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Characterizing the relation between depressive symptoms and Parkinson's disease in a sample of Swedish twins

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**Characterizing the Relation Between Depressive Symptoms
and Parkinson's Disease in a Sample of Swedish Twins**

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ABSTRACT

Characterizing the Relation Between Depressive Symptoms and Parkinson's Disease in a Sample of Swedish Twins

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Depression commonly co-occurs with Parkinson's disease (PD). Psychosocial stressors and biochemical changes associated with PD have both been implicated in the etiology of depression in PD. The purpose of the current study was to examine whether genetic or environmental influences contribute to the increased risk for depressive symptoms among individuals with PD in a population of twins. Among individuals with PD, 24% endorsed a moderate-severe level of depressive symptoms, and 64% endorsed at least a mild level of depressive symptoms. Case-control results indicated that PD is a significant risk factor for both mild (OR = 3.11, CI = 1.82-5.31) and moderate-severe (OR = 3.23, CI = 1.77-5.89) depressive symptoms, adjusting for age, sex, and prior history of major depression. Odds ratios were not significantly attenuated in the co-twin control analysis compared to the case control analysis for either mild or moderate-severe depressive symptoms, suggesting that genetic influences are unlikely to account for the increased risk of depressive symptoms among PD patients. Further support for environmental rather than genetic influences on the PD-depression relation was revealed by examining the risk of depressive symptoms among co-twins of PD patients versus co-twins of non-PD controls. Controlling for age, sex, and prior history of depression, PD in the co-twin was not a risk factor for mild or moderate-severe depressive symptoms in twins without PD. These findings indicate that environmental influences likely play an important role in the etiology of depressive symptoms in individuals with Parkinson's disease. Alternatively, brain changes associated with PD may heighten biological vulnerability to depressive symptoms.

Author Note

The purpose of the current study was to examine whether genetic influences contribute to increased risk for depressive symptoms among individuals with PD, using a case control and co-twin control design. Of note, the original purpose of the study was to examine the role of genetic and environmental factors in explaining the relation between depressive symptoms and PD. The initial analysis plan included bivariate twin modeling and phenotypic comorbidity models to decompose the variance in the PD-depressive symptom relation into genetic and environmental components. Due to the lack of concordance for PD in the sample, however, twin modeling was rendered uninformative. As such, the study aims were revised to evaluate PD as a risk factor for depressive symptoms using an unrelated comparison group (classic case control study) and co-twin controls, allowing inferences to be drawn regarding the presence of a genetic influence upon the risk for depressive symptoms within PD. The aims, hypotheses, and analyses presented below are reflective of this change. As both the original and current designs allow investigation of the role of genetics in the PD-depression relation, however, the overall goal of the study remains the same: to shed new light on the etiology of PD-depression.

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Parkinson's disease (PD) is the most common neurodegenerative movement disorder,

affecting roughly 0.3 percent of the US population (Barrero, Ampuero, Morales, Vives, de Dios

Luna del Castillo, Hoenicka, & Yébenes, 2005; de Lau, Giesbergen, de Rijk, Koudstaal, &

Breteler, 2004). PD is related to aging, however, and prevalence estimates increase to 4 to 5

percent for individuals of age 85 years and older (de Lau et al., 2004). For older adults, PD is the

second most frequent movement disorder, following essential tremor (Albin, 2006). Cardinal

features of PD include distal resting tremor, rigidity, bradykinesia, gait disturbance, and

asymmetrical onset (Rao, Hofmann, & Shakil, 2006). A progressive disorder, PD can lead to

disability and a decrease in quality of life.

Depression in PD

Community-based studies have found that psychological disorders such as anxiety and

depression are more common among individuals with PD as compared to healthy age- and sex-

matched individuals (e.g., Tandberg, Larsen, Aarsland, & Cummings, 1996). Of the

psychological comorbidities associated with PD, depression is the most common (Cummings,

1992; Starkstein, Preziosi, Bolduc, & Robinson, 1990; Schneider, Althaus, Backes, & Dodel,

2008). Indeed, in James Parkinson's original description of the "shaking palsy," he described

"melancholy" as a central symptom of the disorder (Edwards, Kitt, Oliver, Finkelstein, Wagster,

& McDonald, 2002). Though prevalence estimates of depression in PD patients have ranged

from 4% (Hoehn & Yahr, 1967) to 70% (Bieliauskas & Galntz, 1989), recent reports document a

prevalence of major depressive disorder of approximately 8% in PD patients (Tandberg et al.,

1996), with clinically-significant depressive symptoms occurring in 35-50% of PD patients

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(Althaus et al., 2008; Cummings, 1992; Dooneief, Mirabello, Bell, Marder, Stern, & Mayeux, 1992). In the current proposal, depression in PD will be referred to as PD-depression.

Clinical presentation. Research suggests that PD-depression may present differently from primary major depression. Specifically, the symptoms observed most frequently in PD-depression include irritability, difficulty concentrating, expressions of sadness and pessimistic thinking, and a loss of interest in previously pleasurable activities (Cummings, 1992; Slaughter, Slaughter, Nichols, Holmes, & Martens, 2001). Evidence also suggests that, compared to primary major depression, PD-depression may be characterized by greater anxiety but less guilt and self-blame (Barbas, 2006; Starkstein, Merello, Jorge, Brockman, Bruce, Petracca, et al., 2008). Regarding suicidal behavior, research indicates that both suicidal ideation (Miyoshi, Ueki, & Nagano, 1996) and suicide attempts (Merschdorf et al., 2003) are less frequent in PD-depression than in primary major depression.

Historically, PD-depression has typically been considered to be of mild severity, with low to moderate levels of depressive symptoms (Cummings, 1992; McDonald, Richard, & DeLong, 2003; Serrano-Dueñas, 2002). More recently, however, Ehrt and colleagues (2006) compared the depressive symptoms of 145 non-demented depressed patients with PD to those of 100 elderly non-demented depressed individuals without PD, and found that depressive severity was comparable for the two groups. Findings also revealed no significant difference in the level of cognitive functioning between the PD and non-PD depressed groups, although depressed PD patients did report more concentration problems than non-PD depressed patients. In contrast to earlier studies that noted sadness as a frequently observed symptom in PD-depression, the findings of Ehrt et al. indicated that depressed patients with PD less frequently reported feelings of sadness. Depressed patients in the PD group also reported feelings of guilt, anhedonia, and

loss of energy less frequently than depressed older adults without PD. Ehrt and colleagues concluded that the differences in depressive symptom profiles for PD and non-PD individuals may indicate that the brain changes of PD affect the clinical picture of depression. Specifically, Ehrt et al. concluded that depression in PD may be more influenced by noradrenergic deficiency than primary major depression, as noradrenergic depletion appears to disrupt concentration. Taken together, the literature to date is inconclusive regarding whether PD-depression is truly milder in form and different in symptom profile as compared to primary major depression.

Implications. The consequences of experiencing depression in PD are numerous. Depression is a critical factor in the quality of life for PD sufferers (Behari, Srivastava, & Pandey, 2005; Kuopio, Marttila, Helenius, Toivonen, & Rinne, 2000; Schrag, Jahanshahi, & Quinn, 2000; Slawek, Derejko, & Lass, 2005), and has been associated with poorer cognitive functioning among PD patients (Norman, Tröster, Fields, & Brooks, 2002; Uekermann, Daum, Peters, Wiebel, Przuntek, & Müller, 2003). PD-depression also is associated with an exacerbation of PD impairments, in both sensory and functional domains, as well as a steeper decline in functioning (Chen, 2004; Nilsson, Kessing, Sørensen, Andersen, & Bolwig, 2002). Hughes and colleagues (2004) reported that depression is related to an increased risk of mortality for PD patients. In addition to the implications for the patient, PD-depression also presents an increased burden for caregivers (Schrag et al., 2000). Finally, depression is a significant predictor of the health care costs associated with PD (McCrone, Allcock, & Burn, 2007). Considering the many negative effects of PD-depression, a fuller understanding of its etiology may be an important step towards its prevention and treatment.

Etiology of PD-Depression

Much empirical work has focused on understanding the etiology of depression in PD (see reviews by Lieberman, 2006; McDonald et al., 2003; Slaughter et al., 2001; and Veazey, Aki, Cook, Lai, & Kunik, 2005), particularly findings that contribute to the debate of whether depression in PD is organic or reactive in nature. Historically, depression in PD has been considered a reaction to the illness and disability of PD (Kearney, 1964). Chafetz and colleagues (1955) conducted group therapy with a sample of PD patients and concluded that PD-depression resulted from a denial of the PD symptoms due to an underlying fear of illness, disability, and dependency. Psychodynamic research dominated early investigations into the psychological aspects of PD and described tendencies for PD sufferers to have personalities that were characterized as rigid, driving, worrying, and pessimistic (Booth, 1948; Sands, 1942); from a psychodynamic perspective, an individual's reaction to PD, including the development of depression, would depend in large part upon his or her personality and childhood experiences (e.g., abusive parenting). More recently, explanations for PD-depression have emphasized the roles of biological (e.g., neurological, genetic) and psychosocial processes; evidence for these etiological explanations will be examined next. Research regarding the issue of depression preceding PD also will be presented, as depression that antedates PD may indicate either a risk factor for PD or a prodromal symptom of the disorder.

