit (i.e., prefrontal cortex, anterior cingulate gyrus, entorhinal cortex, and the basal ganglia), which seems to play a central role in conveying emotionally relevant information, elaborating drive, and in planning and monitoring motivated behavior, may mediate the association found between apathy and executive functioning. Dysfunction of this region may result in executive deficits, amotivation, and/or of the capacity to organize goal-directed behavior.

Apathy and Depression: Independent Clinical Phenomena

While certain symptoms may be *shared* among apathy and depression (i.e., diminished interest, psychomotor retardation, fatigue/hypersomnia, lack of insight), several researchers have suggested that certain symptoms are *unique* to apathy (i.e., blunted affect, indifference, low social engagement, diminished initiation, poor persistence) and certain symptoms are *unique* to depression (i.e., dysphoria, suicidal

ideation, self-criticism, feelings of guilt, pessimism, hopelessness, sleep disturbance) (Marin et al., 1993, Marin 1990, Landes et al., 2001).

Various methods have been employed to examine the discriminability of apathy and depression as independent clinical phenomena. Depression is a syndrome in which apathy may be present, in which case it may be termed apathetic depression (Marin, 1990). In this instance, a depressed person's apathy may be described by a person's inactivity and expressed loss of interest in usual activities. However, there are several instances in which depression may exist in the *absence* of apathy. In the case of the depressed person who demonstrates deliberate and active avoidant behavior, or in the extreme case of suicide, clearly apathy (which describes passivity or a lack of goal-directed behavior) is not an accurate descriptor (Marin, 1990). Further, apathy may exist as a distinct syndrome, in which, by definition, there is absence of emotional distress.

Weitzner, Kanfer, and Booth-Jones (2005) described four cases of pituitary disease patients who appeared to be suffering from depression, but when diagnosed and treated for depression they showed little response to treatment. When the patients were asked about their mood, all stated that they were experiencing chronic fatigue and lack of motivation, and were not feeling depressed. When the diagnosis of apathy syndrome was considered and treatment with methylphenidate was implemented, the patients' condition improved subjectively and on objective cognitive tasks (i.e., verbal and nonverbal learning, several executive tasks, and psychomotor speed).

One method of distinguishing apathy and depression is to evaluate the rates and relationships between apathy and depression in different diagnostic groups. Marin et al.

(Marin, Firinciogullari, and Biedrzycki, 1994) evaluated patients diagnosed with Alzheimer's disease (AD), stroke, and major depression using the Apathy Evaluation Scale (AES; Marin, Biedrzycki, and Firinciogullari, 1991) and the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). Despite the fact that there was a significant correlation found between apathy and depression scores when all five diagnostic groups were included in the analysis, proportions of patients with apathy and/or depression varied considerably among groups. Specifically, AD patients showed high levels of apathy and low levels of depression, left hemisphere stroke patients and patients with major depression showed high levels of depression and low levels of apathy, and patients with right hemisphere stroke showed equivalent levels of apathy and depression. The authors used this evidence to suggest that apathy and depression are clinically distinct neuropsychiatric syndromes.

Levy et al. (1998) evaluated whether apathy and depression may be produced by different neuroanatomical or neurochemical substrates by evaluating these two symptoms in different diagnostic groups, including patients diagnosed with PD, AD, frontotemporal dementia (FTD), progressive supranuclear palsy (PSP) and Huntington's disease (HD). Firstly, apathy and depression were *not* correlated in the combined sample. Secondly, the frequency of apathy and depression significantly varied across groups with a large number of AD, FTD, and PSP patients having apathy without depression, and many PD and HD patients having depression without apathy. This disparity was especially notable in patients with PD and PSP. Few PD patients presented with apathy alone compared to those who had depression with or without apathy, and few PSP patients presented with

depression, but a high frequency of PSP patients presented with apathy. These findings suggest that the relationship between apathy and depression appears to be disease-specific.

Landes et al. (2005) explored the differential relationship of apathy, dysphoria, and depression with other clinical variables (i.e., stage of disease, cognitive impairment, and functional impairment) in patients diagnosed with Alzheimer's disease to provide support for the differentiation of apathy and mood disturbance. Their analyses revealed that apathy occurs more frequently than dysphoria in AD. Apathy was strongly related to disease severity, cognitive impairment, activities of daily living, while dysphoria was weakly related or unrelated to these variables. Landes et al. (2005) provided these results as evidence for the importance of a syndrome-based approach, with emphasis on the importance of distinguishing dysphoria from apathy syndrome.

Apathy, Depression and Cognition

Another method of dissociating apathy and depression as distinct constructs is to evaluate their independent influences on cognitive functioning. Some studies have revealed an effect of apathy on cognitive functioning in PD that is distinct from that of depression. Starkstein and colleagues (2005) demonstrated a significant association of apathy and global cognitive abilities, as measured with the Mini Mental Status Exam (MMSE), but no significant association of depression and global cognitive abilities. In their sample of Alzheimer's disease patients, those with apathy had significantly more severe cognitive deficits than those without apathy. Levy (1998) also found that apathy

correlated significantly with increased cognitive impairment as measured with the MMSE whereas depression did not.

To investigate depression, apathy, and cognition in a sample of patients diagnosed with Alzheimer's disease, Kusiz and colleagues (1999) classified patients into four groups: (1) depression-only (without apathy); (2) apathy-only (without depression); (3) both depression and apathy; and (4) controls with neither depression nor apathy. Patients meeting the DSM-IV criteria for major depression or dysthymia were considered depressed, whereas patients scoring more than two standard deviations above the mean apathy scale score were considered apathetic. Using ANOVA and post hoc t-tests to compare groups, Kusiz and colleagues found that patients with apathy only (without depression) had significantly lower scores on verbal memory and confrontational naming compared to patients without apathy (depression-only and control). Patients with apathy only (without depression) and patients with both apathy and depression had significantly lower scores on a dexterity task as compared to patients with neither apathy nor depression (controls) and had significantly lower scores on two executive measures as compared to patients without apathy (depression-only and control). Overall, their results suggest that memory and executive deficits were associated with apathy rather than depression.

In a sample of non-demented older adults diagnosed with major depressive disorder (MDD), Feil and colleagues (2003) examined apathy, depression, and cognitive performance using correlations and individual stepwise regression analyses. Results of correlational analyses revealed significant correlations between apathy and two cognitive

measures: nonverbal executive (WCST-Other Responses) and processing speed (Stroop B). Near-significant relationships were found between apathy and two verbal executive measures (FAS and Stroop C). Depression was significantly correlated with two information processing speed measures (Stroop A and Stroop B) and near-significant relationships were found between depression and verbal executive performance (Stroop C).

