

EXAMINING APATHY AND DEPRESSION IN PARKINSON'S DISEASE

By

LINDSEY ELIZABETH KIRSCH

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By

Lindsey Elizabeth Kirsch

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Chair: Dawn Bowers

Major Department: Clinical and Health Psychology

Purpose: The purpose of the present study was to examine the hypothesis that apathy is a core feature of Parkinson's disease (PD) and that apathy can be dissociated from depression.

Background and Hypotheses: Emotional changes frequently accompany PD, and a high proportion of patients experience anxiety and depression. Recently, attention has focused on the occurrence of a "syndrome of apathy," reflecting a primary loss of motivation, loss of interest, and loss of effortful behavior. It has been argued that "apathy" is distinct from depression, and reflects dysfunction of connections between basal ganglia and anterior cingulate cortex in PD patients. Therefore, we hypothesized that a) PD patients would have significantly more apathy than a clinical control group (Dystonia), b) apathy is not simply a symptom of depression and thus a large proportion of PD patients would exhibit apathy in the absence of depression, and c) apathy symptoms would be significantly increased in more severe stages of Parkinson's disease.

Methods: Eighty patients with PD and twenty patients with Dystonia completed a variety of depression and apathy measures including the Marin Apathy Evaluation Scale (AES), the Beck Depression Inventory (BDI), the Centers for Epidemiological Studies-Depression Scale (CES-D), and the Beck Hopelessness Scale (BHS). Data were analyzed using chi squared tests for independence, independent samples *t*-tests, and one-way Analyses of Variance.

Results: There was a significantly higher prevalence of apathy in PD patients (freq. = 51%, 41/80) than in Dystonia patients (freq. = 20%, 4/20). The prevalence of apathy in the absence of depression was substantial in PD patients and nonexistent in Dystonia patients (PD = 28.8%, Dystonia = 0%). Further, there was a significantly higher severity of apathy in PD patients than in Dystonia patients. When PD patients were examined based on mild, moderate, and severe stages of disease (based on the Hoehn-Yahr Staging criteria for PD), apathy had a tendency to increase as severity of disease increased.

Conclusions: The present study found that there were a significantly higher prevalence and an increased severity of apathy in PD when compared to a clinical control group of Dystonia patients. Further, approximately thirty percent of PD patients showed apathy in the absence of depression. It appears that apathy is a “core” feature of PD and is not limited to co-occur within depression. The distinction between apathy and depression may become increasingly important as more is discovered about the differential pathophysiology, clinical correlates, and potential treatments for these mood disturbances in PD.

CHAPTER 1 INTRODUCTION

Parkinson's disease (PD) is one of the most common late life neurodegenerative diseases. PD produces substantial morbidity and mortality; over one million Americans have Parkinson's disease, and approximately 60,000 new cases are diagnosed every year (Okun & Vitek, 2002). Additionally, the incidence of Parkinson's disease increases with age, and this incidence is predicted to triple over the next 50 years as the aging population increases (Tanner et al., 2002). PD typically onsets in a patient's 50s or 60s and is notable for a slow, insidious onset and a chronic progression over time. The majority of PD cases are idiopathic (of unknown cause), and are 1.5 to 2 times more likely to occur in males (Mayeau et al., 1995; Tanner et al., 2002).

Historically, Parkinson's disease has been thought of as primarily a motor disease—producing symptoms such as tremor, rigidity, and bradykinesia (slowness of movement). However, there are salient emotional changes that have been increasingly recognized in Parkinson's disease in addition to motor symptoms. One salient emotional change that has received recent attention is the occurrence of a “syndrome of apathy,” reflecting a primary loss of motivation, loss of interest, and loss of effortful behavior. This “syndrome of apathy” has potential clinical and theoretical importance. However, there are relatively few studies examining this aspect of PD. The goal of the present study was to examine the occurrence of apathy and whether it presents as a “core” feature of Parkinson's disease distinct from depression. To do this, Parkinson's disease patients and a group of clinical control patients completed a battery of apathy and depression

scales. Apathy and depression symptoms were then compared on their prevalence, severity, and relationship to disease variables. Before turning to specific hypotheses and predictions of the present study, a review of pertinent literature will be presented as follows: 1) the hallmark motor symptoms of Parkinson's disease will be presented, 2) the emotional symptoms of Parkinson's disease will be presented, and 3) the term apathy will be defined and discussed.

Motor Symptoms in Parkinson's Disease

The hallmark motor symptoms of Parkinson's disease include a resting tremor, bradykinesia, akinesia, muscular rigidity, and a gait disturbance. Resting tremor is the most recognizable symptom of PD. However, only about 50% of patients show tremor as their presenting symptom and approximately 15% of patients never show tremor during the course of the disease (Martin et al., 1983). Other patients experience a postural tremor in addition to a resting tremor. Postural tremors occur during activity and thus may be more disabling than the resting tremor since they interfere with the use of the limb (Jankovic, 1992). Bradykinesia and akinesia are distinctive features of PD. Bradykinesia is slowness in execution of a movement, while akinesia is difficulty initiating a movement. Akinesia can be observed when a patient has difficulty arising from a chair or difficulty initiating the onset of gait ("gait hesitation"). Rigidity is also a common complaint in PD, and is experienced by patients as a tightness of the muscles. Rigidity in PD has been termed as "cogwheel" or "ratcheting" rigidity because of the increasing resistance when an examiner moves patients' arms and legs (Lieberman, 1995). Tremor, rigidity, and bradykinesia onset unilaterally, but as the disorder progresses they become bilateral, though the severity often remains asymmetrical. Gait in PD is characterized by stooped posture, shuffling steps, festination (short steps that

become quicker and quicker as if the patient were about to run) and propulsion (forward inclination of the body as if the patient were about to fall forward) (Lieberman, 1995; Tyler, 1992). In addition, patients may experience motoric “freezing,” where they halt mid-gait and are unable to take any steps forward. Parkinson’s patients may also experience diminished facial expressivity (“masked facies”), reduced speech volume, and small, illegible handwriting (“micrographia”).

Motoric symptoms of PD are caused by the loss of dopaminergic neurons in the substantia nigra pars compacta. The substantia nigra (translated “black substance”) are a pair of small darkly pigmented bodies below the basal ganglia that synthesize dopamine. It is estimated that motor signs begin occurring in PD when approximately 70% of the dopamine producing cells in the substantia nigra pars compacta have been lost (Fearnley & Lees, 1991; Halliday et al., 1996). Dopamine depletion in the substantia nigra affects a cascade of other structures including the basal ganglia and feedback loops communicating between the basal ganglia and frontal circuits (see Figure 1-1). Medications that replace dopamine (e.g., levodopa, dopamine agonists) are the treatment of choice for Parkinson’s disease. Dopaminergic medication treatment is associated with fluctuations in motor symptom severity. “On” periods are characterized by good clinical control of symptoms by the medications, where as “off” period are marked by poor symptom control. Both “on” and “off” periods can be complicated by dyskinesias, excessive involuntary movements resulting from levodopa usage over time.

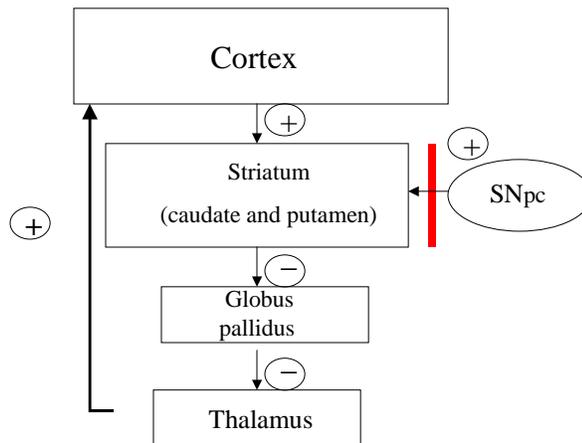


Figure 1-1. Simplified pathophysiological model of motor dysfunction in PD. Steps are as follows: 1) the substantia nigra has reduced excitatory influence on the striatum, 2) the striatum has reduced inhibition influence on the globus pallidus (disinhibition), 3) the globus pallidus is now disinhibited and exerts stronger inhibitory influence on the thalamus, 4) the thalamus has reduced excitatory influence on the cortex—leading to poverty of movement. (SNpc=substantia nigra pars compacta).