Biological Hypotheses of PD-Depression

Neurological hypotheses. Neurological accounts of PD-depression posit that depressive symptoms result from the neurodegeneration of PD. Researchers have argued that the associations between higher depression rates and specific clinical characteristics of PD, such as the akinetic rigid type of PD (Barrero et al., 2005; Starkstein et al., 1998) and right-sided motor

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symptoms (Starkstein et al., 1990), support a relation between PD-depression and the neurodegeneration of PD (McDonald et al., 2003). The primary neurological or organic explanations for PD-depression are the dopaminergic hypothesis and the serotonergic hypothesis. The evidence for each hypothesis is presented below.

Proposed by Fibiger, the dopaminergic hypothesis is based upon the fact that, in addition to the nigrostriatal, the mesocortical and mesolimbic dopaminergic projections also deteriorate in PD (Fibiger, 1984). Fibiger hypothesized that it is damage to these projections that poses a risk for depression in individuals with PD, as dopamine is considered one of three neurotransmitters, along with serotonin and norepinephrine, involved in the pathophysiology of depression (Weintraub et al., 2005). Empirical evidence for the dopaminergic hypothesis is currently inconclusive, as some (Cantello et al., 1989; Torack & Morris, 1988), but not all (Broussolle et al., 1999) imaging studies of PD-depression have indicated dopaminergic deficiency in the mesocortical and mesolimbic dopaminergic projections, in addition to deficiency in the nigrostriatal projections. More recently, Weintraub and colleagues (2005) examined the integrity of the striatal dopamine transporter (DAT) in relation to PD-depression in a neuroimaging study, and found that depressive symptoms were not reliably associated with overall DAT availability. In contrast, Remy and associates (2005) examined the binding of the [^{11}C]RTI-32 PET marker in 20 PD patients and found support for relations between deficiencies in both dopaminergic and noradrenergic binding in the limbic system and PD-depression. Taken together, the research to date offers conflicting findings regarding the dopaminergic hypothesis of PD-depression.

The serotonergic hypothesis, proposed by Mayeux and colleagues (1984, 1990), posits that an overall reduction in serotonin levels occurs in PD to compensate for decreased striatal dopamine, and that this reduction in serotonin presents a risk factor for depression. As with the

dopaminergic hypothesis, findings regarding the serotonergic hypothesis are inconclusive. An

early study examining levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in

the cerebrospinal fluid (CSF) of depressed and non-depressed PD patients demonstrated

decreased 5-HIAA levels in the CSF of PD patients with major depression as compared to non-

depressed PD patients, but no difference in 5-HIAA levels between dysthymic and non-

depressed patients (Mayeux, Stern, Williams, Cote, Frantz, & Dyrenfurth, 1986). While

decreased 5-HIAA levels also were found in the CSF of depressed PD patients compared to non-

depressed PD patients in a study by Kostic and colleagues (1987), results from the most recent

empirical examination of the serotonergic hypothesis do not support the hypothesis. Conducted

by Leentjens and colleagues (2006), the double-blind, placebo-controlled study experimentally

manipulated serotonin levels of PD cases and non-PD controls using an acute tryptophan

depletion (ATD) procedure, and found no evidence for a specific serotonergic vulnerability for

depression in PD patients. Replication studies of the ATD paradigm are needed before

conclusions regarding the serotonergic hypothesis of PD-depression are drawn.

Genetic hypotheses. A second category of biological hypotheses of PD-depression has

examined a potential genetic susceptibility for both depression and PD, as well as genetic

susceptibilities for PD-depression specifically. Regarding the heritability of depression, a recent

population-based study of major depression in Swedish twins found that heritability of liability

to major depressive disorder (MDD) was approximately 37% (Kendler, Gatz, Gardner, &

Pedersen, 2006b), an estimate consistent with other familial behavioral genetic studies (e.g.,

Middeldorp et al., 2005). Genetic factors also have been shown to influence liability to

depressive symptoms among older adults (Gatz, Pedersen, Plomin, Nesselroade, & McClearn,

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1992; Jansson et al., 2004). In contrast, estimates of heritability for PD are small and confined to rare familial forms of PD (Warner & Schapira, 2003).

Regarding the heritability of PD-depression specifically, Fahim and colleagues (1998) studied the familial aggregation of depression, dementia, and PD in a population-based sample of 6,596 individuals in order to investigate the possibility of a common, or shared, genetic origin underlying the three disorders. Although their findings revealed a significant relation between depression and a family history of psychiatric disorders in first degree relatives, no association was found between depression and a family history of PD in first degree relatives, refuting their hypothesis of a shared genetic origin for both depression and PD. More recently, however, Arabia and colleagues (2007) investigated the possibility of a shared genetic susceptibility between PD and depression by comparing the risk of depressive disorders among first-degree relatives of PD patients to the risk of depression among first-degree relatives of controls. In their population-based, historical cohort study, Arabia et al. did find an increased risk of depression among first-degree relatives of PD patients compared to relatives of controls (hazard ratio, 1.54; 95% CI, 1.21-1.95, $p < .001$), and therefore concluded that depressive disorders may share familial susceptibility factors with PD. As the two familial studies to date produced conflicting findings, additional familial studies are needed to investigate a shared genetic susceptibility for PD and depression

Genetic susceptibilities for PD-depression specifically also have been studied using molecular genetic methodology. Barrero and colleagues (2005) conducted a study with 48 PD patients and 41 age- and sex-matched controls to test for a genetic risk factor for depression in PD related to the polymorphisms of the cannabinoid receptor gene (CNR1), which has been implicated in depression and hypomanic features (Barrero et al., 2005). The rate of depression,

as determined by categorization of scores on the Hamilton scale for depression (i.e., no depression, mild depression, moderate depression, and severe depression), was not significantly greater for PD cases than for controls. For PD cases, however, the presence of one or two short alleles on the CRN1 genotype was associated with a significantly higher frequency of depression (85.7%) than the presence of two long alleles (14.3%). The sample size for genetic analyses was limited, however, as only 14 PD patients (29.2%) and five controls (12.2%) met criteria for a diagnosis of depression. Also, analyses with non-PD controls did not find a significant role of the genotype polymorphism for depression. Although the work of Barrero et al. (2005) provides preliminary support that PD patients with short alleles in the CNR1 gene may be more susceptible to PD-depression, additional molecular genetic studies with larger samples are necessary to establish a firmer association between the cannabinoid system and PD-depression.

Finally, Burn and colleagues (2006) examined the hypothesis of a genetic susceptibility to experiencing depression in PD by investigating allelic variation in a functional polymorphism in the serotonin transporter (*5-HTTLPR)* gene. Their study was based on the possibility that genotypic variability in the serotonergic system may account for the variable depression rates in PD (Menza, Palermo, DiPaola, Sage, & Ricketts, 1999). Burn et al. examined the influence of allelic variation in the *5-HTTLPR* gene upon mood for 108 PD patients and 82 spousal age-matched controls, and found no relation between either *5-HTTLPR* genotype or allelic variation and depression. They concluded that the *5-HTTLPR* gene does not likely contribute to risk of depression in PD. Taken together, the molecular genetic studies to date do not provide strong support for a genetic origin of PD-depression.

Psychosocial Hypotheses of PD-Depression

Contrasting the biological explanations, a psychosocial etiological hypothesis of PD-depression proposes that depressive symptoms in PD are "reactive," or secondary to the disability and/or psychological stress of the disease (Brown, MacCarthy, Gotham, Der, & Marsden, 1988; Chen, 2004). McDonald and colleagues (2003) note that the stressors of adjusting to a chronic illness and the accompanying life changes (e.g., loss of job, marital discord), the awareness that PD treatments decrease in effectiveness over time, and the lack of a cure for the disease may contribute to a reactive depression for some individuals. In a recent qualitative study, Oehlberg and colleagues (2008) found that the majority of PD patients with clinically significant depressive symptoms attributed their depression to psychosocial, rather than to biological or PD-specific, factors. The evidence related to the psychosocial hypothesis of PD-depression is presented below.