Individual stepwise regression (i.e., entry of the independent variables, IVs, is determined by the statistical software based on the magnitude of correlations with the dependent variable) was performed on the four cognitive measures that significantly correlated with apathy (i.e., Stroop B, Stroop C, FAS, and WCST) to determine whether apathy uniquely accounted for test score variance over and above that accounted for by depression, health status, age, and education. Regression analyses on the four IVs revealed that apathy alone accounted for a significant amount of test score variance on a nonverbal executive task (WCST; $R^2 = 0.13$) and that apathy plus demographic variables together accounted for a significant amount of variance on two verbal executive measures (FAS and Stroop C). Specifically, education was the best predictor of one verbal executive measure (FAS; $R^2 = 0.074$), followed by apathy ($R^2 = 0.070$). Age was the best predictor of the second verbal executive measure (Stroop C; $R^2 = 0.171$), followed by apathy ($R^2 = 0.100$). Apathy, depression, and age together accounted for a significant amount of variance on a processing speed task (total $R^2 = 0.308$). Specifically, depression was the best predictor of processing speed (Stroop B; $R^2 = 0.219$), followed by age ($R^2 = 0.046$), then apathy ($R^2 = 0.043$). Overall, both apathy and depression were associated

with some cognitive variables, but apathy was a greater influence on executive functioning than was depression severity.

Apathy, Depression and Cognition in PD

Only four studies have investigated depression, apathy, and cognition in a sample of patients diagnosed with PD using a more extensive battery of neurocognitive assessments (Starkstein et al., 1992a; Isella et al., 2002; Pluck and Brown, 2002; Aarsland et al., 1999). All four studies revealed a significant relationship between apathy and cognitive impairment, particularly in executive functioning.

Starkstein and colleagues (1992a) examined correlates of apathy, depression, and cognition by comparing PD patients with apathy only, depression only, apathy plus comorbid depression, and neither depression nor apathy (control subjects). This research team found that the patients with apathy (with or without depression) showed significantly more deficits on *time-dependent* executive tasks (specifically, poorer verbal fluency/executive as measured by FAS and slower performance on Trail Making Test B), whereas depressed patients showed significantly more deficits in an *untimed* executive task (i.e., Wisconsin Card Sorting Task, WCST). Both apathy and depression were significantly associated with impaired episodic verbal memory.

Aarsland and colleagues (1999) found a significant correlation between apathy and number of errors on the Stroop test, a measure of executive functioning. This relationship was not found between depression and cognition or between apathy and

depression, suggesting that the relationship between apathy and cognitive decline is not due to depression.

Isella and colleagues (2002) compared PD patients with low, moderate, and high levels of apathy and found a clear association between apathy and executive functioning, with the high-apathy group showing significantly greater impairment in executive functioning [i.e., Executive Interview (EXIT), letter fluency and category fluency] compared to the other two groups. Depression was not significantly correlated with apathy or any cognitive abilities measured. The research group did not, however, examine the independent influence of depression on cognitive abilities.

Pluck and Brown (2002) found similar results showing that apathy, but not depression, was related to deficits in global cognitive ability (especially on the memory and language subscales) and on three measures of executive functioning (i.e., category fluency, Stroop Color-Word test, and WCST). A series of exploratory regression analyses demonstrated that, while none of the clinical or demographic variables (age, sex, education, duration of illness, Hoehn and Yahr stage or Schwab and England score) predicted apathy ratings, category fluency and Stroop Interference were the best predictors of apathy scores.

Overall, these studies suggest that apathy and depression are independent clinical phenomena that negatively affect memory, language, and executive functioning. Further, they suggest that apathy may account for cognitive deficits over and above that of depression, particularly in the cognitive domain of executive functioning.

Limitations of Previous Research

Although several studies have examined the relationships between apathy, depression, and cognitive functioning in patients with neurological conditions (e.g., Alzheimer's disease, Frontotemporal Dementia, and Huntington's disease), only four have examined *specific* domains of neurocognitive impairment in patients diagnosed with PD. The few studies have examined these relationships are limited in several ways.

First, many have used measures of apathy and/or depression with questionable ability to measure symptoms unique to the target construct. Symptom overlap hinders discriminability among constructs. For instance, Starkstein et al. (1992a) used the Hamilton Depression Rating Scale (HDRS), a widely used measure that has been accused of being a weak index of depressive severity due to poor content validity and a multidimensional factor structure (Gibbons, Clark, and Kupfer, 1993; Bagby, Ryder, Schuller, and Marshall, 2004). Aarsland et al. (1999) used the Neuropsychiatric Inventory (NPI; Cummings et al., 1994), a measure commonly used in dementia to measure dysphoria, apathy, and anxiety, among several other neuropsychiatric disturbances. Factor analysis of the NPI showed that apathy and anxiety existed together on one factor, revealing that the NPI measures *shared* symptoms of apathy and anxiety.

Pluck and Brown (2002) measured depressive symptoms using the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, et al., 1961), which includes numerous somatic items that overlap with symptoms of PD itself. Use of such measures may artificially inflate depressive symptom severity in medical populations (Taylor, Lovibond, Nicholas, Cayley, and Wilson, 2005).

In the present study, the Apathy Evaluation Scale – self-rating form (AES-S; Marin, 1991), a scale specifically designed to discriminate apathy from depression, will be used to measure apathetic symptoms. The self-rating version of the AES was chosen based on the consideration that motivation is an internal state that informants may not be able to adequately assess. Further, informants may have difficulty distinguishing between emotional symptoms of apathy (i.e., unchanging affect) and "masked facies," a common deficit in PD patients that refers to decreased facial expression. A multitrait-multimethod matrix procedure was used to support the convergent validity and discriminant validity of the AES-S (Marin, 1991). While apathy scales, such as the AES, have been designed to discriminate between apathy and depression, no depression scales have been developed with the intent to eliminate symptoms that overlap with apathy.

The present study will utilize *select* items from the Beck Depression Inventory – II (BDI-II) in an attempt to assess a continuum of depressive symptoms that do not overlap with *apathy* symptoms or with *somatic* symptoms of PD itself. A total of 13 items will be retained from the BDI-II that assess the same content domains as identified in cognitive/affective scale of the BDI-I. Use of the full BDI-II is not ideal for a PD population since many of these patients may experience somatic symptoms that are unrelated to depression (Taylor et al., 2005). Items corresponding to the cognitive/affective scale of the BDI-I will be retained (e.g., sadness, pessimism, sense of failure, etc.) with the exception of the item related to lack of interest due to its possible overlap with apathy. Items that correspond to the somatic/behavior scale of the Beck Depression Inventory – I (BDI-I) (e.g., sleep disturbance, appetite, tiredness/fatigability,

etc.) will be eliminated to protect against artificial inflation of depressive symptom severity.

As mentioned above, most studies investigating the relationships between depression, apathy, and cognition have used measures of global cognitive ability (e.g., MMSE), rather than measures assessing specific cognitive domains. The present study will examine verbal memory and executive functioning, two cognitive abilities that have shown to be associated with depression, apathy, and PD.