Emotional Symptoms in Parkinson's Disease

Psychiatric symptoms and syndromes are highly prevalent in PD. Depression, anxiety, and apathy are all common in PD (Brown & Pluck, 2000; Isella et al., 2002; Poewe & Seppi, 2001). Prevalence rates of depression have been approximated at 40% (Zgaljardic et al., 2003). Breaking this figure down into DSM diagnostic classification, a recent meta-analysis reported that 10 studies using DSM-III or DSM-III-R criteria classified approximately 25% of their PD patients with major depression, and 23% as having dysthymia (Slaughter JR, Slaughter KA, Nichols, Holmes, & Martens, 2001). In addition, 21 studies that used depression rating instrument such as the Beck Depression Inventory (BDI), or Hamilton Rating Scale for Depression (Ham-D) classified 38% of PD patients as depressed. Thus, depression is highly common in PD. It is thought that depression may occur in high levels as a reaction to disability.

Clearly, adjusting to a having a medical illness, especially one that does not have a “cure” but treatments that are temporary and lessen in effectiveness over time can cause reactive depression. The early stages in which the patient is initially diagnosed may be the most vulnerable to this reaction (McDonald, Richard, & DeLong, 2003). However, depression in PD is also considered a primary consequence of brain pathophysiology of the disorder. Depression in PD is proposed to be associated with decreased activation of the orbitofrontal cortex (Cummings, 1993; Masterman & Cummings, 1997).

Apathy Syndromes and Symptoms

Apathy is an important but often overlooked feature of many psychiatric and neurological disorders. Apathy refers to a cluster of behavioral, cognitive, and emotional features such as lack of effort, loss of interest, and flattened emotions. The root of the word “apathy” derives from the Greek “a” “pathos,” meaning lack of passions. In the psychological literature, the concept of apathy began with the use of a broader term—negative symptoms. Descriptions of negative symptoms first appeared in the writings of Hughlings-Jackson in the 1930s (Hughlings-Jackson, 1931). He distinguished the florid or positive symptoms in schizophrenia from the deficit or negative symptoms. Positive symptoms, such as hallucinations and delusions, were seen as an excess or distortion of normal function, whereas negative symptoms, such as alogia, apathy, and poverty of speech, were seen as a reduction or loss of normal function. Yet, this loss of normal function is seen in disorders beyond schizophrenia. Robert Marin highlighted this fact in the early 1990s. He proposed that apathy could manifest in *neurological* disorders as both a symptom and a syndrome. His key paper in 1991 proposed diagnostic criteria for a syndrome of apathy (Marin 1991). Apathy includes a primary lack of motivation that manifests itself in 3 domains of symptoms: behavioral, cognitive, and affective. The

behavioral domain includes symptoms such as lack of effort, lack of productivity, and dependence on others to structure one's activities. The cognitive domain includes symptoms such as loss of interest in new experience and lack of concern about one's personal problems. The affective domain includes symptoms such as flattened affect and lack of response to positive or negative events. Marin emphasized that the lack of motivation in a **syndrome** of apathy is primary, and not purely accounted for by intellectual impairment, emotional distress, or diminished consciousness such as drowsiness or delirium.

Apathy and Depression: Are They Dissociable?

Despite Marin's delineation of criteria for apathy, doubts have been raised about whether apathy is a unique syndrome, or whether it is purely a symptom of depression. Marin uses the term apathy as a symptom of other syndromes **and** as a syndrome all to itself. Depressed patients will often present with the symptom of apathy—specifically manifesting as loss of interest and decreased pleasure in activities they would normally find enjoyable. In fact, diagnostic criteria for a Major Depressive Episode requires at least 5 symptoms, with one symptom necessarily being either (1) depressed mood, or (2) markedly diminished interest or pleasure in all or most all activities. Yet, this latter symptom is also a cognitive symptom of a syndrome of apathy. Therefore, a syndrome of depression can include symptoms of apathy. However, it can be argued (and will be discussed further) that apathy can occur in the absence of depression and depression can occur in the absence of apathy. One important difference between apathy and depression is the notable lack of sadness, depressed mood, and dysphoria in apathy. Apathy presents as blunted affect in both directions—neither happy nor sad.

Studies of frontal lobe disease and Alzheimer's disease have attempted to disentangle apathy and depression syndromes. In frontal lobe disease, damage to the mesial frontal lobe/anterior cingulate cortex and related subcortical feedback loops are thought to produce a syndrome of apathy including lack of motivation, poverty of behavior, reduced response initiation and creative thought, and emotional flattening. It can also present with motoric slowness and deficits in sustained attention. Lesions in the regions of the anterior cingulate cortex and supplemental motor area may produce a syndrome of extremely severe apathy termed akinetic mutism. In this syndrome, the patient makes no effort to communicate or initiate activities: they appear content to lie silent and motionless. Patients may recover from this state, and after recovery one patient reported that while she had exhibited these signs, she felt 'empty,' 'had nothing to say,' and 'nothing mattered' (Damasio & Van Hoesen, 1983; Tranel, 1992). Akinetic mutism is more clearly related to a syndrome of apathy than one of depression.

Apathy has been examined in Frontotemporal dementia (FTD). FTD is a progressive cortical dementia affecting the frontal lobes and anterior temporal lobes; it is associated with a profound alteration in personality and social conduct, often characterized by lack of motivation or social disinhibition. In FTD, a syndrome of apathy may manifest as emotional blunting, inappropriate emotional shallowness, unconcern, and loss of empathy. It may include the behavior symptoms of reduced initiation of speech and reduced personal hygiene and the cognitive symptoms of decreased mental flexibility and loss of interest (Neary, Snowden, Gustafson, Passant, Stuss, Black et al., 1998). Using a caregiver rating scale that includes questions in regards to apathy and depression (the Neuropsychiatric Inventory), Neary and colleagues (1998) rated 28

patients with FTD in terms of their apathy and depression symptoms. A full sixty-one percent of the patients showed apathy symptoms in the absence of depression symptoms, while 29% showed both types of symptoms, and 11% showed depression symptoms alone (Levy et al., 1998). Similar distinction has been made between apathy and depression in Alzheimer's disease. Patients have been classified with the Marin Apathy Evaluation Scale (AES; based on Marin's diagnostic apathy criteria) caregiver version and the DSM-IV depression criteria (Starkstein, Petracca, Chemerinski & Kremer, 2001). Results indicated that 13% of 319 Alzheimer's patients had apathy in the absence of depression, 21.6% had depression alone, and 23.5% had both apathy and depression. Thus, both of the above studies provide preliminary evidence that apathy and depression can be dissociated in progressive neurological disorders.

CHAPTER 2 STATEMENT OF THE PROBLEM

Depression is a common occurrence in PD and has been studied extensively. In fact, there have been one hundred published English language studies specifically examining depression in PD. Apathy, in contrast, is an understudied aspect of PD. Only 6 studies have investigated apathy in PD (Aarsland et al., 1999; Aarsland, Litvan, & Larsen, 2001; Isella et al., 2002; Levy et al., 1998; Pluck & Brown, 2002; Starkstein et al., 1992). There are several weaknesses and gaps left to be addressed by this small body of literature. These weaknesses include the following: no control groups or inappropriate control groups, inconsistency in method of reporting prevalence values, and instrument/assessment problems.

Two out of the 6 studies of apathy in Parkinson's disease had no control group (Aarsland et al., 1999; Starkstein et al., 1992). This presents the problem of lack of an appropriate comparison group. Apathy and depression can be examined in PD by itself, but doing so does not provide a clear understanding of how aspects of apathy or depression might be unique to PD. There is no way of knowing for example, whether rates of apathy are comparable to those found in another movement disorder, or whether rates of apathy are specifically higher in PD. Some studies have used a normal elderly control group or an Osteoarthritis control group (Isella et al., 2002; Pluck & Brown, 2002). While these are important groups to consider, they still leave one wondering how PD compares to other neurological disorders and specifically, other neurological movement disorders. It is critical to examine apathy and depression in relation to another

movement disorder in order to understand whether apathy is, as we hypothesize, uniquely present in high rates in PD. Thus, a control group that is a movement disorder with similarly disabling motor symptoms and pathology will be the strongest test of whether apathy is indeed a “core feature” of Parkinson’s disease.