Research that demonstrates the role of individual psychological factors upon distress and mood disorders in PD has been used to support psychosocial etiological explanations of PD-depression. Allott and colleagues (2005), for example, argued that the role of metacognitive style upon distress in PD refutes the notion that distress and mood disorders in PD are primarily a consequence of neuropathology. They found that maladaptive metacognitive style, particularly strong negative beliefs about worry, was a significant, independent predictor of distress beyond PD disease factors such as age, disease severity, and disease duration. Allott et al. emphasize the role of cognitions in the development and maintenance of emotional disorders, including anxiety and depression; their research is based upon Wells and Matthews' (1994) "self-regulatory executive function model," a model that stresses the role of negative beliefs (e.g., "worrying is bad") and responses (e.g., rumination) in the etiology of psychological disorders. From this

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perspective, it is possible that negative cognitive styles may predispose an individual to "reactive" depression in PD. Alternatively, however, strong negative beliefs may arise from a depressive state. Longitudinal studies are therefore needed to assess the temporal precedence of metacognitive style, depressive symptoms, and PD onset before definitive conclusions may be drawn regarding metacognitive style as a risk factor for "reactive" PD-depression.

Additionally, Moore and Seeney (2007) have identified certain biopsychosocial predictors of depressive mood in PD patients. In a cross-sectional study that assessed various correlates and predictors of depressed mood in 82 PD patients, blaming one's self, avoidance, and lack of recreational intimacy with one's spouse or partner were significant predictors of depressive mood, in addition to the PD characteristics of symptom severity and gross motor impairment. The authors concluded that interventions aimed at increasing recreational intimacy, reducing reliance on emotion-focused coping strategies, and educational programs on PD symptoms would promote positive adjustment and improved mood among PD patients.

Although the individual psychological factors noted above likely influence mood in PD patients, findings that PD sufferers have greater rates of depression than individuals with other chronic illnesses with comparable disability levels (e.g., Ehmann, Beninger, Gawel, & Riopelle, 1990) argue against the theory that PD-depression is a reaction to the disability of the disease. Additionally, greater rates of depression have been found in PD as compared to chronic and disabling conditions that do not affect the central nervous system, such as arthritis and diabetes (Edwards et al., 2002). It is possible that social support moderates the relation between disability and depression in PD, though, as Simpson and colleagues (2006) recently demonstrated a relation between less satisfaction with social support and greater rates of depression in PD.

Depression in early-onset PD represents a subset of research with potential implications for both the psychosocial and biological explanations of PD-depression etiology. Brown and colleagues (1988) have suggested that patients with early-onset PD may be particularly susceptible to depression due to experiencing greater financial and career disruption. Additional psychosocial challenges associated with early-onset PD include greater marital and family problems, higher rates of unemployment and early retirement due to disability, and stress from living longer with the disease (Calne, Lidstone, & Kumar, 2008). Findings that patients with early-onset PD (PD onset ≤ age 55) have increased rates of depression (e.g., Cole, Woodard, Juncos, Kogos, Youngstrom, & Watts, 1996) have been interpreted as supportive of the concept of reactive depression. Alternatively, however, early-onset PD may represent a subset of PD sufferers that are uniquely predisposed to PD-depression or, as hypothesized by Starkstein and colleagues (1989), depression may have a different etiology for early- vs. late-onset PD. While the research to date (Giladi et al., 2000; Santamaria et al., 1986a, 1986b; Starkstein et al., 1989) does indicate a relation between PD-depression and earlier age of PD onset that cannot be explained by disease progression aspects such as severity, duration, and disability (Widoe, 2007), the studies thus far have been correlational in nature and plagued by small sample sizes and monomethod measures of depression assessment. As such, inferences regarding etiology of PD-depression based upon early-onset PD findings are inappropriate at this time.

Depression Preceding PD

Two additional alternative etiological explanation for PD-depression are the notions that premorbid depression may either: 1) heighten the brain's susceptibility to PD (e.g., depression as a risk factor for PD), or 2) indicate an early non-motor manifestation, or prodome, of PD. Ishihara and Brayne (2006) conducted a systematic review of studies that examined depression

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preceding PD diagnosis and concluded that, in three cohort studies and five of six case-control studies, premorbid depression was significantly more common among PD cases than among controls. The researchers hypothesized that both PD and depression are caused by similar, underlying neuropathology, or that the neurological changes of depression predispose the brain to be more susceptible to PD (Ishihara & Brayne, 2006).

Empirical findings demonstrating that depression predates PD diagnosis also have been used to argue against the theory of reactive depression in PD. In a retrospective cohort study, Schuurman and collaborators (2002) demonstrated that depression is a risk factor for the development of PD even after controlling for age, sex, and socioeconomic status. Schuurman et al. concluded that the serotonergic hypothesis of PD-depression is a reasonable explanation to account for the association between depression and subsequent PD diagnosis, as patients may have a biological vulnerability to the underlying mechanism of PD and premorbid depression may represent a preclinical stage of PD. Although this hypothesis merits additional study, the serotonergic hypothesis, as noted above, currently lacks strong empirical support. Furthermore, it is possible that depression poses an environmental risk factor for the subsequent development of PD, although no research to date has examined the extent to which premorbid depression may explain depression in PD.

Taken together, research supports a relation between depression and subsequent occurrence of PD, a finding that is not consistent with the notion that PD depression may be fully explained as a psychosocial reaction to the illness. As patients have not yet been diagnosed with PD, a psychological reaction to the diagnosis or disability cannot account for premorbid depression. These findings could indicate either: a) depression predisposes an individual to the development of PD either neurologically or environmentally, or b) depression prior to PD

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represents a pre-clinical manifestation of the disorder. Although a higher incidence of premorbid depression in PD patients compared to non-PD patients has been documented in retrospective register studies (e.g., Leentjens et al., 2003), the investigations to date have not concluded whether premorbid depression operates as either a risk factor or a prodromal symptom of PD. Determining whether depression that precedes PD represents a risk factor for PD or a pre-clinical manifestation of the disorder has important implications for understanding the etiology, and potentially the prevention, of PD.

Etiological Summary

Although there is support for a biological or organic etiology relating PD-depression to the biochemical changes of PD (e.g., Mayberg & Solomon, 1995), other researchers have highlighted the role of personal and social factors in explaining PD-depression as a reaction to the disease (e.g., Brown & Jahanshahi, 1995). Of note, the two primary hypotheses of PD-depression as biological or psychosocial are not mutually exclusive (Veazey et al., 2005). Findings that greater rates of depression occur in both the early and late stages of PD have been cited as evidence that PD-depression results from a mixture of both subjective psychological factors and underlying neuropathology of the disease (Veazey et al., 2005). The majority of the reviews to date have concluded that PD-depression is most likely a combination of environmental (e.g., psychosocial) and biological (e.g., neurochemical) changes. The etiology of PD-depression remains unclear, however, and is the question driving the present study. The proposed study seeks to advance science by investigating whether genetic influences contribute to increased risk of depressive symptoms among individuals with PD, thereby informing theories of the etiology of PD-depression.

Statement of the Problem

Depression in PD is common and has several negative implications. Although several risk factors for PD-depression have been investigated (e.g., genetic polymorphisms of CNR1, clinical characteristics of PD, metacognitive style) to shed light on the etiology of PD-depression, no twin studies to date have examined whether genetic influences contribute to the increased rate of depressive symptoms within PD. The current study therefore fills an important gap in the literature by being the first study to explore depressive symptoms in PD in a sample of twins. Furthermore, the two familial studies conducted to date to examine a possible shared genetic susceptibility to PD and depression (Arabia et al., 2007; Fahim et al., 1998) have produced conflicting findings, leaving the question of a shared genetic susceptibility to these disorders unanswered. Finally, empirical investigations of PD-depression have predominantly relied upon clinical, rather than population-based, samples. As findings from population-based studies are more generalizable than findings from clinical studies (e.g., avoid the sampling bias associated with recruiting from tertiary PD clinics), these findings may uniquely contribute to the literature.

Further complicating the investigations to date, depression is also a risk factor for the development of PD (Behari, Srivastava, Das, & Pandey, 2001; Hubble, Cao, Hassanein, Neuberger & Koller, 1993; Kanner, 2005; Schuurman et al., 2002). Depression may be an early manifestation of PD, a result of the neurodegeneration of the illness, a psychological reaction to the diagnosis or disability of PD, or an amalgamation of two or more of these factors. Certain factors (e.g., increasing age) also serve as risk factors for both PD and depressive symptoms and the two phenotypes are both likely to have multifactorial causes. A better understanding of the possible genetic influences upon the comorbidity between depressive symptoms and PD has

etiological importance and, in turn, potential to inform preventative or treatment efforts. The current study represents an important contribution to the literature on PD-depression by being the first population-based twin study to evaluate PD as a risk factor for both mild and moderate-severe depressive symptoms.