Lastly, most of the studies described above have used correlational analyses and ANOVAs with post-hoc comparisons, with the exception of two (Pluck and Brown, 2002; Feil et al., 2003). While such designs are elegant in their ability to evaluate emotional and cognitive differences among groups of individuals, they do not provide information regarding the *degree* to which apathy or depression influences cognition over and above the other. In the present study, hierarchical regression analyses will allow for investigation of the influence of depression on cognitive performance while controlling for the independent influence of apathy, and vice versa.

Purpose of the Proposed Study

The purpose of this study is to examine the independent influence of depression and apathy on cognitive functioning (specifically, memory and executive functioning) in PD patients. Depression is the most common psychiatric symptom in PD and has been shown to be associated with cognitive deficits. Apathy, a symptom related to motivational and

self-initiation impairment, is also prevalent in PD and has gained recent attention in this population.

Several studies have demonstrated evidence to suggest that apathy and depression are independent clinical phenomena. Recent research suggests that apathy may account for cognitive deficits over and above that of depression. However, few studies have examined the *independent* influence of depression and apathy on cognitive abilities in patients diagnosed with PD. The majority of these studies have used simple screening measures of global cognitive ability that are insensitive to specific cognitive abilities, such as executive functioning and verbal memory. In addition, only two studies have examined these relationships using hierarchical regression, only one of which was in a PD population. Hierarchical regression allows us to pit apathy and depression against each other in a test that provides an estimate of the *degree* of influence that depression has on cognitive performance while controlling for the independent influence of apathy, and vice versa

Hypotheses/Predictions

It is hypothesized that increased levels of depression and apathy will be associated with decreased performance on measures of executive and memory abilities. This hypothesis will be examined in two ways: magnitude of correlation coefficients and hierarchical regression. It is predicted that 1) significant negative correlations will observed between measures of depression/apathy and executive/memory abilities and 2)

depression and apathy will significantly predict level of executive and memory abilities when entered as the first variable in hierarchical regression analyses.

It is hypothesized that apathy will be more strongly associated with executive functioning than depressive symptoms. This hypothesis will also be examined in two ways: magnitude of correlation coefficients and hierarchical regression. Using correlational analyses and Hotelling's t-test to compare correlations, it is predicted that the correlation between apathy and executive functioning will be significantly greater than the correlation between depression and executive functioning. Using hierarchical regression, it is predicted that apathy will account for a significant proportion of added variance in executive functioning scores over and above that accounted for by depression alone, but that depression will not account for a significant proportion of added variance in executive functioning scores over and above that accounted for by apathy alone.

Examination of additional findings from regression analyses will also afford exploration of possible independent effects of apathy and depression on memory abilities although hypotheses and predictions for this variable are less clear based on prior literature.

2. Method

Participants

Sixty-eight individuals (44 men, 24 women) diagnosed with idiopathic, non-fluctuating PD, ages 56-82, were included in the present study. Number of participants required was determined by a priori power analysis using G-Power computer program (Faul and Erdfelder, 1992). Sixty-eight participants was needed to yield a power of 0.80 given a medium effect size of d = 0.15. All participants were recruited from Movement Disorder clinics of the University of South Florida Parkinson's Disease Center of Excellence and monthly PD support group meetings in the Tampa Bay area.

Patients with atypical Parkinson's disease (i.e., known cause, including previous exposure to toxins or atypical presentation of symptoms), early onset PD, or current or past history of other neurological disorder, cardiac arrest, psychiatric disturbance (other than depression or anxiety), or head injury with loss of consciousness were excluded from participation. In addition, patients scoring below 24 on the Mini-Mental Status Exam were excluded from participation. All patients were tested during the "on" phase, when medication is effective and motor symptoms are reduced.

Measures

Beck Depression Inventory – II (BDI-II). The BDI-II (Beck, Steer, and Brown, 1996) is a 21-item self-report instrument intended to assess the existence and severity of

depressive symptoms consistent with the depression criteria of the *Diagnostic and Statistical Manual of Mental Disorders – 4th Edition* (DSM-IV; 1994). BDI-II items are scored on a four-point Likert scale (0-3), with statements arranged to represent increasing intensity of a particular symptom of depression. For the purposes of this study, the following 13 items of the BDI-II will be used as a measure of depressive symptom severity: Sadness, Pessimism, Past Failure, Loss of Pleasure, Guilty Feelings, Punishment Feelings, Self-dislike, Self-criticalness, Suicidal Thoughts or Wishes, Crying, Indecisiveness, Worthlessness, and Irritability (see Appendix A). This well-established measure and has excellent reliability and validity. One-week test-retest reliability was reported as $r = 0.93$ (Beck et al., 1996) and internal consistency across studies is excellent ($\alpha = 0.89 – 0.94$) (Dozois and Covin, 2004). Evidence for construct validity has stemmed from several factor analyses (Dozois and Covin, 2004) and convergent, discriminant, and content validity are well-supported (e.g., Beck et al, 1996; Osman et al., 1997; Dozois and Covin, 2004).

Apathy Evaluation Scale – Self-Rating (AES-S) and Informant-Rating (AES-I). The AES-S (Marin, 1991) is an 18-item self-rating scale that was developed to assess apathetic symptoms within behavioral, cognitive, and emotional domains (see Appendix B). Items are scored on a four point Likert scale (1 = "Not at all true"; 2 = "Slightly true"; 3 = "Somewhat true"; 4 = "Very true") and scoring is arranged so that higher scores represent greater apathy. This has been used in a number of clinical groups, including PD and has been found to have good construct validity, internal consistency ($\alpha = 0.86$) and test-retest reliability ($\alpha = 0.76$) (Marin et al., 1991). Multitrait-multimethod matrix

procedures show support for convergent and discriminant validity (Marin, et al, 1991). The AES-I is a parallel measure completed by a relative/spouse who has regular contact with the research participant in order to provide an outside perspective. This was administered when possible in order to investigate informant ratings, however, the AES-S was used for analyses.

Mini Mental State Exam (MMSE). The MMSE (Folstein, Folstein, and McHugh, 1975) is an 11-item examination and the most widely used cognitive screening test. Research provides widespread support for its validity in assessing global cognitive status. Each item assesses one of the following domains: orientation to time, orientation to place, registration, attention, recall, naming, repetition, comprehension, reading, writing, and drawing. Patients scoring less than 24 will be excluded from the study to avoid confounds of significant cognitive impairment, which may affect patients' ability to validly complete self-report measures.