Methodologically, in order to clarify distinctions between apathy and depression symptoms, it is important to separate groups into those with apathy symptoms in the absence of depression, those with depression symptoms in the absence of apathy, and those endorsing both types of symptoms. Not all studies break down their prevalence figures into these groups. Thus, it is unknown whether their percent “depressed” also includes those with apathy and their percent “apathetic” also includes those with significant depressive symptoms. In addition to this methodological concern, there are concerns with the measures used by previous studies to quantify apathy and depression. In several studies, only one depression instrument was utilized. Furthermore, “cognitive” symptoms of depression (e.g., hopelessness, guilt, worthlessness, anhedonia) have not been examined separately from “somatic” symptoms of depression (e.g., sleep disturbance, appetite disturbance, fatigue). Studies of depression in medical illness have often been criticized for the potential overlap between somatic depression symptoms and symptoms of the medical illness. Certainly in Parkinson’s disease, there is such overlap (examples from the BDI include: “It takes an extra effort to get started at doing something,” Item 15, “I get tired more easily than I used to,” Item 17). It is important to use more than one measure of depression to ensure that results are corroborated. In addition, using measures of cognitive depression items only or analyzing total scores to separate out somatic and cognitive components would be useful.

Three out of the six studies examining apathy in Parkinson's disease have used a caregiver rating scale (the Neuropsychiatric Inventory) to document the occurrence and severity of apathy and depression in the patient. The use of this scale poses interpretation problems. While informant based information can be useful, it is questionable for the use of assessing apathy. By definition, apathy is defined as a primary internal lack of motivation that manifests in emotional, cognitive, and behavioral symptoms. Motivation, emotions, and cognitions are all internal states, and as such may be difficult for others to assess accurately. This is especially true in light of the fact that Parkinson's patients have documented difficulties expressing and conveying emotions (e.g., "masked facies"). Therefore, misinterpretation of internal states is likely. It is more accurate (and arguably simpler) to allow the patient themselves to answer questions about mood and motivation.

The present study attempted to address the issues cited above. To do this, several self-report questionnaires (3 depression scales [Beck Depression Inventory, Centers for Epidemiologic Studies-Depression scale, Beck Hopelessness Scale] and 1 apathy scale [Marin's Apathy Evaluation Scale]) were administered to a group of 80 Parkinson's disease patients and a group of 20 clinical control patients. Primary idiopathic adult-onset Dystonia was chosen as a clinical control group for PD. Dystonia, like PD, is a movement disorder that is progressive and disabling. It is characterized by involuntary, sustained muscle contractions of opposing muscles, causing twisting movements and/or abnormal postures. Dystonic movements can occur when the limbs are at rest, but most often occur during voluntary movement. Like PD, it may occur with increased muscle tone (rigidity), bradykinesia, and also may occur with tremor (Hallett, 1998; Jankovic & Fahn, 2002).

The pathophysiology of Dystonia is not completely understood. However, studies have shown that dystonic movements are associated with abnormal electromyographic (EMG) activity (Cohen & Hallett, 1988; Farmer et al., 1998). Specifically on the level of the muscles, co-contraction of antagonistic muscles and overflow into extraneous muscles occurs. At the central nervous system level, studies have shown that there is decreased amplitude of movement-related cortical potentials and decreased amplitude of contingent negative variation (e.g., the electroencephalogram potential that appears between a “warning” and a “go” stimulus in reaction time tasks). Further, decreased blood flow has been shown to occur in the motor cortex and premotor cortex (specifically in the caudal supplemental motor area and bilateral primary sensorimotor cortex, Ceballos-Baumann et al., 1995). Current theory suggests that the pathology of Dystonia, like Parkinson’s disease, involves the basal ganglia circuitry. It is hypothesized that in Dystonia there is overactivity in the direct pathway (e.g., globus pallidus interna → thalamus → cortex, excitatory in nature) and underactivity in the indirect pathway (e.g., globus pallidus interna → pedunculopontine nucleus → brainstem and spinal cord, inhibitory in nature). Both pathways result in overactivity of the cortex, causing the excessive movements in dystonia. For the purposes of this study, of most importance is the fact that both PD and Dystonia are progressive movement disorders involving basal ganglia abnormalities. However, PD has been hypothesized to disrupt basal ganglia connections to mesial frontal/anterior cingulate cortex (putatively involved in apathy), whereas Dystonia has been hypothesized to disrupt basal ganglia connections to prefrontal cortex and the supplemental motor area.

The aims, hypotheses, and predictions of the present study are the following:

Aim 1: To determine the prevalence of apathy and depression in patients with PD relative to that of a clinical control group of Dystonia patients. It is hypothesized that PD patients will have a significantly higher apathy than Dystonia, and that this difference may be due to differential involvement of frontal circuitry in PD (e.g., anterior cingulate/mesial frontal cortex) versus Dystonia. Therefore, it is predicted that PD patients will show a significantly higher prevalence of apathy (as defined by ≥ 14 on the Apathy Evaluation Scale) than Dystonia patients. It is further predicted that PD patients will show significantly more severe apathy scores on the Apathy Evaluation Scale than Dystonia patients.

Aim 2: To investigate whether apathy is indeed a core feature of PD and not simply a symptom of depression. It is hypothesized that a large proportion of PD patients will have apathy in the absence of depression. It is predicted that a significantly greater proportion of PD patients will exhibit apathy in the absence of depression (e.g., ≥ 14 on the Apathy Evaluation Scale without a ≥ 14 on the Beck Depression Inventory) than Dystonia patients.

Aim 3: To examine the relationship between severity of PD and depression and apathy. It is hypothesized that apathy will occur more severely in the later stages of PD and depression will occur more severely in the earlier stages of illness. It is predicted that Apathy Evaluation Scale scores will be significantly higher at increasing Hoehn-Yahr Stages and that depression Beck Depression Inventory scores will be significantly higher at earlier Hoehn-Yahr Stages.

CHAPTER 3 METHODS

Participants

Participants included eighty patients with idiopathic Parkinson's disease and a clinical control group of twenty patients with idiopathic adult-onset Dystonia. Participants were recruited through the Movement Disorders Center of the University of Florida. They were invited to participate in the present study during their routine medical appointment. As part of their routine workup with a movement disorders neurologist, Parkinson's patients received standard measures for staging the severity of their motor symptoms and the course of their disorder. These included the *Unified Parkinson's Disease Rating Scale*-motor examination (UPDRS [Fahn & Elton, 1987]), a modified *Hoehn-Yahr scale* (Hoehn & Yahr, 1976), and the *Schwab and England Activities of Daily Living Scale* (Schwab & England, 1969). Additionally, Parkinson's patients received a scale assessing "disease specific" quality of life (*Parkinson's Disease Quality of Life Scale-39* [Peto, Jenkinson, & Fitzpatrick, 1995]). Dystonia patients received standard measures for the staging of the severity of their motor symptoms (*Unified Dystonia Rating Scale* [Comella et al., 2002; Dystonia Study Group, 1997]) and a scale assessing quality of life (*Short Form Health Survey 36* [Ware & Shelbourne, 1992]).

To be included in the present study, Parkinson's (PD) and Dystonia (DYS) patients had to be between 40 and 90 years of age, meet stringent diagnostic criteria for their respective neurological disorders, be free of co-morbid neurological illness, and be free from previous neurosurgical treatments such as deep brain stimulation or

pallidotomy. Patients in the present study were not selected for any known cognitive or psychiatric state. The clinical diagnostic criteria for idiopathic PD was based on the following: a) the presence of at least two of four cardinal motor signals (i.e., akinesia, bradykinesia, resting tremor, rigidity), and b) a demonstrated therapeutic response to dopamine replacement therapy defined by a sustained improvement of Parkinson's motor symptoms (based on the Unified Parkinson's Disease Rating scale-motor subscale) after administration of dopaminergic medication during their diagnostic neurological examination. A positive response to dopaminergic therapy was necessary to exclude patients with Parkinson's plus syndromes (e.g., Lewy body disease, corticobasal degeneration, multiple systems atrophy). The clinical diagnostic criteria for idiopathic adult-onset Dystonia was based on the following: a) an illness characterized by the development of isolated dystonic movements and postures, b) a normal perinatal and developmental history, and c) no antecedent illness or drug intake known to cause the syndrome (Fahn, Bressman, & Marsden, 1998). All participants were adult onset, and thus by definition were diagnosed after 20 years of age.

The PD patients included fifty-five men and twenty-five women who ranged in age from 46 to 87 years ($M = 68.9$, $SD = 9.5$). Seventy-three (91.2%) patients were Tremor-predominant PD subtype and seven (8.8%) were Akinetic-rigid PD subtype. (See Table 1-1). On average, the PD patients had been experiencing parkinsonian symptoms for six years ($M = 6.4$, $SD = 5.7$, range 1-34 years) and were in the middle stages of PD based on the staging criteria from the Hoehn-Yahr scale. Approximately ninety-nine percent of PD patients were taking dopaminergic medications (e.g., levodopa/carbidopa, dopamine

agonists, with one patient prescribed levodopa/carbidopa *on* the day of their evaluation) and fifty-one percent were taking anti-depressant medication.