Primary Aim

The primary aim of this study was to test whether genetic influences contribute to the increased risk for depressive symptoms among individuals with PD, using a large, population-based sample of twins. As noted above, several factors have been implicated in the etiology of depression in PD, including the psychosocial stressors and biochemical changes associated with PD. Twin studies provide a unique opportunity to examine whether an association is related to genetic influences (Gatz et al., 2006). In the current study, multiple methods were utilized to test whether genetic influences contribute to the PD-depression relation, after it was confirmed that PD was a risk factor for both mild and moderate-severe depressive symptoms in the current sample. In addition to examining the cross-twin cross-trait tetrachoric correlations for PD and depressive symptoms, two different inferential statistical approaches were utilized to examine whether genetic influences contribute to the increased risk of depressive symptoms among PD cases. The first approach involved a case control and co-twin control analysis. The case control design utilized all depressive symptom cases and examined PD as the exposure, or risk factor, for depressive symptoms. The co-twin control analysis addressed potential concern about genetic confounding, as this design used only unaffected co-twins as the control cases. If the association between depressive symptoms and PD is attenuated when co-twins are used as the control cases, a genetic contribution to the PD-depressive symptom relation is implied.

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Additionally, the co-twin control analysis was repeated using only monozygotic twins, to control completely for genetic factors.

The second approach to test whether genetic influences contribute to the risk of depressive symptoms among PD involved a logistic regression analysis to test, among individuals without PD, whether co-twins of PD cases are at a higher risk of depressive symptoms compared to co-twins of non-PD cases. This analysis tested whether PD status in one's twin increases personal risk of depressive symptoms, which would imply an underlying genetic influence between PD and depressive symptoms. Conducting this logistic regression analysis with only unaffected co-twins provides an inferential test to determine whether the differences in the tetrachoric correlations are meaningful.

For the study's primary aim – testing whether genetics contribute to PD's role as a risk factor for depressive symptoms – it was hypothesized that genetics would not contribute significantly to the PD-depressive symptom risk. This null hypothesis for the role of genetics was based on research findings that the etiology of PD is primarily environmental (Hardy, Cai, Cookson, Gwinn-Hardy, & Singleton, 2006; Warner et al., 2003; Wirdefeldt, Gatz, Schalling, & Pedersen, 2004) and on the inconclusive findings from familial studies of depression and PD regarding a shared genetic origin for the two disorders (Arabia et al., 2007; Fahim et al., 1998). As such, genetic influences were not expected to contribute to the risk of depressive symptoms among PD patients. Specifically, it was not expected that the odds ratios for the co-twin control analysis would be significantly smaller than the odds ratios for the case control analysis. Regarding the unaffected co-twin analysis, it was not expected that PD status in one's co-twin would significantly predict an individual's personal risk of depressive symptoms.

Secondary Aims

Clinical presentation of PD-depression. A secondary aim of the current study was to explore whether depressed PD cases responded differently to the depressive symptoms items, as measured by the 11-item Iowa version of the Center for Epidemiological Studies – Depression scale (CESD-I), compared to depressed individuals without PD. A series of ANCOVAs was conducted to compare PD cases and non-PD cases on each depressive symptom on the CESD-I, after controlling for age, sex, and overall level of depressive symptoms.

Early age of PD onset. Exploratory analyses also were conducted to examine whether depressive symptoms were more likely for PD cases with an early age of onset (PD onset ≤ age 55) as compared to later, or more typical, age of onset. Age of PD onset is important to examine because an earlier age of onset has been related to greater rates of PD-depression (e.g., Giladi et al., 2000; Starkstein et al., 1989) in clinical samples, leading some researchers to conclude that the etiology of depression may differ for early- versus late-onset PD patients. Also, as a greater genetic influence has been suggested in the etiology of early-onset than for late-onset PD (Hardy et al., 2006), it may be that, for early-onset cases, genetic factors influence the liability of PD-depression to a greater extent than for late-onset cases. Due to a limited sample size of early-onset cases in the current dataset (i.e., 21 cases), these questions were explored descriptively in the current study.

Method

Participants

  This study involved analysis of data from a study of Parkinson's disease in the Swedish

Twin Registry (STR; Wirdefeldt, Gatz, Bakaysa, Fiske, Flensburg, Petzinger, et al., 2008). The

STR is a registry containing approximately 70,000 twin pairs born in Sweden between 1886 and

1990 (Lichtenstein, De Faire, Floderus, Svartengren, Svedberg, & Pedersen, 2002). Participants

for the Parkinson's study were obtained through the Screening Across the Lifespan Twin study

(SALT; Pedersen, Lichtenstein, & Svedberg, 2002). The SALT study involved a complete

telephone interview screening of all cooperative twins born in 1958 or earlier who were alive at

the time of contact; a 73% response rate was obtained (Wirdefeldt et al., 2008). Detailed

information regarding the SALT data collection has been reported elsewhere (Lichtenstein et al.,

2002; Wirdefeldt et al., 2004). The Parkinson's study population, 49,814 individuals, included

all twins eligible for the SALT who were at least 50 years of age by the date of their interview,

or if no interview was completed, the date of a letter notifying them of the SALT project.

  Demographics. Relevant demographic variables collected include age, sex, and vital

status (i.e., living status or date of death). Demographic data for the study sample are presented

in Table 1. Consistent with twin samples from Sweden as compared to North American samples,

the percentage of dizygotic twins was greater than the percentage of monozygotic twins.

  Zygosity. As detailed elsewhere (Lichtenstein et al., 2002), zygosity classification within

the STR was made using an algorithm of self-report questions regarding twin similarity (e.g.,

"How often did strangers have difficulty distinguishing between you and your twin partner when

you were children?"). Zygosity classification was validated in the SALT-pilot study using 13

DNA markers; the algorithm correctly classified zygosity in 99% of twin pairs (Lichtenstein et

al., 2002). For the present study, twin pairs were classified as monozygotic, dizygotic – same sex, dizygotic – opposite sex, or unknown zygosity. Zygosity data are presented in Table 1. Twins with unknown zygosity were not included in the analyses.

      Complete twin pairs vs. incomplete twin pairs. Complete PD data (i.e., status as PD case or non-PD control) is known for 12,999 twin pairs. PD status is known for an additional 9,828 singletons (i.e., PD status is known for one twin of the pair). Using the CESD-I, complete depressive symptom data is known for 12,229 twin pairs. Depressive symptoms are known for an additional 9,504 singletons (i.e., depressive symptoms are known for one twin of the pair).

Measures

      Depressive symptoms. An 11-item version of the Center for Epidemiological Studies – Depression scale, the "Iowa form" developed by Kohout and colleagues (referred to in the present report as the CESD-I; Kohout, Berkman, Evans, & Cornoni-Huntley, 1993), was used to measure depressive symptoms. Respondents were asked to rate the frequency with which they experienced 11 depressive symptoms (e.g., "I felt lonely") during the past week on a 4-option Likert scale ranging from 0 (*Rarely/None – less than one day*) to 3 (*Most/All the Time – 5 to 7 days*). Two items were reverse-scored. The range of possible scores is 0-33, with higher scores indicating greater depressive symptomatology. If one or two items were missing, a prorated score was calculated. Individual items are given in Appendix A. A cut-off score of 9 on the 11 items is utilized in the current study, as Gatz and colleagues (1993) demonstrated that this cut-off best corresponds to the cut-off of 16 for the 20-item CES-D. In particular, a cut-off of 9 had a sensitivity against the cut-off of 16 on the complete 20-item CES-D of 94.8%, with 84.3% specificity.

The full 20-item CES-D (Radloff, 1977) has good internal consistency (α = .89; Fiske, Gatz, & Pederson, 2003) and fair stability, with test-retest correlations ranging from .51 to .67 tested over two to eight weeks (Radloff, 1977) and .61 tested over 3 months (Devins et al., 1988). The scale has strong concurrent and known-groups validities (Himmelfarb & Murrell, 1983; Radloff & Teri, 1986), and is an acceptable measure of depressive symptoms for older adults (Fiske & O'Riley, 2007). Lewinsohn and colleagues (1997) have documented the efficacy of the CES-D in identifying clinical depression, as confirmed by a diagnostic interview to determine the presence of depressive disorder, among community-based older adults.

Kohout and colleagues (1993) tested the 11-item version of the CES-D against the original 20-item measure in a sample of 10,296 individuals aged 65 and older and found that the shortened version correlated well with the 20-item version (r = 0.95). Factor analyses indicated that the shorter form assessed the same dimensions of depressive symptoms as the original CES-D without significantly reducing reliability (Cronbach's alpha = 0.81) (Kohout et al., 1993), findings that have been replicated by Carpenter and colleagues (1998). In addition, using data from the SALT pilot study, Suthers, Gatz, and Fiske (2004) demonstrated that the 11-item version (CESD-I) provides meaningful information about depression in addition to depression diagnoses, as assessed by the short form of the Composite International Diagnostic Interview – Short Form (CIDI-SF; Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998).