Wisconsin Card Sorting Test-64 (WCST-64). The WCST-64 (Kongs, Thompson, Iverson, and Heaton, 2000) is a shortened version of the Wisconsin Card Sorting Test, Revised and Expanded (WCST; Heaton, Chelune, Talley, Kay, and Curtiss, 1993), one of the most widely used measures of executive functioning. The test provides detailed feedback regarding specific aspects of problem-solving abilities, such as inefficient initial conceptualization, perseveration, failure to maintain a cognitive set, and inefficient learning. In this task, subjects are required to match 64 cards to one of four target cards. Matching rules are color, shape/form, or number of symbols. Subjects infer these rules from feedback about whether the match was correct, which is provided by the tester

immediately following the match. After ten consecutive correct matches, the tester changes the rule without preannouncement. The Number of Categories Completed score will be selected for the present analysis as it reflects the ability to shift set from one activity to the next. Past research shows that PD patients are particularly sensitive to this type of task (eg., Cools, Barker, Sahakian, and Robbins, 2001). The WCST-64 has excellent interscorer and intrascorer reliability (0.88-0.93 and 0.91-0.96, respectively) (Paolo et al., 1996; Axelrod, Goldman, and Woodard, 1992), and has demonstrated sensitivity to executive impairment in PD, Alzheimers disease, and in individuals who have suffered frontal lobe injury (e.g., Paolo et al., 1996; Robinson, Heaton, Lehman, and Stilson, 1980).

Hopkins Verbal Learning Test-Revised (HVLT-R). The HVLT-R (Benedict, Schretlen, Groninger, Brandt, 1998) is a verbal learning and memory test that consists of a list of 12 words, each belonging to one of three semantic categories. There are three immediate memory trials, one delayed recall trial (20-25 minutes after completion of the third immediate memory trial), and a recognition trial. The Total Recall score, which is the sum of the three immediate memory trials, will be selected for the present analysis because prior research shows that PD patients have more pronounced impairments on immediate memory tasks compared to delayed memory tasks (Sagar et al., 1988). Literature supports the reliability of the HVLT-R (e.g., six-week test-retest reliability for Total Recall is 0.74 in healthy elderly) (Benedict et al., 1998) as well as construct discriminative, and predictive validity. Shapiro and colleagues (1999) demonstrated that HVLT Total Recall was correlated with a prose verbal memory test (i.e., Logical

Memory) at $r = 0.75$, showed 95% sensitivity and 83% specificity, had a positive predictive value of 0.84, and a negative predictive value of 0.94.).

Procedure

Eligible participants were recruited from the Department of Neurology and Movement Disorders Clinics at the University of South Florida and from support group meetings in the Tampa Bay area. Patients were invited to participate by clinic neurologists during regular patient visits or by a research assistant on the present study. Diagnosis and staging of PD was determined by board-certified neurologists using the Hoehn and Yahr scale (1967), a standard staging scale commonly used in PD research.

After giving informed consent, participants were screened with the MMSE to ensure that they met basic cognitive requirements. Those with an MMSE score below 24 were excluded from further participation. Next, included participants were asked to complete a series of self-report measures to determine their affective status. Some participants completed these questionnaires after their appointment and returned them by mail within one week of participation. A memory test was then administered by the primary investigator, followed by a test of executive functioning.

Statistical Analyses

Two approaches were used to examine the relationship between cognitive functioning (memory and executive functioning) and psychological symptom severity (depression and apathy) in the present study: (1) correlation coefficients, and (2)

regression analyses. First, correlation coefficients were calculated between psychological and cognitive variables, revealing a total of four correlation coefficients (i.e., 1. executive function and depression, 2. executive function and apathy, 3. memory and depression, 4. memory and apathy).

Hierarchical regression analyses were then conducted to compare the degree of influence that depression and apathy have on cognitive impairment. Executive function and memory served as criterion variables and were evaluated independently. In the two hierarchical regression analyses of *executive* ability, the independent effects of depression and apathy on executive functioning were assessed. In the first hierarchical regression analysis, the selected items of the BDI-II were entered to account for the influence of depressive symptoms. Finally, the AES-S was entered, leaving a final change in R^2 that reflects the amount of variance in executive functioning that is accounted for by apathy above and beyond the influence of depression (i.e., while controlling for the effects of depression). In the second hierarchical regression analysis of executive ability, the AES-S was entered to account for the influence of apathy symptoms. Finally, the selected items of the BDI-II were entered, leaving a final change in R^2 that reflects the amount of variance in executive functioning that is accounted for by depression above and beyond the influence of apathy (i.e., while controlling for the effects of apathy).

The same two hierarchical regression analyses were repeated to assess the independent influence of depression and apathy on *memory*. The final R^2 in both hierarchical regression analyses reflects the amount of variance in memory that is accounted for by the independent influence of depression or apathy.

3. Results

Diagnostics

SPSS 15.0 for Windows was used to manage and analyze data. Prior to conducting analyses to investigate the above stated hypotheses, data point distributions were examined for significant departures from normality and data was examined to ascertain that regression assumptions were met. Examination of boxplots and standardized residuals confirmed that data points of interest fell within acceptable limits (+/- 3 standard deviations from the mean) for analysis. Cook's d (range: 0.000 – 0.218), hat values (range: 0.004 – 0.174), and Mahalanobis distance (range: 0-.256 – 11.672) values revealed that no individual cases were producing undue influence on the regression model. Examination of boxplots and descriptive statistics confirmed the absence of skewness and kurtosis among the variables. Scatterplots of regression standardized residuals and predicted values verified the assumptions of homoscedasticity and linearity. The inspection of VIF (all values ≤ 1.466) and tolerance statistics (all values ≥ 0.682), eigenvalues and variance proportions, as well as correlation coefficients between predictors ($r < 0.60$) revealed that the assumption of no multicollinearity was met. Durbin-Watson statistic values (range: 1.729 – 2.545) fell within acceptable limits, supporting the assumption of independent errors.

Descriptives

Data was obtained from 68 Parkinson's disease patients between the ages of 56 and 82 years (mean = 69.96, SD = 7.03). Subjects were majority male (n = 45, 66.2%) and Caucasian (n = 63; 92.6%), Education level ranged from 12-22 years (mean = 15.74, SD = 2.62). All patients were in the mild to moderate stages of diseases (Hoehn and Yahr Stages 1-3). Depression severity ranged from no symptoms of depression to moderate levels and apathy severity ranged from no apathy symptoms to severe levels. Cognitive performance ranged from better than expected to severe impairment. A summary of demographic, clinical, and experimental variables from this sample is provided in Tables 1 and 2.