Adult-onset Dystonia patients included six men and fourteen women who ranged in age from 43 to 87 years ($M=60.9$, $SD=11.9$). For all patients in the present study, symptoms began after age 30 ($M= 53.5$, range=31-87). Ten (50%) were Focal dystonia subtype (i.e., affects a single body part) and ten (50%) were Segmental dystonia subtype (i.e., affects one or more contiguous body parts). On average, they had been experiencing symptoms of Dystonia for eight years ($M=8.0$, $SD=7.8$, range 0.5-30 years). Twenty percent of Dystonia patients were prescribed anti-depressant medications.

Table 3-1. Parkinson and Dystonia Patient Characteristics

Characteristic	PD patients ($N=80$)	DYS patients ($N=20$)	
Disease Subtype	91.2% Tremor 8.8% Akinetic	50% Focal 50% Segmental	
Age	68.9 (9.5)	60.9 (11.9)	$p < .01$
Men: Women	55:25	6:14	$p < .01$
Yrs. Ed	14.8 (3.0)	15.1 (2.1)	Ns
DOPA meds	98.8%	--	
Anti-depress	51%	20%	$p < .01$
Yrs. Symptoms	6.4 (5.7)	8.0 (7.8)	Ns
Hoehn-Yahr stage	2.4 (.67)	--	
Parkinson's motor score(UPDRS)	29.5(10.8)	--	

A comparison of PD patient and DYS patient demographic variables is presented in Table 1-1. As shown, the PD and DYS groups did not significantly differ with respect to the number of years they have experienced disease symptoms, $t(96) = -1.04$, $p = .30$. However, they did significantly differ with respect to age, gender, and the percentage of patients prescribed anti-depressant medications. PD patients were significantly older

($t(98) = 3.22, p < .01$), more likely to be male ($t(98) = -3.32, p < .01$), and more likely to be taking anti-depressant medications ($t(96) = 2.47, p < .01$).

Procedures and Assessment Instruments

Prior to participation in the present study, informed consent had been obtained from each participant according to University and Federal guidelines. All testing was conducted at the Medical Plaza at the University of Florida during routine neurological appointments. During the present study, participants completed a variety of mood questionnaires including the following in order of completion: *Beck Depression Inventory* (BDI [Beck, 1978]), modified *Apathy Evaluation Scale* (AES [Marin, 1991] modified by Starkstein et al., 1992), *Center for Epidemiological Studies-Depression* scale (CES-D [Radloff, 1977]), and the *Beck Hopelessness Scale* (BHS [Beck, Weissman, Lester, & Trexler, 1974]). Completion of questionnaires took approximately 30 minutes.

Depression Assessment Instruments

Beck Depression Inventory (BDI). The BDI is a 21 item scale widely used for both research and clinical purposes. Each item addresses an aspect of the experience and symptoms of depression (i.e., mood, guilt, indecisiveness, appetite and sleep changes). Items include statements rated on a 0-3 Likert scale based on severity of feelings of depression over the last week. For example, “0—I do not feel sad,” “1—I feel sad,” “2—I am sad all the time and I can’t snap out of it,” “3—I am so sad or unhappy that I can’t stand it.” The score is the sum of all items, with higher scores indicating more severe depression. Classification of depression severity has been defined in multiple ways. Lezak (2004) refers to the following classification of depression: minimal ≤ 13 , mild = 14-19, moderate = 20-28, severe ≥ 29 . This classification is used in the present study.

The BDI can be divided into items that focus on depressive cognitions and ideations (i.e., ‘*ideational symptoms*,’ items 1 through 13), and items that focus on bodily concomitants of depression (i.e., ‘*somatic symptoms*,’ items 14-21). These domains are particularly useful to examine in the present study because elderly and medically disabled patients may endorse somatic items that may not be related to depression (e.g., fatigue caused by medical disorder vs. depression). The BDI has been shown to have substantial support for its reliability and validity. Beck, Steer, & Garbin (1988) reviewed the psychometric properties of the BDI in a meta-analysis. They found that the internal consistency reliability as measured by Cronbach’s coefficient alpha ranged from .73 to .95 and that the concurrent validity with scales such as the Hamilton Psychiatric Rating Scale, the Zung Self-Reported Depression Scale, and the MMPI depression scale ranged from .60 to .76 (Beck, Steer, & Garbin, 1988). The BDI is thought to have excellent reliability and validity in use with Parkinson’s patients (Levin, Llabre, & Weiner, 1988). In addition, previous studies that have examined apathy and depression together have used the BDI (Pluck & Brown, 2002).

Center for Epidemiologic Studies-Depression Scale (CES-D). The CES-D is a 20 item scale that measures depressive symptoms. Example items include the following: “I felt that I could not shake off the blues even with help from my family or friends,” “I though my life had been a failure.” Each item is rated on a 0-3 Likert scale based on the frequency with which the symptom occurred in the last week (“0= Less than 1 day,” “1—1-2 days,” “2—3-4 days,” “3—5-7 days). A score of ≥ 16 has typically been used to classify significant depressive symptoms in the general population. However, this has been criticized as producing a high false-positive rate and poor specificity in medical

outpatients and inpatients (Schein & Koenig, 1997; Schulberg et al., 1985). Therefore, Schein and Koenig's (1997) recommended cut-score of 20 was used for the present study. The CES-D has shown good internal consistency reliability for older adults (between .86 and .89) (Davidson et al., 1994; Williamson and Schulz, 1992). It has been widely used in assessing medical patients in epidemiological studies (e.g., Bodurka-Bervers et al., 2000; Chwastiak et al., 2002; Lyketsos et al., 1993).

Beck Hopelessness Scale (BHS). The BHS is a 20 item scale of true-false statements that assess hopelessness/negative beliefs about the future. It is useful for the present study because of its focus on cognitive symptoms (e.g., hopelessness, pessimistic thoughts). It does not contain somatic items. Example items are: "I might as well give up because there is nothing I can do about making things better for myself," "All I can see ahead of me is unpleasantness rather than pleasantness." A total score is calculated by summing up the pessimistic responses for each of the 20 items. Beck and Steer (1988) reported high internal consistency reliability across diverse clinical populations (ex. Major Depressive Disorders, Dysthymic Disorders, etc), with Kuder-Richardson reliabilities ranging from .87 to .93. One week test-retest reliability was adequate (.69). Patients with high scores on the BHS and/or BDI and CES-D were followed up, and when needed, provided with appropriate referrals.

Apathy Instrument

Apathy Evaluation Scale-modified (AES). The AES-modified is a 14 item scale measuring cognitive, emotional, and behavioral symptoms of apathy. Some examples of items are: "Are you interested in learning new things?" "Are you indifferent to things?" "Does someone have to tell you what to do each day?" Each item is rated on a 0 to 3 Likert scale, with 0=not at all, 1=slightly, 2= some, 3= a lot.

The scale is an abridged version of the original 18 item version developed by Robert Marin (1991). He validated the original scale on approximately 90 subjects aged 55-85 years with a diagnosis of either stroke, Alzheimer's disease, or Major depressive disorder. He compared these diagnostic groups with normal elderly controls. Internal consistency reliability average was .86, test-retest reliability (X=25.4 day interval) was .76. Convergent and divergent validity with other scales (e.g., anxiety and depression scales) was clearly established with the multitrait-multimatrix method (Marin, Biedrzycki, & Firinciogullari, 1991). Interestingly, predictive validity and external validity were investigated by observing participants in various scenarios (e.g., playing video games, examining novelty gadgets in a waiting area). Self-reported apathy scores negatively correlated with total score on the videogames and difficulty level at which participants chose to play. Thus, it appeared that there was a behavioral correlate with self-reported symptoms.

The original scale was shortened by 4 items, and modified in wording to be simpler by Starkstein et al. in 1992. This modified AES was reported to have excellent psychometric properties in PD (Internal consistency reliability/Cronback's alpha = .76, test-retest reliability of 1 week $r = .90$). The modified version was used in the present study.

Statistical Analyses

To test the first prediction (PD patients will exhibit a significantly higher *prevalence* of apathy as defined by ≥ 14 on the apathy scale than DYS patients), a 2-way Chi square test for independence was used with categories of group type and apathy presence/absence. To test the second prediction (PD patients will exhibit a significantly

greater *level* of apathy than DYS patients), an Independent samples t-test was used with apathy score as the dependent variable. Next, both of types of analyses (e.g., both prevalence and level) were repeated with depression score from the Beck Depression Inventory and the Centers for Epidemiological Studies-Depression Scale (prevalence cut scores of ≥ 14 BDI, ≥ 20 CES-D). To control for uneven distribution of anti-depressant usage between groups, anti-depressant usage was used as a covariate in the depression analyses. As a further check, post-hoc groups of all patients not prescribed anti-depressants were created and were analyzed in the same manner as the complete set.