Prior history of major depression. Both the short form of the Composite International Diagnostic Interview –Short Form (CIDI-SF) and report of prior antidepressant use were utilized to identify a prior history of depressive disorder. Specifically, prior history of major depression was classified as either: 1) antidepressant use prior to SALT, or 2) an affirmative response to either the dysphoria or anhedonia screening question on the CIDI-SF, in addition to a CIDI-SF

score of 4 or greater. The CIDI-SF cut-off of 4 or greater has been shown to have adequate

agreement with the full criteria of major depression with the Structured Clinical Interview for

DSM-III-R (Kendler, Gatz, Gardner, & Pedersen, 2006a).

Procedure

     PD diagnosis. As part of SALT, through population-wide screening of all Swedish twins

aged 50 years or older, the Parkinson's study was designed to ascertain all cases of PD in the

STR (Wirdefeldt et al., 2008). Twins in the study population were ascertained for PD in three

phases. Please refer to Figure 1 for an overview of the study design.

     In the first phase, twins were screened for PD and PD symptoms by telephone as part of

SALT. In the second phase, twins who were PD suspects due to symptoms related to diseases

other than PD were excluded from further follow-up. Twins with suspected PD in the SALT

interview were given a second telephone interview including detailed questions about PD

symptoms and other diseases. The third phase involved clinical evaluations of twins who were

still suspects after the second screening, twins with self- or proxy-reported PD from SALT, twins

with suspected PD from a previous dementia study (HARMONY), and a sample of co-twins.

Each of the three phases of PD ascertainment is elaborated upon next.

     Phase 1: SALT screening. Between 1998 and 2002, all living twins born in 1958 or

earlier were contacted using computer-assisted telephone interviews. The interview included a

checklist of common diseases including PD, as well as a series of questions specific for PD

(originally developed by Tanner, Ellenberg, Mayeux, Ottman, & Langston, 1994) that was

administered to individuals aged 50 or older by the date of their interview. These questions were

about the use of anti-parkinson medication and a variety of PD symptoms.

PD symptoms included trouble arising from a chair, small handwriting, poor balance, feet getting stuck to the floor, little facial expression, shaking arms or legs, difficulty buttoning buttons, shuffling feet or taking tiny steps when walking, soft voice and slow movements. If the twin said "yes" to two symptoms or more, the twin was asked age of onset and whether onset was gradual or sudden. If it was not possible to talk to the twin (for example, due to cognitive impairment or hearing problems), interviewers requested to speak with a proxy. In these cases, questions about a previous PD diagnosis and anti-parkinson medications were included, but questions about PD symptoms were omitted. Of 49,814 individuals aged 50 years and older eligible for SALT, 36,197 (72.7%) responded to the interview either themselves or through a proxy. In total, 36,033 individuals responded to the specific questions about PD, 35,031 (97.2%) themselves and 1,002 (2.8%) through a proxy.

To identify twins who exhibited early symptoms of PD but who did not report having received a PD diagnosis, an algorithm was constructed to evaluate responses to the PD symptom questions in SALT. This algorithm was intended to map onto the diagnostic criteria for PD based on results from previous validation studies of screening questions (Wirdefeldt et al., 2008). Twins were considered positive for the "parkinsonian algorithm" if they said "yes" to the symptom shaking arms or legs plus "yes" to one of the following four symptoms: small handwriting, feet stuck to the floor, difficulty buttoning buttons, and soft voice. A second algorithm, referred to as the "bradykinesia algorithm," also was constructed in order to capture PD cases characterized by bradykinesia but not resting tremor. Twins were considered positive if they said "no" to the symptom shaking arms or legs and "yes" to three of the four symptoms mentioned above. Those who reported sudden onset of symptoms, multiple sclerosis, polio as a child, or neuroleptic drug use were excluded prior to the second phase.

Taken together, in the first phase, 637 twins were considered PD suspects from SALT based on the symptom algorithms described above or anti-parkinson medication use, and 60 had been worked up in the HARMONY study and they were therefore not contacted for the second screening. An additional 57 twins were not contacted due to an administrative error. Of the remaining 520 PD suspects, 452 were alive and had agreed to be contacted further by the STR.

Phase 2: Second screening to exclude obvious non-PD. Beginning in May of 2002, PD suspects from SALT were contacted again for a second screening interview. The purpose of this interview was to make the clinical work-up process more efficient by excluding PD suspects from further follow-up who reported symptoms and PD medication due to diseases other than PD. Twins who were positive for the parkinsonian algorithm in SALT were excluded from further follow-up if they screened negative for resting tremor, or if they screened positive for resting tremor and negative for bradykinesia. Twins who were positive for the bradykinesia algorithm in SALT were excluded from further follow-up if they screened negative for bradykinesia. If the twin said "yes" to a cardinal symptom, follow-up questions were asked aimed at identifying any reasons for reporting the symptom that were clearly not related to parkinsonism, in which case the symptom was considered negative for screening purposes. Twins who were on regular neuroleptic treatment prior to the onset of symptoms also were excluded. To be excluded, the twin had to say "no" to the question about PD diagnosis and "no" to anti-parkinson medication. Answers to the second screening interview for PD suspects, who were not excluded by the exclusion algorithm, were reviewed by the study physician. On the basis of that review, additional PD suspects were excluded, in some instances due to simple misunderstandings in the initial SALT interview (for example, one twin reported a PD diagnosis when actually his wife had PD), and in other instances due to obvious reasons for reporting

parkinsonian symptoms other than PD (e.g., hydrocephalus or previous severe brain trauma). In the latter cases, information from medical records also was available.

In the second screening phase, 349 PD suspects participated (corresponding to a participation rate of 77.2%), 203 (58.2%) were excluded from further follow-up due to their answers to the second screening questions, 182 directly by the exclusion algorithm, and 21 after review of answers by the study physician. Details regarding non-participation have been reported by Wirdefeldt et al. (2008). Of the 60 PD suspects worked up in HARMONY, 53 twins (88.3%) were excluded based on the neurological examination that was part of their dementia workup. In total, 146 twins were still considered a PD suspect after completing the second screening interview, and an additional 7 PD suspects from HARMONY also remained, for a total of 153 PD suspects.

In the second screening interview, attempts to contact co-twins of twins with suspected PD and co-twins of twins with self-reported PD who participated in the second screening were made, so that twin pairs would have equivalent screening. Among co-twins of the 153 twins with suspected PD, ten were PD suspects themselves, resulting in 143 co-twins who were contacted. Of 154 twins with a self- or proxy-reported PD diagnosis in SALT, 131 participated in the second screening interview and two of these had co-twins who were themselves probands, resulting in 129 co-twins who were contacted. Of these 272 co-twins, 19 were already included in HARMONY, 61 were dead, and 24 refused SALT and were therefore not contacted again. Of the remaining 168 co-twins, 134 (79.8%) participated in the interview, 23 refused, five could not be reached, two were not possible to interview, and four were not contacted due to administrative error.

Phase 3: Clinical work-up. The 154 twins with self- or proxy-reported PD in SALT, the

34 twins with PD suspicion by HARMONY, and the 153 twins still considered PD suspects after

the PD second screening interview were referred for a clinical work-up in the third phase. In

addition, the first 102 co-twins also were referred for a clinical work-up. As detailed below, for

most of the PD suspects and co-twins, the clinical work-up consisted of an in-person somatic

examination in addition to medical record review; for most of the twins with self- or proxy-

reported PD, the clinical work-up was based on medical record review alone plus telephone

interview.

The in-person clinical work-up consisted of a home visit by the study physician for a

complete neurological examination with relevant signs and symptoms, general somatic and

psychiatric examinations, an inventory of current medications, and medical history. Average

duration of a visit was two hours. The Unified Parkinson's Disease Rating Scale (UPDRS; Fahn

et al., 1987) was used to evaluate parkinsonian signs and symptoms. The examination was

documented on video according to a standardized protocol. Twins with suspected memory

problems were evaluated by neuropsychological testing and proxy interviews.

Of the 153 PD suspects after the second screening, 119 (77.8%) underwent a somatic

examination and 15 (9.8%) were worked up by medical records. Of the 19 remaining PD

suspects, 11 did not have a diagnostic work-up because they refused, seven died after the second

screening, and one was not worked up due to logistical difficulties. An additional two twins who

were considered PD suspects after SALT but did not participate in the second screening were

also worked up. Diagnostic work-ups were completed for 102 co-twins, 97 by somatic exam,

and 5 by medical records.