Table 1: Summary of demographic and clinical characteristics

	Range	Mean (SD)
Age	56 - 82	69.96 (7.03)
Years of education	12 - 22	15.74 (2.62)
Disease duration (yrs)	<1 - 24	7.07 (4.96)

	n	%
Gender		
Male	45	66.2 %
Female	23	33.8 %
Ethnicity		
White	63	92.6 %
Black	1	1.5 %
Hispanic	4	5.9 %

Table 1 (Continued)

	n	%
Stage of disease		
1	15	22.1 %
2	33	48.5 %
3	9	13.2 %
data not obtained	11	16.2 %
Side of onset		
R	32	47.1 %
L	31	45.6 %
data not obtained	5	7.4 %

Table 2: Summary of mood and cognitive scores including age-adjusted T-scores

	Raw scores		T-scores	
	Range	Mean (SD)	Range	Mean (SD)
Depression (21-item BDI)	0-23	10.62 (5.26)	37-76	44.75 (9.16)
Depression (13-item BDI)	0-14	4.10 (3.49)	--	--
Apathy (AES-S)	18-50	30.29 (7.51)	34-84	46.57 (11.73)
Imm Memory* (HVLT Total Recall)	8-33	21.31 (5.84)	20-70	43.34 (10.97)
Executive Fx** (WCST Categories)	0-5	2.06 (1.71)	17-64	38.75 (10.06)

* T-scores adjusted for age and education
** T-scores adjusted for age

Correlation analyses were used to evaluate the relationships between demographic and clinical variables (i.e., age, years of education, disease duration), and experimental variables (i.e., depression, apathy, memory, executive functioning) (see Table 3). Raw scores were used in all correlation and regression analyses. Increasing age was significantly associated with decreases in memory and executive performance (r = -0.279, $p < 0.01$ and r = -0.312, $p < 0.05$, respectively). Years of education and disease duration were not associated with cognitive performance.

Table 3: Correlations

	Depression (21-item BDI)	Depression (13-item BDI)	Apathy (AES-S)	Memory (HVLT Total Recall)	Executive Fx (WCST Categories)
Age	**.303****	0.189^{ns}	**.233**^{t}	**-0.279***	**-0.312****
Education	0.022^{ns}	0.086^{ns}	0.150^{ns}	-0.026^{ns}	0.053^{ns}
Disease duration	-0.056^{ns}	-0.096^{ns}	-0.061^{ns}	0.111^{ns}	0.158^{ns}

* *p<0.05* ** *p<0.01* ^{t} *trend, p<0.10* ^{ns} *not significant, p>0.10*

Frequencies of apathy and depression

The frequency of apathy, using AES-S ≥ 38 as representative of clinically significant elevations in apathy (Pluck and Brown, 2002; Rabkin, Ferrando, van Gorp, et al., 2000), was 20%. This rate appears to be lower than reported frequencies of apathy in other studies using self-ratings (Kirsch-Darrow, Fernandez, Marsiske, Okun, and Bowers, 2006) and may be due to measurement differences or to the restricted range of disease severity in the present sample, as all of our participants were in the mild to moderate

stages of disease. When using the more commonly used BDI cut-off score of 10, the frequency of mild or greater depressive symptoms was 52%, which is similar to percentages reported in previous studies (e.g., Brooks and Doder, 2001; Cummings, 1992). When using a cut-off score of 16/18, suggested for more accurate identification of diagnosable depression in mild to moderate PD patients (Silberman et al., 2006; Leentjens, Verhey, Luijckx, and Troost, 2000), the frequency of depression was 13.3%. The majority of patients with depression severity scores above this cut-off were in the mild range and fewer fell within the moderate range.

Based on AES and BDI cut-off scores of 38 and 18, respectively, patients in present study were assigned to four categories for frequency analyses (i.e., apathy-only, depression-only, apathy and depression, and no apathy or depression). The majority of patients (72.1%) were classified as neither apathetic nor depressed, whereas 14.7% of patients were classified as apathy-only, 7.4% as depression-only, and 5.9% as apathy and depression.

Findings related to Hypothesis #1

To investigate the hypothesis that increased levels of depression and apathy will be associated with decreased performance on measures of executive and memory abilities, four correlation coefficients and four simple regressions were examined.

Correlations

Table 4 displays the results of correlation analyses. Increases in depressive symptoms were associated with decreases in memory scores ($r = -0.273$, $p < 0.05$) but were not significantly associated with executive functioning. Increases in apathy symptoms were associated with decreases in both memory ($r = -0.331$, $p < 0.01$) and executive functioning ($r = -0.305$, $p < 0.05$). Apathy and depressive symptoms were positively and moderately correlated ($r = 0.548$, $p < 0.01$).

Table 4: Correlations between mood and cognitive variables

Variable	Depression (13-item BDI)	Apathy (AES-S)	Memory (HVLT Total Recall)	Executive Fx (WCST Categories)
Depression	1.000			
Apathy	**.548****	1.000		
Memory	**-.273***	**-.331****	1.000	
Executive Fx	-.141^{ns}	**-.305***	**.478****	1.000

* *p<0.05* ** *p<0.01* ^{ns} *not significant, p=.251*

Regressions

These relationships are corroborated by four simple regression analyses, in which level of depressive symptoms or apathy symptoms were entered as the sole independent variable (IV) and memory or executive functioning was entered as the sole dependent variable (DV) (see Table 5). First, it was found that level of depressive symptoms significantly predicted memory scores (ß = -.273, $t(66) = -2.309$, $p < 0.05$), with 7.5% of

the variance explained (R^2 = .075, $F(1,66) = 5.331$, $p < 0.05$). Second, level of depressive symptoms did not significantly predict executive functioning scores, as evidenced by a non-significant ß value (ß not significantly different from 0) and a non-significant *F* value. The third simple regression revealed that level of apathy symptoms significantly predicted memory scores (ß = -.331, $t(66) = -2.849$, $p < 0.01$), with 10.9% of the variance explained (R^2 = .109, $F(1,66) = 8.115$, $p < 0.01$). The final simple regression revealed that level of apathy significantly predicted scores of executive functioning (ß = -.305, $t(66) = -2.602$, $p < 0.05$), with 9.3% of the variance explained (R^2 = .093, $F(1,66) = 6.770$, $p < 0.05$).

Table 5: Simple regression analyses

Criterion	*Predictor*	*SB*	*T*	*Sig T*	R^2	*F*	*Sig F*
Memory	Depression	-.273	-2.309	.024*	.075	5.331	**.024***
Exec. Fx	Depression	-.141	-1.158	.251	.020	1.341	.251
Memory	Apathy	-.331	-2.849	.006**	.109	8.115	**.006****
Exec. Fx.	Apathy	-.305	-2.602	.011*	.093	6.770	**.011***

** p<0.05 **p<0.01*
SB=Standardized Beta

Findings related to Hypothesis #2

To investigate the hypothesis that apathy will be more strongly associated with executive functioning than depressive symptoms, two correlation coefficients (1. correlation between executive functioning and depression, and 2. correlation between executive functioning and apathy) and two hierarchical regressions were examined.

Correlations

As mentioned above (see Table 4), executive functioning was significantly correlated with apathy (r = -.305, p < 0.05), but not with depression (r = -.141, p = .251). Due to the non-significant correlation between executive functioning and apathy, the proposed Hotelling's t-test to compare correlations was not conducted.