To investigate whether a larger proportion of PD patients exhibited apathy in the absence of depression than DYS patients, patients were analyzed with respect to those who exhibited apathy only (≥ 14 on the Apathy Evaluation Scale without ≥ 14 on the Beck Depression Scale), depression only (≥ 14 on the Beck Depression Scale without ≥ 14 on the Apathy Evaluation Scale), and both apathy and depression (≥ 14 on the both scales). Two-way Chi squared tests for independence were utilized to examine prevalence for each of the categories listed above.

A final set of analyses examined the relationship between apathy and depression symptoms and severity of PD (prediction being that apathy would be significantly greater in more severe stages disease and depression would be significantly greater in earlier stages of disease). Parkinson's patients were divided into mild, moderate, and severe stages of illness based on the Hoehn-Yahr Staging Scale. A one-way ANOVA was conducted with apathy score as the dependent variable and Severity Stage as the independent variable. A one-way ANOVA was then conducted with depression score as the dependent variable and Severity Stage as the independent variable. Correlational

analyses were performed between apathy symptoms and the disease and demographic variables of age, motor UPDRS score, and duration of illness.

CHAPTER 4
RESULTS

Apathy Prevalence and Severity

The initial analysis examined whether Parkinson's patients exhibited a significantly higher prevalence of apathy (defined by ≥ 14 on the Apathy Evaluation Scale) than Dystonia patients. A 2 x 2 Chi squared test for independence was conducted with Group (PD, DYS) and Apathy (presence, absence) as categories. Results indicated that Parkinson's patients (freq.= 51%, 41/80) had a significantly higher prevalence of apathy than Dystonia patients (freq.= 20%, 4/20), $\chi^2(1, N = 100) = 6.31, p = .012, \phi$ correlation coefficient=.25]. See Figure 4-1 below.

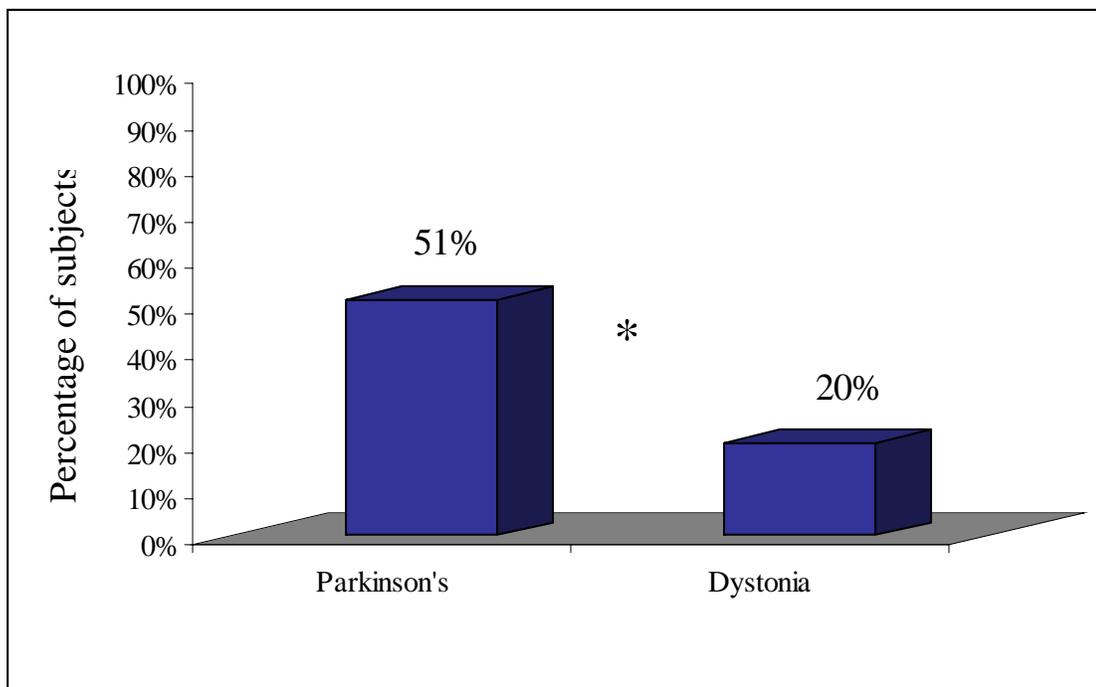


Figure 4-1. Prevalence of apathy in Parkinson's disease and Dystonia controls.

Next, the *severity* of apathy was examined between groups. It was predicted that Parkinson's patients would show significantly greater apathy scores than Dystonia patients. An independent samples t-test was conducted with Group as the independent variable and apathy score as the dependent variable. The apathy scores of the Parkinson's patients ($M = 13.06, SD = 7.28$) were significantly higher than those of the Dystonia patients ($M = 9.4, SD = 7.25$), $t(98) = 2.01, p = .041, d = .5$. Thus, Parkinson's patients had more severe apathy than Dystonia patients, and the effect size was moderate.

Depression Prevalence and Severity

The prevalence of depression was examined between the two groups using the Beck Depression Inventory and the Centers for Epidemiologic Studies-Depression Scale (defined by scores of ≥ 14 BDI, ≥ 20 CES-D). A 2 x 2 Chi squared test for independence was conducted with Group (PD, DYS) and depression (presence, absence) as categories. Results from the BDI indicated that the prevalence of depression in Parkinson's patients (freq.= 26.3%, 21/80) was *not* significantly different from the prevalence in Dystonia patients (freq.= 30%, 6/20), $\chi^2(1, N = 100) = .114, p = .74, \phi$ correlation coefficient = .034. This result is depicted in Figure 4-2. Similar findings occurred with the CES-D. The CES-D depression scores were *not* significantly different between groups (PD freq.= 31.2%, 24/77¹, DYS freq= 30.0%, 6/20, $\chi^2 = 0.01, p = .92, \phi$ correlation coefficient = .01).

¹ Note: CES-D data were missing from 3 participants.

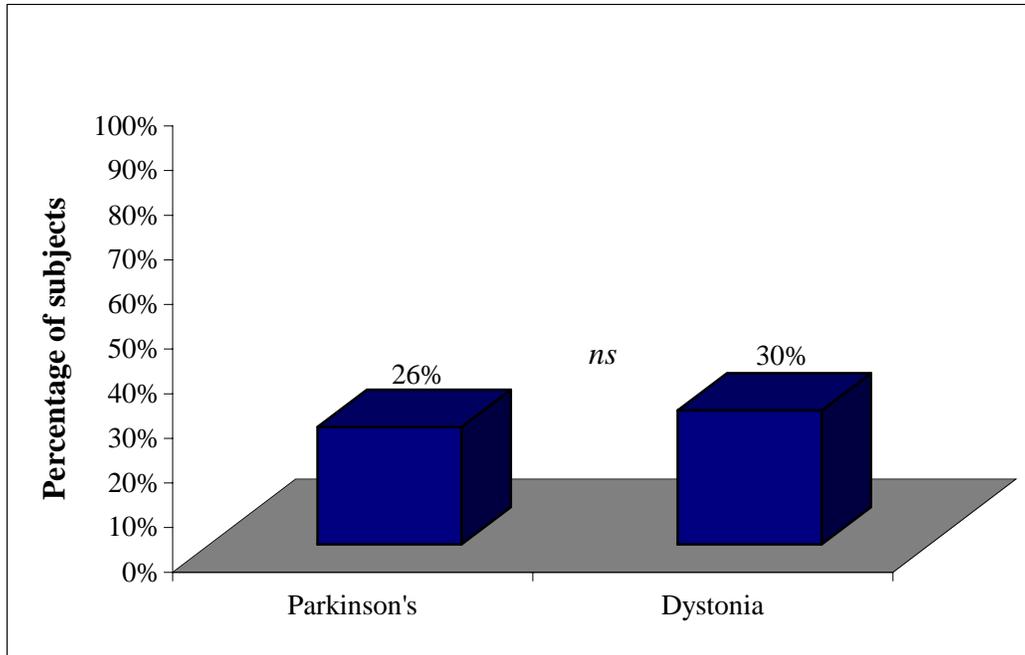


Figure 4-2. Prevalence of BDI depression in Parkinson's disease and Dystonia controls.