For the 188 twins with self- or proxy-reported PD in SALT or PD suspicion by HARMONY, the clinical work-up consisted of a review of all relevant medical records. A nurse also performed a telephone interview with these twins, including detailed questions about symptom onset and manifestation of the disease. For twins who died between screening and clinical work-up, a modified interview was performed with a relative. Twins with insufficient information in medical records to assign a diagnosis, or with a record of PD diagnosis only by a general practitioner, were visited by the study physician according to the same protocol as the PD suspects. PD diagnostic work-ups were completed for 182 of the 188 twins (173 by medical records only and nine by somatic exam in addition to medical records). In the remaining cases, a diagnosis could not be assigned due to insufficient information (for example, medical records could not be obtained).

Assignment of Parkinson disease diagnoses. Diagnoses based on somatic exams were assigned by the study physician, together with a movement disorder specialist. Another movement disorder specialist independently assigned diagnoses based on reviewing the videotaped examination and the notes made during the somatic exam. Cases in which there was disagreement between the study physician and the diagnosis based on the videotaped examination were reviewed by a third movement disorder specialist. Final consensus diagnoses were all agreed upon by two movement disorder specialists. Diagnoses based on medical records were assigned by the study physician, together with one movement disorder specialist. The National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria for PD, described in Appendix B, were used to classify possible and probable PD. Consensus clinical diagnoses for the study population are shown in Table 2 (Wirdefeldt et al., 2008). Ninety-nine twins with probable PD (mean age of onset: 64.3 years ± 10.6 years, range: 39 – 90) and 33

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twins with possible PD (mean age of onset: 71.7 years ± 8.5 years, range: 44 – 88) were

identified. Individuals with diagnoses of parkinsonism, rather than PD, were included in the

current study, but were classified as non-PD.

Definition of PD cases. All twins diagnosed with possible or probable PD by diagnostic

work-up were regarded as PD cases, for a total of 132 cases. More detailed information about

PD case ascertainment in the STR has been recently presented elsewhere (Wirdefeldt et al.,

2004; Wirdefeldt et al., 2008). Because the STR is population-based, the risk of ascertainment

bias was minimal compared to other sampling strategies (Wirdefeldt et al., 2004).

For the proposed study, of the 49,814 individuals in the study population, PD status (i.e.,

PD or not-PD) was known for 35,681 individuals (71.63%). Of the 35,681 individuals for whom

PD status was known, 132 (0.37%) had PD and 35,549 (99.63%) did not have PD. The

proportion of the study population for which PD status was unknown (28.37%) was attributable

primarily to non-participants in the SALT screening phase (e.g., refusal to participate, death prior

to SALT).

Of note, only individuals whose PD onset was prior to the SALT interview were included

in the current study, to ensure concurrence of measurement time for PD and depressive

symptoms. For 7 of the 132 PD cases, the onset of PD was after the SALT interview, reducing

the sample to 125 PD cases. Of these 125 cases, CESD-I information was available for 96

individuals. For the 29 PD cases missing depression information, 12 had a comorbid diagnosis

of dementia, precluding the collection of CESD-I data.

Rearing status was descriptively examined for the PD cases, to assess possible

differences in concordance rates for PD cases reared together compared to reared apart. Of the

125 PD cases, 4 were reared apart from their co-twins; all four were dizygotic twins. Of these

four, three of their co-twins were classified as non-PD and one co-twin was missing information on PD status. Due to the limited number of PD twins reared apart from their co-twin, it was not possible to conduct analyses separately for PD twins reared together versus reared apart. On visual inspection, the records for these four twins revealed no apparent systematic differences from the records of PD twins reared with their co-twin.

Definition of depression cases. Depressive symptoms were assessed by the 11-item CES-D, or CESD-I. Moderate-severe depressive symptom cases were identified as those participants who met the clinical cut-off of 9 or greater on the CESD-I. Overall, depressive symptom status was known for 33,910 (68.07 %) in the study population. As with the missing PD status, depressive symptom totals are unknown primarily for non-responders in the SALT screening phase. Of the 33,910 individuals for whom depressive symptoms are known, 4,024 (11.87%) had clinically significant depressive symptoms (CESD-I total score $\geq$ 9) and were considered moderate-severe depressive symptom cases in the current study. The status of the remaining 29,886 (88.13%) individuals was non-depressive symptom cases.

Two different cut-off points were used to determine depressive symptom status in the current study, and analyses were conducted for both definitions of depressive symptom status. The first cut-off, described above, defined clinically significant depressive symptoms as a score of 9 or greater on the CESD-I. Because depression in PD is usually considered to be of milder severity than primary major depression, however, (Cummings, 1992; McDonald et al., 2003; Serrano-Dueñas, 2002) and prevalence estimates of PD-depression typically range from 40-50% (e.g., Tandberg et al., 1996; Wichowicz, Slawek, Derejko, & Cubala, 2006), all analyses were repeated with a cut-off that defined clinically significant depressive symptoms as the CESD-I total score that most closely approximated the upper 40% of CESD-I scores in the current PD

sample. Because CESD-I scores ≥ 4 represent the top 38.1% of CESD-I scores in the sample, a score of 4 or greater was used as the second cut-off point used to determine mild depressive symptom status. In addition to its relevance for PD patients, milder, or sub-threshold, depressive symptoms have been shown to have a variety of clinical implications for older adults (e.g., Horowitz, Reinhardt, & Kennedy, 2005; Rollman & Reynolds, 1999). There is also evidence that major and minor depression among medically ill older adults varies by prior history of depression (Koenig, 1997), one of the covariates in the current study. As such, the use of two CESD-I cut-offs was employed to allow examination of both mild and moderate-severe depressive symptoms.

Covariates. Age and sex were included as covariates in all case control analyses. Age and sex were controlled for by design in co-twin control analyses with same sex pairs. For both case control and co-twin control analyses, prior history of major depression was added as a covariate.

Statistical Analyses

Concordance rates and correlations. Probandwise concordance rates were calculated to explore whether twin similarity for the PD phenotype, moderate-severe depressive symptoms phenotype, and mild depressive symptoms phenotype differed by zygosity. Probandwise concordance is an index of familial resemblance for dichotomous traits, and can also be interpreted as the risk one has to develop a disorder if one's twin has the disorder (Plomin, DeFries, McClearn, & Rutter, 1997). If members of a twin pair both have PD, for example, they are considered to be concordant for the disorder. If only one member of a twin pair has PD, the pair is discordant for the disorder. A pattern of greater MZ concordance rates compared to DZ concordance rates is suggestive of a genetic influence upon a phenotype.

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Two types of tetrachoric correlations were estimated: within-trait tetrachoric correlations and cross-twin cross-trait tetrachoric correlations. First, within-trait tetrachoric correlations were calculated separately for: 1) PD cases, 2) moderate-severe depressive symptom cases, and 3) mild depressive symptom cases. Within-trait tetrachoric correlations indicate the extent to which twin pairs are similar for a phenotype, providing information about univariate heritability. These correlations were conducted for the MZ, same-sex DZ, and opposite-sex DZ twin pairs. Within-trait tetrachoric correlations were calculated to detect the similarity of twins within a pair; genetic effects are implied if MZ twins display higher tetrachoric correlation coefficients than DZ twins.

Second, cross-twin cross-trait tetrachoric correlations were calculated to provide information about the genetic influence upon the relation between PD and depressive symptoms. Specifically, cross-twin cross-trait correlations indicate the extent to which PD in one twin is informative of depressive symptoms in the other twin. To the extent that MZ twin pairs have greater cross-twin cross-trait similarity compared to DZ twin pairs, genetic influence on the comorbidity, or relation, between PD and depressive symptoms is implied. Additive genetic effects are implied if the tetrachoric correlation is doubled in MZ pairs compared to DZ twin pairs, as MZ twins share 100% of their genetic material and DZ twins share approximately 50% of their segregating genes.

Case control and co-twin control analyses. Odds ratios were calculated to estimate the relative risk for depressive symptoms given PD status as the exposure. The association between depressive symptoms and PD was analyzed in the case control design using alternating logistic regression (ALR), utilizing all controls. First, the odds ratio (OR) and 95% confidence intervals (CI) for PD as a risk factor for depressive symptom status was estimated controlling for age and

sex. Second, the OR and CI for PD were estimated with prior history of major depression included as an additional covariate. Confidence intervals were adjusted using robust standard errors for having two members from the same family included in the analysis, to correct for non-independence of observations. The adjustment was achieved by use of a SAS macro. The macro increases the variance estimates in magnitude proportional to the degree of correlation between twin pairs. This procedure effectively widens the confidence intervals to be more conservative (Gatz, Mortimer, Fratiglioni, Johansson, Berg, Reynolds, et al., 2006; Lin, 1994).

In the co-twin control analyses, odds ratios were obtained from conditional logistic regression, using twin pair as a stratification variable. Co-twin analyses utilized all discordant depressive symptom cases and their co-twins. By design, a co-twin control analysis controls for sex and age; prior history of major depression was added as a covariate. The test provides an OR and 95% confidence interval based on Wald tests. In addition, co-twin control analyses were repeated using monozygotic twins (MZ) only. As MZ twins share 100% of genes, this test fully controlled for unmeasured confounding by genetic effects.