Regressions

Examination of the first hierarchical regression analysis reveals the influence of apathy on executive functioning scores while controlling for the influence of depressive symptoms (see Table 6-A). In this analysis, depression (IV) is entered in the regression first and apathy (IV) is entered second to assess whether apathy contributed *unique* variance in accounting for executive performance above and beyond that of depressive symptoms. As noted above, depressive symptoms did not account for any significant portion variance in executive performance when entered alone. However, the addition of apathy reveals that apathy accounts for 9.4% of the variance in executive performance, with a significant change in the value of the F-test with the addition of this variable (R^2 = .094, p <0.05; $F(1,65) = 3.372$, p < 0.05).

Table 6-A: Hierarchical regression analyses related to executive functioning

Criterion	*Predictor*	*Unstandard. beta*	*SE*	*SB*	R^2	$R^2\Delta$	$F\Delta$	*Sig* $F\Delta$
Exec. Fx	(Constant)	4.229	.875	--	--	--	--	--
	Depression	.018	.069	.037	.020	.020	1.341	.251
	Apathy	-.074	.032	-.325	.094	**.074**	5.315	**.024***

** p<0.05 **p<0.01*
SE=Standard Error; SB=Standardized Beta

Age effects. Due to the fact that age was significantly correlated with the DV (executive functioning) and was approaching significance ($p = 0.056$) when correlated with one of the IVs (apathy), age was entered into regression equations first in order to control for its influence on executive functioning (see Table 6-B). Following the entry of age, apathy was entered to assess its unique influence on executive functioning while controlling for age. Depression was not entered into this model due to the nonsignificant relationship between depression and executive functioning described above, and to the potential unfavorable effect that entering three predictors may have on power. Analyses revealed that age accounted for 9.7% of the variance in executive performance and apathy accounted for an additional 5.7% of the variance in executive performance.

Table 6-B: Hierarchical regression analyses related to executive functioning, controlling for age

Criterion	*Predictor*	*Unstandard. beta*	*SE*	*SB*	R^2	$R^2\Delta$	$F\Delta$	*Sig* $F\Delta$
Exec. Fx	(Constant)	8.245	2.029	--	--	--	--	--
	Age	-.063	.029	-.258	.097	**.097**	7.095	**.010****
	Depression	.029	.067	.060	.104	.007	.510	.478
	Apathy	-.063	.032	-.278	.157	**.053**	3.989	**.050***

** p<0.05 **p<0.01*
SE=Standard Error; SB=Standardized Beta

Ancillary Analyses

Exploration of the Influence of Apathy and Depression on Memory

In order to explore the independent effects of apathy and depression on memory abilities, two additional hierarchical regressions were conducted and examined. Examination of the first hierarchical regression analysis reveals the influence of apathy on memory scores while controlling for the influence of depressive symptoms (see Table 7-A). In this analysis, depression (IV) is entered in the regression first and apathy (IV) is entered second to assess whether apathy contributed *unique* variance in accounting for memory performance above and beyond that of depressive symptoms. As noted previously, depression accounts for 7.5% of the variance in memory scores when entered first into the regression. The addition of apathy reveals that apathy accounts for an additional 4.7% of unique variance in memory performance, as evidenced by a change in the value of the F-test that *approaches* significance with the addition of this variable (R^2 = .122; R^2 change = .047, p = .067; $F(1,65) = 4.499$, $p < .05$).

For exploratory purposes, a second regression analysis was conducted to evaluate the influence of depressive symptoms on memory performance while controlling for the influence of apathy (see Table 7-A). In this analysis, apathy was entered in the first step and depression was entered second to assess whether depression contributed *unique* variance in accounting for memory performance above and beyond that of apathy symptoms. As noted previously, apathy accounts for 10.9% of the variance in memory scores when entered first into the regression. The addition of depression reveals that depression does not account for any additional or unique variance in memory scores over

and above that of apathy, as evidenced by a non-significant ß value (ß not significantly different from 0) and a non-significant *F* value.

Table 7-A: Hierarchical regression analyses related to immediate memory

Criterion	*Predictor*	*Unstandard. beta*	*SE*	*SB*	R^2	$R^2\Delta$	$F\Delta$	*Sig* $F\Delta$
Memory	(Constant)	28.308	2.943	--	--	--	--	--
	Depression	-.220	.232	-.132	.075	**.075**	5.331	**.024***
	Apathy	-.201	.108	-.259	.122	**.047**	3.467	**.067**^{t}
Memory	(Constant)	28.308	2.943	--	--	--	--	--
	Apathy	-.201	.108	-.259	.109	**.109**	3.115	**.006****
	Depression	-.220	.232	-.132	.122	.012	.896	.347

** p<0.05 **p<0.01 ^{t}trend, p<0.10*
SE=Standard Error; SB=Standardized Beta

Age effects. Due to the fact that age was significantly correlated to the DV (memory) and was approaching significance ($p = 0.056$) when correlated with one of the IVs (apathy), age was entered into regression equations first in order to control for its effect on memory (see Table 7-B). Following the entry of age, depression was entered second and apathy was entered last. Analyses revealed that age accounted for 7.8% of the variance in memory performance ($p = 0.02$), depression accounted for an additional 5.1% of the variance in memory performance ($p = 0.057$), and apathy no longer accounted for a significant portion of additional variance in memory performance (R^2 change = 3.3%, $p = 0.116$). Considering the p-value associated with the entry of apathy last ($p = 0.116$), it is quite possible that the reduction in power caused by entering a third predictor variable into the model (power = 0.75) may have resulted in the inability to adequately identify a significant R^2 change when apathy was entered as the third variable. Interestingly, when

apathy was entered into the regression analysis before depression, level of apathy symptoms significantly accounted for an additional 7.5% of the variance in memory performance ($p = 0.02$), after accounting for the influence of age. In this order of operations, level of depressive symptoms no longer accounted for a significant portion of additional variance in memory performance (R^2 change = 0.9%, $p = 0.411$), consistent with the two-predictor model described previously, which did not include age in the model.

Table 7-B: Hierarchical regression analyses related to immediate memory, controlling for age

		Unstandard.						
Criterion	*Predictor*	*beta*	*SE*	*SB*	R^2	$R^2\Delta$	$F\Delta$	*Sig* $F\Delta$
Memory	(Constant)	39.261	6.907	--	--	--	--	--
	Age	-.171	.098	-.206	.078	**.078**	5.573	**.021***
	Depression	-.190	.229	-.114	.128	**.051**	3.767	**.057t**
	Apathy	-.172	.108	-.221	.162	.033	2.534	.116
Memory	(Constant)	39.261	6.907	--	--	--	--	--
	Age	-.171	.098	-.206	.078	**.078**	5.573	**.021***
	Apathy	-.172	.229	-.221	.153	**.075**	5.733	**.020***
	Depression	-.190	.108	-.114	.162	.009	.685	.411

** p<0.05 **p<0.01 ttrend, p<0.08*
SE=Standard Error; SB=Standardized Beta

Use of the 21-item versus 13-item Version of the BDI-II

All analyses described above included an altered version of the BDI-II (13-item BDI) as the measure of total depressive symptoms, which excluded somatic and apathy-related items in order to reduce potential confounds of these items on the measure of depression. Comparisons were made between regression analyses that used the 13-item

BDI-II and the full 21-item BDI-II in order to assess whether the decision whether or not to include somatic and apathy-related items in the measurement of depressive symptoms would result in disparate findings. Notably, when the full 21-item BDI-II was included in the regression analyses (i.e., 1. memory regressed on apathy and depression, 2. executive functioning regressed on depression and apathy) in place of the 13-item version, results were comparable. In addition, there was little difference in the correlations between apathy and depression severity regardless of whether the full 21-item version or the altered 13-item version was used in the analysis ($r = 0.548$ versus $r = 0.563$, respectively). These findings suggest that the omission of "overlapping" somatic and apathy-related items from the BDI for the purpose of measuring symptoms unique to depression may not be beneficial.