Severity of depression was investigated between the two groups via Independent samples t-tests. Neither BDI score nor CES-D score were significantly different between groups. Statistics for the BDI and CES-D scores were, respectively, $t(97) = 1.15, p=.25, d = .29$ and $t(95) = .588, p=.34, d = .15$. See Table 4-1 for means and standard deviations.

The BDI contains items that detect cognitive/ideational depression symptoms, and items that detect bodily/somatic depression symptoms. Both the ideational and somatic scores from the BDI were analyzed using separate independent samples t-tests. The results of these analyses indicated that there were no differences between the PD and Dystonic patients in terms of their ideational scores ($t(97) = .397, p = .69, d = .1$) or their somatic scores ($t(97) = 1.7, p = .09, d = .43$). These scores are shown in Table 4-1. Additionally, hopelessness cognitions as measured by the Beck Hopelessness Scale were

not significantly different between the PD and Dystonia groups, $t(94) = .89, p = .38, d = .22$). See Table 4-1.

Table 4-1. Means and Standard Deviations for Depression Scales.

Scale	PD patients (<i>n</i> =80)	DYS patients (<i>n</i> =20)	<i>p</i> value
BDI total	10.2 (6.8)	8.3 (5.5)	.25
BDI-Ideational	3.9 (3.8)	3.5 (3.4)	.69
BDI-Somatic	6.4 (3.7)	4.8 (3.3)	.09
CES-D total	12.8 (10.2)	11.3 (11.2)	.56
BHS total	4.7 (4.6)	3.7 (4.2)	.38

Of potential importance, the Parkinson and Dystonia groups differed according to the percentage of patients who were prescribed anti-depressant medications. Fifty-one percent of Parkinson's patients had been prescribed anti-depressant medication versus only 20% of the Dystonia patients. It is thus possible that the depression scores of the Parkinson's patients may have been "artificially lowered" due to their higher use of antidepressants. Two post-hoc analytic approaches were undertaken to examine this possibility. In the first, the use of anti-depressants was used as a covariate in the examination of depression scores. In the second approach, the subset of Parkinson patients who were NOT taking anti-depressant medications were compared to the Dystonia patients who were not taking anti-depressants.

The results of the first approach indicated that controlling for anti-depressants did not change the earlier finding of no significant difference on BDI score between PD ($M = 10.0, SD = 6.6$) and Dystonia groups ($M = 8.1, SD = 6.4$), $t(94) = .76, p = .56, d = .29$. In the second approach, subgroups of patients who had not been prescribed anti-depressants were created and included 38 PD patients and 14 Dystonia patients. Group comparisons using independent t-tests revealed that the PD patients tended to have higher total BDI scores than the Dystonia patients, $t(50) = 1.93, p = .059, d = .6$. See Table 4-2 for means

and standard deviations. When the BDI scores were further examined, ideational scores did not differ between groups, while somatic symptoms were significantly higher in Parkinson's ($M = 6.6, SD = 3.8$) than in Dystonia ($M = 3.4, SD = 2.4$), $t(50) = 2.88, p = .006, d = .898$. Further, CES-D score and BHS scores were not significantly different between groups, respectively, $t(50) = .720, p = .475, d = .059$ and $t(50) = 1.03, p = .31, d = .32$.

Table 4-2. Means and Standard Deviations for Patients *Not* Using Anti-Depressants

Scale	PD patients ($n=38$)	DYS patients ($n=14$)	<i>p</i> value
BDI total	10.7 (7.6)	6.4 (5.0)	.059+
BDI-Ideational	4.1 (4.2)	3.0 (3.2)	.403
BDI-Somatic	6.6 (3.8)	3.4 (2.4)	.006*
CES-D total	12.5 (11.0)	10.0 (11.6)	.475
BHS total	4.9 (5.3)	3.3 (3.4)	.306

* Denotes that the values are significantly different.

+ Denotes that the values are significantly different at the level of a trend.

Relationship between Apathy and Depression Prevalence

Another set of analyses investigated the relationship between apathy and depression symptoms in the two groups in order to test the prediction that a larger proportion of PD patients exhibited apathy in the absence of depression than did the DYS patients. Patients were analyzed with respect to those who exhibited apathy only (≥ 14 on the Apathy Evaluation Scale without ≥ 14 on the Beck Depression Scale), those who exhibited depression only (≥ 14 on the Beck Depression Scale without ≥ 14 on the Apathy Evaluation Scale), and those who exhibited both apathy and depression (≥ 14 on the both scales). Two-way Chi squared tests for independence were used to examine prevalence for each of the categories listed above. The prevalence of patients exhibiting *apathy alone* (e.g., in the absence of depression) was significantly higher in the

Parkinson's group (freq.= 28.8%, 23/80) than in the Dystonia group (freq.= 0%, 0/20), Fisher's exact significance (used to correct for less than 5 per cell) =.006. The prevalence of *depression alone* (in the absence of apathy) was not significantly different between Parkinson's (freq= 4%, 3/80) and Dystonia (freq.= 10%, 2/20), Fisher's exact significance =.261. Additionally, the prevalence of patients exhibiting apathy and depression together was not significantly different between Parkinson's (freq.= 22.5%, 18/80) and Dystonia (freq.=20.0%, 4/20), Fisher's exact significance= 1.0. See Figure 4-3. Thus, approximately thirty percent of the Parkinson's sample exhibited apathy without depression while none of the Dystonia sample exhibited apathy without depression. There was no significant difference between groups in terms of those exhibiting depression alone or combined apathy and depression.

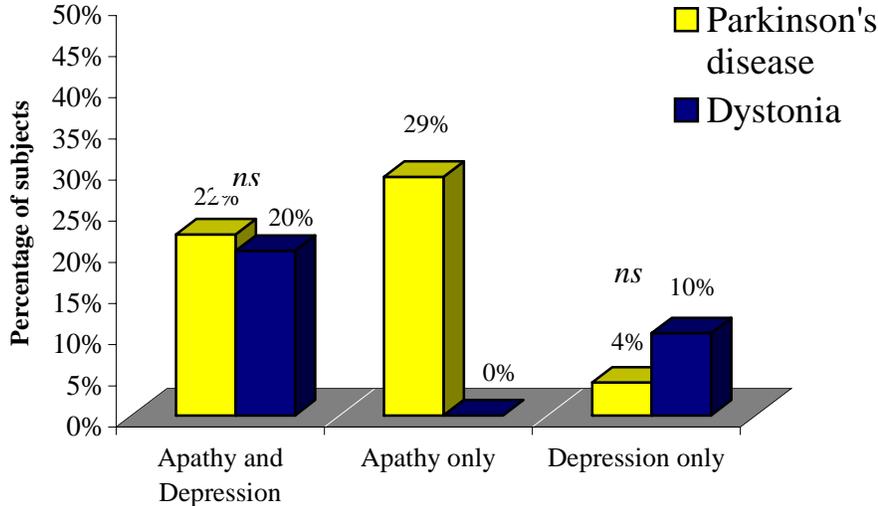


Figure 4-3. Overlap between apathy and depression, apathy alone, and depression alone between groups.

Relationship with Severity of Parkinson's Disease

A final set of analyses was conducted to investigate the relationship between apathy and depression symptoms and severity of Parkinson's disease. It was predicted that apathy would be significantly greater in more severe stages and depression would be significantly greater in earlier stages. As noted earlier, the Hoehn-Yahr is a Staging system of severity of Parkinson's disease and ranges from 0 (no disease) to 5 (bedridden). Three severity groups were created according to Stages of PD: (a) Mild (Stages 1-2, unilateral disease to bilateral disease without impairment of balance, $n = 40$), (b) Moderate (Stages 2.5-3, mild bilateral with recovery on the pull test and mild to moderate bilateral disease with some postural instability, $n = 22$), and (c) Severe (Stage 4, severe disability, unable to walk or stand unassisted, $n = 5$). A oneway ANOVA was conducted with Severity Group as the independent variable and apathy score as the dependent variable. Results suggested that apathy was significantly different between groups, $F(2, 64) = 7.68, p = .001$. However, Levene's test found that the assumption of homogeneity of variance could not be supported, $F(2, 64) = 4.57, p = .014$. Therefore, the more conservative Brown-Forsyth F-statistic is reported. Results indicate that apathy is higher at more severe stages of illness at the level of a trend, $F(2, 6.65) = 4.4, p = .061$. Means and standard deviations are as follows: Mild ($M = 10.6, SD = 6.8$), Moderate ($M = 15.8, SD = 4.9$), Severe ($M = 20.4, SD = 11.3$).