Unaffected co-twin analysis. Logistic regression analyses were conducted to test whether PD status in one's twin increased personal risk for mild or moderate-severe depressive symptoms, after controlling for age, sex, and prior history of depression. This analysis provides a statistical test of whether genetic influences are operating in the relation between PD and depressive symptoms. The sample used included all co-twins of PD cases in discordant pairs, as well as one randomly-selected twin from each pair in which neither twin had PD.

Supplementary analyses. As a preliminary analysis, intra-class correlations were conducted on total depressive symptom scores, by zygosity. In addition, for each symptom on the CESD-I, an ANCOVA was conducted to compare PD cases and non-PD cases, after

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controlling for age, sex, and overall level of depressive symptoms. All analyses were conducted

using SAS 9.1.

Results

Preliminary Analyses

    Prevalence rates. Prevalence rates for cases with mild depressive symptoms (CESD-I $\geq$ 4) and cases with moderate-severe depressive symptoms (CESD-I $\geq$ 9) are shown in Table 3. The prevalence rates for both mild and moderate-severe depressive symptoms were greater among the PD cases than the non-PD individuals. For mild depressive symptoms, the prevalence rate was 63.54% (61/96) for PD cases, a significantly greater rate ($X^2 = 28.57$, $p < .0001$, $df = 1$) compared to the prevalence rate of 37.13 % (12,394/33,377) among individuals without PD. Similarly, for moderate-severe depressive symptoms, the prevalence rate was significantly greater ($X^2 = 14.56$, $p < .0001$, $df = 1$) among PD cases (23.96%, or 23/96) compared to non-PD cases (11.50%, or 12,394/33,377).

    Prevalence rates also were calculated separately for individuals with early-onset PD versus those without an early age of onset, to descriptively explore whether early-onset PD may be a risk factor for depressive symptoms. Of the 125 PD cases, 21 individuals (16.8%) had a PD age of onset at 55 years or earlier. Depressive symptom status was available for 17 of these 21 PD cases. For early age of onset, the rate of moderate-severe depressive symptoms was 35.29% (6/17) compared to a rate of 22.08% (17/77) for cases with later age of onset. The rate of mild depressive symptoms was roughly equivalent, however, for individuals with early age of onset, as 35.29% (6/17) of early-onset cases met criteria for mild depressive symptoms, compared to 38.96% (30/77) for PD cases with later age of onset. Although definitive conclusions are precluded due to the small number of early-onset cases, it is notable that early age of PD onset was associated with a higher rate of moderate-severe depressive symptoms in this population-based sample, whereas rates of mild depressive symptoms did not differ by age of PD onset. Nor

was early age of PD onset associated with prior history of major depression (0/16 early-onset cases had a prior history of depression, while 4/72 later-onset cases had a prior history of depression).

Concordance rates. Probandwise concordance rates are shown in Table 4. Of the 125 PD cases, there were 3 concordant pairs: 1 MZ pair, and 2 DZ pairs. The lack of attenuation in the PD concordance rates for dizygotic twins as compared to monozygotic twins suggests that genetic influences are unlikely in the etiology of PD. Conversely, for both mild and moderate-severe depressive symptoms, slight attenuation is observed in the concordance rates by zygosity, suggesting some genetic influence in the etiology of these phenotypes.

To address one of the secondary study aims, it was originally planned that concordance rates for PD would be calculated separately for early-onset PD (i.e., PD onset at age 55 or younger) and later-onset PD, to explore whether heritability differed significantly for early versus late PD onset. This secondary analysis was rendered uninformative, however, as none of the six twins within the three concordant pairs had an early age of PD onset. For these individuals, age of PD onset ranged from 63 – 76 years of age.

Tetrachoric correlations. The within-trait tetrachoric correlations are shown in Table 5. Results revealed attenuation in the within-trait correlation by zygosity for both mild and moderate-severe depressive symptoms, suggestive of a genetic influence upon these phenotypes. For PD, within-trait correlations did not significantly differ by zygosity, suggesting a lack of genetic etiology of PD.

The cross-twin cross-trait tetrachoric correlations are shown in Table 6. For PD and moderate-severe depressive symptoms (CESD-I $\geq$ 9), the cross-twin cross-trait tetrachoric correlations did not differ by zygosity, suggesting lack of a genetic influence upon the PD-

moderate-severe depressive symptom comorbidity. The cross-twin cross-trait tetrachoric

correlations also did not markedly differ by zygosity for PD and mild depressive symptoms

(CESD-I ≥ 4).

　　　Intra-class correlations. Intra-class correlations were calculated on total CESD-I scores

as a continuous measure of depressive symptoms, for the entire sample, by zygosity. These

results suggested a genetic influence on total depressive symptom score, as the intra-class

correlation was greater for MZ twins ($r = 0.28$, $p < .0001$) as compared to DZ same-sex twins (r

$= 0.13$, $p < .0001$) and DZ opposite-sex twins ($r = 0.07$, $p < .0001$).

Case Control & Co-Twin Control Analyses

　　　Moderate-severe depressive symptoms (CESD-I score ≥ 9). In the case control analyses,

alternating logistic regression results provided in Table 7 confirm that PD was a significant risk

factor for moderate-severe depressive symptoms, after controlling for age and sex. Odds ratios

adjusted for prior history of major depression revealed that PD is a stronger risk factor for

moderate-severe depressive symptoms after this adjustment. The odds ratio for the co-twin

control analysis compared to the case-control analysis was not greatly attenuated (3.15 compared

to 3.23), suggesting that genetic associations are unlikely to account for the relation between PD

and moderate-severe depressive symptoms. When co-twin control analyses were conducted

using only MZ twins, the results did not differ from using all co-twins; although this may be seen

as evidence for no genetic influence upon the PD-moderate-severe depressive symptom relation,

the low number of monozygotic PD cases precludes this conclusion.

　　　Mild depressive symptoms (CESD-I score ≥ 4). In the case control analyses for mild

depressive symptoms, alternating logistic regression results provided in Table 8 confirm that PD

was also a risk factor for mild depressive symptoms, with and without adjusting for prior history

of major depression. As with depressive symptoms at the level of 9 or greater, PD did not have a significantly lower odds ratio for mild depressive symptoms for the co-twin control analysis as compared to the case control analysis (3.22 compared to 3.11). For the co-twin control analysis conducted with only MZ pairs, PD was no longer a significant risk factor for mild depressive symptoms, although the limited number of PD cases in this analysis and the resulting decrease in power likely contributed. Taken together, this pattern of results suggests that genetic influences are unlikely to account for the increased risk of mild depressive symptoms among PD cases.

Unaffected Co-Twin Analysis

Logistic regression results indicated that co-twin PD was not a predictor of moderate-severe depressive symptoms when controlling for age and sex (*Wald* = 3.09, *p* = .08) or when controlling for age, sex, and prior history of depression (*Wald* = 2.89, *p* = .09). Co-twin PD also did not predict mild depressive symptoms after controlling for age and sex (*Wald* = 0.18, *p* = .07) and when controlling for age, sex, and prior history of depression (*Wald* = 0.15, *p* = .70). Because co-twin PD did not relate to twin depressive symptom status, it is unlikely that shared genetic influences are operating between PD and depressive symptoms.

Supplementary Analyses

Clinical presentation of PD-depression. Results from the ANCOVA analyses for each depressive symptom, after controlling for age, sex, and overall level of depressive symptoms, are shown in Table 9. As the results from twin 1 and twin 2 were substantially the same for each symptom, the results reported are from twin 1. Of the eleven CESD-I item ANCOVAs, PD status was a significant predictor of higher scores for item 3 ("I felt sad"), $F (3, 16789) = 4.93$, $p = 0.03$, and for item 7 ("I couldn't get going"), $F (3, 16782) = 6.83$, $p = 0.01$.

Discussion

The current study advances the field of PD-depression by being the first study to use a twin sample to examine the role of genetics upon the increased risk of depressive symptoms within PD patients. In addition, the study included an examination of mild depressive symptoms, which are more prevalent among PD patients than are severe depressive symptoms. The study confirmed that PD patients suffer from greater rates of both mild and moderate-severe depressive symptoms than do non-PD patients, replicating prior findings (e.g., Althaus et al., 2008).

In regard to the primary aim – to examine whether genetics contribute to the increased risk of depressive symptoms among PD patients – the findings were consistent with a null hypothesis for genetic influences upon the PD-depressive symptom relation. In addition to findings from the cross-twin cross-trait tetrachoric correlations that did not suggest a genetic effect on the relation between PD and depressive symptoms, the case control and co-twin control results did not show a significant attenuation in the odds ratios for PD for either mild or moderate-severe depressive symptoms. Furthermore, unaffected co-twin analyses indicated that PD status in one's co-twin did not predict depressive symptoms in the other twin, refuting a genetic influence. These findings are an important contribution to studies of familial aggregation of depression and PD (Arabia et al., 2007; Fahim et al., 1998), which have been inconclusive regarding a shared genetic origin for the two disorders, by suggesting that a shared genetic origin is unlikely.