Use of Informant-Ratings versus Self-Ratings of Apathy

Comparisons were made between regression analyses that used the AES self-rating form (AES-S) and the informant-rating form (AES-I) in order to assess whether the source of this information would have an effect on the findings. In the regression analyses that included executive functioning as the DV, results were comparable regardless of whether the AES-S or AES-I was used. In the regression analyses that included memory as the DV, results were also comparable with the use of the AES-I except that the added influence of apathy over and above that of depression reached full statistical significance ($p < 0.05$) as opposed to being a trend.

4. Discussion

The purpose of the present study was to examine the independent influence of depression and apathy on immediate memory and executive functioning in PD patients using sensitive measures of cognitive performance as well as rating scales that assess symptoms unique to depression and apathy. Due to the potential confounds of including somatic and apathy-related items in the measurement of depression severity, only BDI-II items corresponding to the cognitive/affective scale were retained (e.g., sadness, pessimism, sense of failure, etc.), with the exception of the item related to lack of interest due to its overlap with apathy. In other words, all somatic and apathy-related items from the full BDI-II were eliminated in order to create the modified version of the BDI-II used in the present study. Further, the AES was chosen to measure apathy severity due to its purported ability to discriminate between apathy and depression.

Effects of Apathy and Depression on Memory and Executive Ability

In the present study, two hypotheses were investigated. First, it was hypothesized that increased levels of depressive symptoms and increased levels of apathy *would* be associated with decreased performance on measures of executive and memory abilities. In support of this hypothesis, apathy negatively correlated with memory and executive functioning in correlation analyses and level of apathy predicted level of memory and executive functioning in regression analyses. The hypothesis was further supported in

that depression negatively correlated with memory performance in correlation analyses and level of depression predicted level of memory in regression analyses. Surprisingly, however, a relationship between depression and executive functioning was not identified. The correlation between level of depressive symptoms and executive functioning was not significant. While it was predicted that the magnitude of the relationship between apathy and executive functioning would be significantly larger than that of the relationship between depression and executive functioning, the lack of a significant correlation between depression and executive function was unexpected. Notably, the lack of association between these variables remained when the full 21-item BDI-II was included in secondary analyses, demonstrating that the lack of relationship between depression severity and executive functioning was not explained by the exclusion of somatic and apathy-related items or by the consequent reduction in range of scores.

Unique Effects of Apathy and Depression on Executive Function

Second, it was hypothesized that apathy would be more strongly associated with executive functioning than depressive symptoms as demonstrated by the magnitude of the correlation coefficients and by a significant R^2 change when apathy was entered last in a hierarchical regression analysis. This hypothesis was supported. Increases in apathy, but not depression, were significantly associated with decreases in executive performance. Hierarchical regression analyses revealed that apathy, and not depression, accounted for a significant proportion of added variance in executive functioning. When controlling for age, this finding remained.

It is possible that the relationship between depression and executive function may be a small effect, and that the present study did not have an adequate number of participants, and hence power, to detect that relationship. While the number of participants in the present study (n = 68) is adequate for detecting a medium effect size with power of 0.80, this would not have been enough subjects to detect a small effect. Alternatively, using a shortened version of the BDI-II may have restricted the range of scores on this measure of depressive symptoms. However, this is unlikely for a couple of reasons. First, the lack of association remained when using the full version of the BDI-II as when using the shortened, modified version. Second, a relationship was identified between level of depressive symptoms (i.e., as measured using the shortened BDI-II) and memory, indicating that the memory analyses were not hindered by restriction of range. Regardless, the finding that the relationship between depression and executive function is not significant in the present study, but that the relationship between apathy and executive function is significant, supports the notion that apathy has a greater influence than depression on executive impairment in patients with Parkinson's disease.

The present findings are consistent with other studies reporting similar results. Pluck and Brown (2002) found that apathy, but not depression, was associated with deficits on three measures of executive functioning (i.e., category fluency, Stroop Color-Word test, and WCST). Isella and colleagues (2002) found that PD patients with high-apathy showed significantly greater impairment in executive functioning [i.e., Executive Interview (EXIT), letter fluency and category fluency] when compared to low- and moderate-apathy groups. Significant correlations were identified between apathy and

executive functioning while depression was not significantly associated with apathy or any cognitive abilities measured. Similarly, Aarsland and colleagues (1999) identified a significant association between executive functioning and apathy but not between executive functioning and depression or between apathy and depression.

Unique Effects of Apathy and Depression on Memory

Finally, exploratory analyses were conducted to investigate the possible independent effects of apathy and depression on immediate memory abilities. As stated above, levels of both apathy and depressive symptoms were similarly correlated with memory performance. Hierarchical regression analyses were used to investigate the degree of influence that apathy has on memory performance when controlling for depression and the degree of influence that depression has on memory performance when controlling for apathy. Our findings suggest that while depression does *not* predict memory scores over and above that of apathy, apathy revealed a strong trend to predict memory over and above that of depression (i.e., $p = .067$).

When controlling for age, the findings became less clear. It is important to note that by choosing to investigate the effects of apathy and depression on memory while controlling for age, power was reduced to 0.75 due to the addition of a third independent variable (i.e., age) into the regression equation. A closer look at the *p*-values associated with entering either depression or apathy as the third variable (refer to Table 7-B) reveals that when age is controlled for, apathy likely remains as a significant predictor of memory scores over and above that of depression ($p = .116$). In contrast, it is unlikely

that depression is a significant predictor of memory scores over and above that of apathy ($p = .411$). A larger sample is needed to test whether this is, in fact, accurate, since there was insufficient power to investigate the influence of three independent variables given the sample size in this investigation. An alternative explanation for this finding is that, despite our attempts to use measures that assess non-shared aspects of apathy and non-shared aspects of depression, our measurement did not fully discriminate. This raises question regarding the construct validity of the scales used and begs further investigation into definitions and assessments of apathy.