Apathy score was also examined in relation to patient age, duration of disease, and motor score on the United Parkinson Disease Rating scale (obtained while "on" dopaminergic medications). Bivariate correlations were used to examine these relationships (See Table 4-3). Duration of illness (e.g., years of symptoms) was not significantly related to apathy score ($p = .82$), while UPDRS motor score severity was

significantly positively related to apathy ($r = .25, p = .003$) and age was significantly positively related to apathy ($r = .24, p = .03$).

To examine the effects of severity on BDI depression scores, a one-way ANOVA was performed with Severity Group as the independent variable and depression score as the dependent variable. Levene's test found that the assumption of homogeneity of variance was supported. There was a significant difference between Severity Group and depression score, $F(2, 64) = 10.3, p < .001$. Bonferroni corrected post hoc followup tests were utilized to locate the significant effects. Moderate and Severe Groups were significantly higher in depression than the Mild group, $t(64) = 3.89, p = .001$ and $t(64) = 3.23, p = .008$, respectively. Means and standard deviations are as follows: Mild ($M = 7.78, SD = 5.55$), Moderate ($M = 14.0, SD = 5.66$), and Severe ($M = 16.8, SD = 11.17$). Depression score was also examined in relationship to duration of illness, age, and motor UPDRS score (See Table 4-3). Results indicated that depression (BDI) scores were not significantly related to duration of illness ($p = .98$) or age ($p = .95$), but were significantly positively related to motor score severity ($r = .314, p = .003$).

Table 4-3. Intercorrelations Between PD Apathy Scores, Depression Scores, and Disease Variables

	AES	BDI	CESD	DUR.	AGE	H&Y	UPDRS-M
1. AES	--	.671*	.640*	-.026	.241+	.411*	.250+
2. BDI		--	.817*	.033	.012	.462*	.348*
3. CES-D			--	.033	-.007	.449*	.314*
4. Duration (Years of Symptoms)				--	.022	.353*	.348*
5. Age					--	.395*	.221
6. Hoehn-Yahr						--	.708*
7. UPDRS motor							--

* Significant at $p < .01$.

+ Significant at $p < .05$.

CHAPTER 5 DISCUSSION

The present study investigated three hypotheses. The first hypothesis was that Parkinson's disease patients would display higher levels of apathy than a clinical control group of Dystonia patients. Specifically, we predicted that: a) PD patients would show a significantly higher prevalence of apathy than Dystonia patients, and b) PD patients would show significantly more severe apathy than Dystonia patients. This was based on the idea that certain frontal-subcortical systems putatively involved in apathy (e.g., anterior cingulate/mesial frontal cortex) are more disrupted in Parkinson's disease than in Dystonia. The second hypothesis was that apathy is a core feature of Parkinson's disease and not simply a symptom of depression. Therefore, it was predicted that a larger proportion of Parkinson's disease patients would exhibit apathy in the absence of depression than Dystonia patients. The third hypothesis involved the relationship between apathy and depression and stage of illness of Parkinson's disease. It was hypothesized that greater apathy would occur at more severe stages of disease, and that greater depression would occur at the early stages of disease. This was based on the idea that while both types of mood symptoms may worsen as a direct result of progressing pathology of the illness, apathy may be more linked to this progression whereas depression may also be seen as a reaction to being diagnosed with a progressive neurodegenerative disease.

Summary and Interpretation of the Findings

The first hypothesis was supported by the data. The prevalence of apathy was significantly higher in Parkinson's disease than in Dystonia. Approximately half of the Parkinson's patients showed apathy, whereas only one fifth of Dystonia patients showed apathy. Parkinson's patients had significantly more *severe* apathy scores than Dystonia patients. Both the effect of prevalence and the effect of severity were moderately large. This suggests that the differences between the groups may be large enough to be clinically meaningful in addition to being statistically significant. Further, when depression was examined between groups there was no significant difference found for prevalence using either the Beck Depression Inventory (BDI) or the Centers for Epidemiologic Studies-Depression (CES-D) scale. There was also no significant difference between severity of depression between groups using either scale. Further, groups did not differ on endorsement of hopelessness cognitions-- as measured by the Beck Hopelessness Scale (BHS). Because the Parkinson's patients were significantly more likely to be taking anti-depressant medications than the Dystonia patients (and perhaps scores were "artificially" lowered due to this), post-hoc groups were created of 38 PD patients and 14 Dystonia patients who were *not* taking anti-depressants. Analyses revealed that although the CES-D and BHS continued to show no difference between groups, the BDI scores revealed that Parkinson patients more severe at the level of a trend ($p=.059$). Interestingly, when further examined, it appeared that somatic symptoms were driving this difference—with ideational scores not differing significantly. Therefore, it seems plausible that this difference between groups may be due to Parkinson's patients experiencing more somatic complaints than Dystonia and not depression per se. Although it cannot be completely ruled out that these symptoms represent depression, the

above interpretation seems likely when taken in light of findings from the other two depression scales.

The second hypothesis was also supported by the data. Parkinson's patients had significantly greater prevalence of apathy in the absence of depression than Dystonia patients. Twenty-nine percent of Parkinson's patients showed apathy in the absence of depression, whereas no Dystonia patients showed this result. This was the most dramatic and potentially important finding of the study. It suggests that apathy, in Parkinson's but not Dystonia manifests at a significant level independent of depression level. Further, prevalences of both apathy and depression together and depression alone were not significantly different between groups. Apathy in the absence of depression was a unique finding for Parkinson patients and suggests the importance of this mood symptom specifically in this disorder. It is proposed that some of the differences in apathy expression between the two groups may be due to pathological differences between Dystonia and Parkinson's disease. Both disorders are thought to affect the basal ganglia; however, they are believed to have differential connections to cortex. PD has been proposed to disrupt mesial frontal/anterior cingulate cortex connections. This area of the frontal cortex is reportedly involved in apathy in other neurologic conditions (Cummings, 1993). It is also the area of the frontal cortex thought to be involved in the extreme syndrome of apathy—akinetic mutism (Tranel, 1992). Dystonia, in contrast to PD, has been proposed to disrupt caudal supplemental motor areas, prefrontal cortex, and the caudate nucleus (Hallett, 1998). However, the neuropathology of apathy in PD has not been systematically addressed in the literature. It was not the intent of the present

study to do so. Carefully controlled neuroimaging studies should be undertaken to further the hypotheses about proposed brain area involvement.

The third hypothesis was partially supported. Apathy was associated with greater disease severity as measured by the Hoehn-Yahr Staging scale. Thus, greater severity of illness was related to higher apathy. In addition to severity, apathy was also correlated with age and motor score, but not with duration of illness (e.g., how many years patients had experienced symptoms). It was hypothesized that depression would be greater in the earlier stages. Contrary to the hypothesis, depression was significantly greater in the more severe stages of disease. However, this result is not counter to findings in the Parkinson's disease literature. Findings suggest a relationship between subcortical neuron degeneration (as the disease becomes more severe) and an increase in depressive symptoms (McDonald, Richard, & DeLong, 2003). In regards to the high depression in earlier stages, this often occurs around the time of diagnosis. Patients in this sample had a wide range of year since diagnosis, and the majority were not recently diagnosed. Thus, all of the above factors may have played into the finding that depression was related to later rather than earlier stages of illness. In addition, depression was related to motor severity, but not with duration of illness or age.

The fact that neither apathy nor depression were significantly related to duration of illness, but were related to severity of illness may at first seem counterintuitive. However, it is reasonable given the variability of progression of the disease across patients. Some patients can stay relatively healthy with PD for 10-15 plus years, whereas others may decline more rapidly (Nutt, Hammerstad, & Gancher, 1992; Peretz & Cummings, 1988). Therefore, whereas the occurrence of apathy and depression

symptoms appear to increase with increasing severity of illness, the duration of the illness per se is not associated with increased psychiatric symptoms.

Comparing Prevalence and Severity Across Current Literature

The finding of a high prevalence of apathy in Parkinson's disease is consistent with the current literature. Three studies (Pluck & Brown, 2002; Starkstein et al., 1992; Isella et al., 2002) have examined self-reported apathy in PD and, respectively, each has reported the prevalence of apathy as 38%, 42%, and 43%. These rates are similar to that found in the current study (51%). In addition, two of these studies broke down their prevalence figures into apathy alone, depression alone, and apathy and depression together. Starkstein et al. (1992) reported 12% apathy alone (6 of 50 PD subjects), 21.6% depression alone (13 of 50 PD subjects), and 30% apathy and depression together (15 of 50 PD subjects). The percentage of apathy and depression together is similar to that found in the present study; however, the percentage of apathy alone was lower than the present study (12% vs. 29%). Isella et al. (2002) reported 23.3% apathy alone (7 of 30 PD subjects), 13% depression alone (4 of 30 PD subjects), and 46.6% apathy and depression together (14 of 30 subjects). These prevalence values are similar to those found in the present study. However, these values should be taken with caution because they were based on an Italian translation of the original scale. Turning to the severity of apathy in these two studies, findings indicate that PD showed significantly more severe apathy than normal elderly controls and significantly more severe apathy than Osteoarthritis patients.