Conclusion

Overall, the findings of the present study suggest that apathy and depression may exert unique effects on memory and executive function. These findings provide support for the notion of apathy and depression as discernable constructs. First, apathy and depression were differentially related to cognitive performance, most strongly in the domain of executive functioning. Second, the frequencies of clinical elevations of apathy and depression in the present sample also support the notion that apathy and depression can be considered as distinguishable constructs, with clinically elevated apathy symptoms existing in the absence of clinically elevated depressive symptoms. The presence of clinically elevated apathy in the absence of depression has been even more convincingly and consistently in Alzheimers disease, frontotemporal dementia, progressive supranuclear palsy, and basal ganglia stroke (e.g., Levy et al., 1998; Starkstein et al., 2005).

While unique aspects of depression and apathy may explain their differential influence on executive functioning, shared factors may underlie their relationship with memory. Potential shared mechanisms may include frontostriatal circuitry, reduced processing speed, anergia, avolition, and the emotional concomitants of apathy (e.g., anhedonia). While most of the apathy literature is consistent in defining apathy by behavioral and cognitive dimensions, opinions differ on whether definitions should include an emotion dimension (Starkstein and Leentjens, 2007). According to a preliminary study of patients with dementia, anhedonia is rarely reported in patients who report apathy but no depression, suggesting that anhedonia may be more characteristic of depression than apathy (SE Starkstein, personal communication; as cited in Starkstein and Leentjens, 2007).

Theoretical Implications

Differentiation of apathy and depression and understanding their independent effects has several implications both for clinical treatment and for scientific pursuit. First, apathy appears to be negatively associated with cognitive functioning, daily functioning, and caregiver burden and distress (van Reekum et al., 2005). Secondly, apathy has been associated with increased morbidity and mortality. Apathetic patients devote less attention and time to self-care, which can result in medical complications. Additionally, it may interfere with treatment response and medication compliance and has been associated with increased mortality and financial burden (Stephenson, 2005; van Reekum et al., 2005).

Further, due to the absence of reported or exhibited distress, patients suffering from apathy are often overlooked by the health care system. There is currently a bias in health care favoring diagnosing depression (Schulman, 2000). Cognizance of apathy in patients seeking health care services may help to prevent false positive diagnoses of depression and may increase efficiency in timely and adequate treatment of patients experiencing apathy and not depression. Additionally, making caregivers aware of the prevalence of apathy in Parkinson's disease, among other neuropsychiatric or neurologic diseases, may help them understand that related behaviors are not due to insolence or laziness but, rather, to a disease-related neurologic changes.

Identification of apathy may be improved by the inclusion of apathy in psychiatric classification systems. Currently, apathy is underrepresented in such classification systems. Apathy is not referenced in the ICD-10 (WHO, 1993) and is only mentioned specifically in relation to four disorders of the DSM-IV (APA, 1994), with no inclusion of the term "apathy" in the DSM-IV glossary. Discussion regarding differential diagnosis and on whether apathy should appear as a stand-alone disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)* has begun (Stephenson, 2005). If not included as a stand-alone disorder, potential improvements of the status of apathy, including clarifying the definition of apathy, adding apathy to the glossary of the DSM, or creating a reference to help direct clinicians to the range of disorders commonly associated with apathy, are being considered by DSM-IV Editor, Michael B. First, MD (Stephenson, 2005).

If appropriately identified, preliminary research suggests that symptoms of apathy may be medically or behaviorally treated independently of depressive symptoms. For example, Weitzner and colleagues (2005) described four cases of pituitary disease patients who were diagnosed and medically treated for depression but showed little response to treatment. When the diagnosis of apathy syndrome was considered and treatment with methylphenidate was implemented, the patients' condition improved subjectively and on objective cognitive tasks. Further, Hoehn-Saric, Lipsey, and McLeod (1990) found that apathy and indifference followed treatment with select antidepressant serotonin-reuptake-inhibitors. Notably, these were not randomly, controlled medication trials, which would be a great benefit to the apathy treatment literature.

Behavioral treatments may also provide benefit to patients experiencing disruptive levels of apathy. Boyle and Malloy (2004) have suggested that caregivers may be able to play an important role in behavioral training programs aimed at reducing apathy in patients with Alzheimer's disease. By definition, apathy involves the lack of motivation and initiation. Caregivers may promote behavioral activation by helping patients initiate goal-directed behaviors, increasing their involvement in pleasant activities, and providing increased structure for activities.

Future research elucidating the effectiveness of caregiver-involved behavioral interventions, as well as randomized controlled medication trials, on patients with elevated levels of apathy is warranted. In addition, future studies aimed at understanding the neural underpinnings of depression and apathy may help guide more effective choices of pharmacological and/or behavioral management of these symptoms. Further

investigation into the relationship between apathy and fluctuating on/off periods in PD patients, in which levels of dopamine are adequate or limited in the brain, may provide interesting information regarding the underlying neurotransmitter effects.

Differentiation of apathy and depression has robust implications for the advancement of psychological science and patient care. The utility of investigating symptoms of apathy and depression, as opposed to solely clinical diagnoses, is evident in that even some level of symptomatic apathy and depression appears to influence efficiency of patients' cognitive abilities. A focus on apathy symptoms in patients may optimize treatment approaches, improve patients' daily functioning, increase independence, and result in an improved quality of life for both patients and their caregivers.

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Appendices

Appendix A: Beck Depression Inventory – II

(Note: Items used for the 13-item modified version are highlighted)

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

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11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

_____ Subtotal Page 2

_____ Subtotal Page 1

Appendix B: Apathy Evaluation Scale – Self-Rating form

For each question, circle the answer that best describes your thoughts, feelings and actions during the past 4 weeks.

1. I am interested in things.

Not at All 0 items **1**	Slightly 1-2 items **2**	Somewhat 2-3 items **3**	Very 3 or more items **4**

2. I get things done during the day.

Not at All 0 items **1**	Slightly 1-2 items **2**	Somewhat 2-3 items **3**	Very 3 or more items **4**

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

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

4. I am interested in having new experiences.

Not at All 0 items **1**	Slightly 1-2 items **2**	Somewhat 2-3 items **3**	Very 3 or more items **4**

5. I am interested in learning new things.

Not at All 0 items **1**	Slightly 1-2 items **2**	Somewhat 2-3 items **3**	Very 3 or more items **4**

6. I put little effort into anything.

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

7. I approach life with intensity.

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

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

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

9. I spend time doing things that interest me.

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

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

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

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

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

12. I have friends.

Not at All 0 items **1**	Slightly 1-2 items **2**	Somewhat 2-3 items **3**	Very 3 or more items **4**

13. Getting together with friends is important to me.

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

14. When something good happens, I get excited.

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

15. I have an accurate understanding of my problems.

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

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

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

17. I have initiative.

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**

18. I have motivation.

Not at All Characteristic **1**	Slightly Characteristic **2**	Somewhat Characteristic **3**	A Lot Characteristic **4**