Although problems surrounding the use of caregiver ratings of apathy were presented earlier, it remains of theoretical interest to examine the results from the remaining three apathy studies that relied on the caregiver rated Neuropsychiatric

Inventory (NPI). Overall, these studies found lower rates of overall apathy than the present study. Aarsland (1999) used a comprehensive epidemiological sample of 139 PD patients, and found a prevalence rate for apathy of 16.5% (23 of 139 PD subjects), with 4.3% of the total PD subjects showing apathy in the absence of depression (6 of 139 PD subjects). Aarsland (2001) used a subset of the same data and not surprisingly, reproduced his original result for apathy in PD (e.g., 16.5%, 17 of 103 patients). Finally, Levy (1998) found that 5% of patients showed apathy alone (2 of 40 PD subjects), and 28% of patients showed a combination of apathy and depression (11 of 40 PD subjects). These values on the whole are much lower those that from self-report scales (ex. 38-51% total apathy in self-reported versions vs. 16.5%-33% in caregiver rated versions). There may be several explanations for this. First of all, Levy's data (1998) were based on a selected sample—that of surgery candidates. Participants are often screened for significant psychiatric symptoms before being deemed surgery candidates; therefore they may have a lowered rate of overall psychiatric symptoms. Secondly, the NPI caregiver scale assesses fewer symptoms of apathy (and depression) than rating scales such as the AES or BDI. For example, there is only one item assessing behavioral presentation of apathy on the NPI versus five on the AES. There are approximately 8 questions for each mood category on the NPI (e.g., apathy, depression, anxiety, etc), and they often do not cover the full diagnostic criteria. Not covering as many symptoms as the other versions of the scales could artificially lower the apathy scores for many Parkinson's patients.

Despite the above criticisms, it is important to mention that all studies reviewed found some proportion of their sample to present with apathy in the absence of depression. As such, it appears that apathy and depression may indeed be separable in

Parkinson's disease, and that apathy may have a key place in the mood profile of the disorder. It may be important, therefore, for clinicians to screen for both apathy and depression. In this way, patients can be triaged into appropriate treatment groups. There are currently effective pharmacological and psychotherapeutic treatments for depression in Parkinson's disease. However, some treatments are not necessarily helpful for apathy and may have harmful side effects without benefits. For example, Lexapro (escitalopram) is frequently prescribed for depression in Parkinson's patients.

Escitalopram is not necessarily proven to improve apathy symptoms, but has a possible side-effect profile of agitation/restlessness, blurred vision, diarrhea, difficulty sleeping, drowsiness, dry mouth, fever, indigestion, and nausea. Thus, prescription of this medication for an apathetic patient might cause the above side-effects without relief of apathy symptoms. Additionally, it is helpful for caregivers and spouses to understand that apathy is a characteristic of this disorder, and likely a direct result of disease pathology. This allows caregivers to understand that apathetic behavior is not under the PD patient's voluntary control, and thus is not laziness or oppositional behavior but a symptom of the disease.

More theoretic in nature, it is of interest to understand whether separate neural systems underlie depression and apathy. It may be that orbitofrontal-subcortical connections underlie depression in PD, whereas mesial frontal/anterior cingulate subcortical connections underlie apathy. It may additionally be important to study subgroups of patients that show high levels of apathy. For example, the recent literature proposes a relationship between PD apathy and certain cognitive deficits. High apathy PD groups showed decreased performance compared to low apathy PD groups in terms

of verbal fluency (based on the Category test and Controlled Oral Word Fluency), changing mental categories or “set shifting” (based on the Wisconsin Card Sort categories sorted and errors) speeded task performance (based color naming and word naming on the Stroop and Trails B) and inhibition (Stroop color-word naming) (Isella et al., 2002; Pluck & Brown, 2002). The continued examination of the relationship between cognitive abilities and apathy is an important area of future research.

Limitations of the Present Study

Several limitations of the current study must be addressed. First, although every attempt was made to obtain patients that matched the Parkinson’s group in terms of demographics, this was not possible on all variables. The Dystonia group tended to be younger (Dystonia $M = 60.9$, $SD = 11.9$ vs. Parkinson’s $M = 68.9$, $SD = 9.5$) and composed of more women (Dystonia 70% vs. Parkinson’s 31%). They also were less likely to be on anti-depressant medications (Dystonia 20% vs. Parkinson’s 51%). The possibility that the findings were driven by these demographic differences cannot be completely ruled out. However, reassuringly, it appears that at least some of the findings from the present study are not those that would be expected if demographic variables were driving the results. For example, by virtue of the increased general population incidence of depression for women over men, the Dystonia group should have shown more depression than the Parkinson’s group. However, findings were that groups did not differ in terms of depression. Additionally, post hoc analyses were utilized to explore possible biases due to the Parkinson’s disease group having more anti-depressant usage. Results of these analyses revealed no differences between BHS and CES-D scores, but a trend for Parkinson’s disease to be more severe on the somatic symptoms of the BDI. It

cannot be completely ruled out that this is due to depression differences given the ambiguity of interpretation of somatic symptoms with medical illnesses.

Turning to a methodological critique of the study, one limitation is the use of depression symptom checklists rather than using psychiatric interviews and DSM-IV diagnoses. This would have allowed for distinctions between depression symptoms, and produced concrete diagnoses of Major Depressive Disorder, Dysthymia, and other depressive mood disorders. Individual interviews with each patient would also have allowed us to examine previous psychiatric history. Inability to compare current results to past psychiatric histories is a limitation of this study.

A further limitation to using symptom checklists is that apathy and depression have overlapping symptoms, and as such, the scales overlap in content. For example, the BDI includes item content that overlaps with apathy (e.g., Item 4: “I don’t enjoy things the way I used to,” Item 12: “I am less interested in other people than I used to be”). Thus, it is possible that a particular symptom endorsement on the BDI might better represent apathy, but is actually being counted in the depression total score. Clearly, this is a disadvantage to using total scores for BDI and AES instead of examining individual item endorsement.

Directions for Future Research

One way to address the limitation of apathy and depression total scores is to use a different methodological approach. This would be to use item factor analysis to investigate whether apathy and depression factors can be identified. Items that are thought to relate more to depression or more to apathy would be delineated a priori, and data would be examined whether responses fall into proposed groups. Based on the

requirements of factor analysis, this approach will require several hundred subjects.

Efforts are currently underway to continue subject recruitment in order to meet this goal.

Further, it should be noted that the present study was based on an outpatient population presenting to a Movement Disorders Specialty clinic. It is of interest for future studies to examine the prevalence based on this sample to those of epidemiological samples using self-report apathy and depression scales. In this way, differences between types of samples and levels of apathy/depression can be examined.

Another potentially important future line of research is to examine whether there is a relationship between reduced physiological reactions to emotion in PD (e.g., palm sweating and startle eyeblink response) and level of apathy. Recent research from our laboratory has shown that Parkinson's patients have a blunted physiological reaction to emotional pictures. It is of interest to examine whether the more apathetic patients are the ones that also show the most physiological blunting. Related, it may be of interest examine how apathy changes in response to dopaminergic therapy. It is unknown how "on" "off" fluctuations relate to the experience of apathy.

To conclude, findings from the present study provide support for the hypothesis that apathy and depression may be similar, but separable experiences of mood states. Further, apathy in the absence of depression appears to play a key role in the profile of patients presenting with Parkinson's disease. This suggests that clinicians would be well advised to screen for both apathy and depression during clinical care. As the presentation of apathy is delved into further, differential pathology, clinical correlates, and effective treatments may be discovered.

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BIOGRAPHICAL SKETCH

Lindsey Kirsch was born in Atlanta, GA, and received her B.S. in neuroscience from Furman University. She obtained research experience at the Centers for Disease Control & Prevention, Atlanta, GA. She is currently pursuing her doctorate in clinical psychology, with a specialty in neuropsychology, at the University of Florida. She currently co-directs a NIH clinical trial involving Parkinson's disease and deep brain stimulation's effects of mood, motor, and cognitive symptoms. Current research and clinical interests include cognition in Parkinson's disease, Alzheimer's disease, and Mild Cognitive Impairment. Current clinical interests also include treatment of psychogenic movement disorders.