The results of the present study indicate that environmental influences likely play an important role in the etiology of depressive symptoms in individuals with Parkinson's disease. Possible non-genetic influences that may contribute to the development of PD-depression

include psychosocial stressors associated with PD (e.g., sadness related to receiving a diagnosis of a progressive illness), disease-related stressors (e.g., disability, pain), higher rates of premorbid depression, and shared environmental factors that may contribute to the development of both PD and depression (e.g., toxin exposure). Alternatively, brain changes associated with PD that are not genetically influenced may heighten biological vulnerability to depressive symptoms.

While the current study cannot elucidate the relative importance of various environmental factors as opposed to possible increased biological vulnerability to depressive symptoms among PD patients, the findings do provide additional evidence suggesting that PD patients with an early age of PD onset experienced moderate-severe depressive symptoms at a higher rate compared to PD patients with a later age of onset. This outcome is noteworthy from an etiological standpoint not only because early age of PD onset is a documented risk factor for depression in PD, but also because the one familial study supporting a shared genetic origin between PD and depression (Arabia et al. 2007) concluded that the underlying familial association was primarily driven by relatives of patients with a younger age of PD onset. Taken together, this pattern of findings underscores the importance of examining the role of early age of PD onset in the etiology of depressive symptoms in PD. In regard to the PD-depression comorbidity, it is possible that a shared genetic origin is present for PD and depressive symptoms only for patients with a younger age of PD onset.

The study also provides evidence for a genetic underpinning to both mild and moderate-severe depressive symptoms in late life, consistent with prior findings of heritability in late-life depressive symptoms in other studies of Swedish twins (Jansson et al., 2004; Kendler, Gatz, Gardner, & Pedersen, 2006b).

Conclusions on Secondary Aims

   Clinical presentation of PD-depression. To explore potential differences in depressive symptom responding for PD versus non-PD individuals, ANCOVA analyses were conducted to evaluate whether individual CESD-I item scores differed between individuals with versus without PD. These analyses revealed that, compared to non-PD individuals with similar overall depressive level, PD patients had higher scores on two of the eleven CESD-I items: sadness and difficultly with the initiation to "get going." The increased endorsement of sadness among PD cases is consistent with prior research (Cummings, 1992; Slaughter, Slaughter, Nichols, Holmes, & Martens, 2001) documenting that expression of sadness is one of the depressive symptoms most frequently observed in PD-depression. The current finding that depressed PD patients endorsed sadness above and beyond equally-depressed non-PD individuals may reflect the added psychosocial stress of living with a progressive illness such as PD, and the associated increases in quality of life factors such as disability and pain.

   Although prior studies have not documented increased difficulty "getting going" in PD-depression compared to primary major depression, this finding is not surprising given that fatigue often co-occurs with PD (Albin, 2006) and may affect one's volition or energy. Alternatively, the increased endorsement of difficulty "getting going" may be due to PD symptoms of bradykinesia and rigidity, and therefore may simply reflect the nature of PD as a movement disorder.

   Other depressive symptoms considered to be more common among PD than non-PD depressed patients, including irritability and difficulty concentrating, are not included on the CESD-I scale. Future research evaluating how the clinical presentation of PD-depression may differ from primary major depression will be useful in characterizing the unique expression of

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depression in PD, to ensure accurate diagnoses of PD-depression and appropriate tailoring of depression treatments to this specific clinical presentation. The implications of the current findings reinforce the importance of screening for depression among PD patients, particularly those who evidence signs or complaints of sadness or avolition.

Early age of PD onset. Although the current study included only a small number of early-onset PD cases, prevalence rates conducted separately for early-onset PD cases did provide some support for the relation between early-age of PD onset and depressive symptoms. For moderate-severe level of depressive symptoms (CESD-I $\geq$ 9), individuals with an earlier age of PD onset appeared to have a higher rate (35.29%) compared to individuals with a later age of PD onset (22.08%). This outcome is consistent with prior literature that documents greater rates of depression among early-onset PD patients compared to PD patients with a later age of onset (Giladi et al., 2000; Starkstein et al., 1989). As the prior studies examining age of PD onset have been conducted with clinical samples only, the current study provides some preliminary support for a relation between PD-depressive symptoms and early-age of onset within a population-based sample of PD patients. Additional studies will be useful in delineating whether this relation is due to a different etiology of PD-depression for early-onset cases, or to psychosocial differences (e.g., greater career disruption) that vary as a function of age of disease onset.

Strengths & Limitations

The strengths of the study include the utilization of a large, population-based sample with reliable ascertainment of PD cases. The careful ascertainment of PD diagnosis, as validated by movement disorder specialists, was a significant asset to the study. The identification of PD cases was based on an extensive diagnostic process, which decreased measurement error and the

risk of biases introduced by including various types of parkinsonism in the sample. The study

also utilized a valid measure of clinically significant depressive symptoms (Suthers et al., 2004).

The study was limited in the number of PD cases (i.e., 125) and by the low overall

concordance of PD in twin pairs. Because the sample included only three concordant PD pairs,

the lack of similarity between twins on PD rendered bivariate twin modeling uninformative. Had

the concordance rate been higher, bivariate twin modeling could have been conducted to reveal

relative estimates for the proportion of the PD-depressive symptom relation attributable to

genetic versus environmental influences. This limitation notwithstanding, the current study

represents the largest population-based twin sample of PD patients.

Finally, within the co-twin control sample, there may be pairs in which the non-PD twin

will later develop PD. However, the average number of years between age of onset of PD in the

PD twin and assessment of the non-PD twin was 7.4, slightly greater than the mean number of

years (7.0) separating PD age of onset for our three concordant pairs.

Conclusions

Understanding whether genetic influences contribute to the relation between PD and

depressive symptoms has the potential to inform both etiological theories and interventions. In

summary, the findings of these analyses suggest that genetic influences do not explain the

association between PD and mild or moderate-severe depressive symptoms. As such, future

etiology studies may be wise to focus on possible environmental factors that may explain this

relation.

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Table 1
Sample Characteristics by Sex, Zygosity, and Age Group

	Study population N
All twins	49814
Sex	
Men	22948 (46.07%)
Women	26866 (53.93%)
Zygosity [a]	
MZ	10861 (21.80%)
DZ	17560 (35.25%)
OS	17413 (34.96%)
Unknown	3980 (7.99%)
Age group	
50-59 years	23035 (46.24%)
60-69 years	13013 (26.12%)
70-70 years	9571 (19.21%)
80-89 years	3762 (7.55%)
90+ years	433 (0.87%)

[a]MZ = monozygotic twins, DZ = same-sexed dizygotic twins, OS = opposite-sexed twins.

Table 2

Clinical Diagnoses for Study Population (Wirdefeldt et al., 2008)

Diagnosis	N
PD	
Possible PD	33
Probable PD	99
Parkinsonism	
PSP[a]	6
MSA[b]	3
Cerebrovascular parkinsonism	32
Parkinsonism due to neuroleptics	11
Parkinsonism in dementia other than LBD	5
Parkinsonism of unknown cause	5
Other neurological diseases	
Lewy body dementia	11
Cerebellar disease	6
Essential tremor	52
Other[c]	6
No neurological disease	151
Total	420

[a]PSP = Progressive supranuclear palsy
[b]MSA = Multiple system atrophy
[c]Includes restless legs, hereditary dystonia, polyneuropathy, tics

Table 3

Prevalence of Mild and Moderate-Severe Depressive Symptom Cases by PD Status

	No PD	PD	Chi-Square (DF = 1)
CESD-I Total			
4+	37.13% (12394/33377)	63.54% (61/96)	28.57**
9+	11.50% (3838/33377)	23.96% (23/96)	14.56**

** *p < .0001*

Table 4
Probandwise Concordance Rates (N = 13,320 twin pairs)

	N Pairs concordant unaffected: discordant: concordant affected	Proportion Affected	Probandwise concordance rate
Parkinson's Disease (PD)			
MZ [a]	3318 : 15 : 1	0.25%	11.8%
DZ	4754 : 34 : 2	0.40%	10.5%
OS	4551 : 28 : 0	0.31%	NA
Mild Dep. Sym.[b]			
MZ	1429 : 1205 : 557	36.34%	48.0%
DZ	1884 : 1884 : 736	37.26%	43.9%
OS	1793 : 1930 : 636	36.73%	39.7%
Mod.-Severe Dep. Sym.[c]			
MZ	2548 : 545 : 98	11.61%	26.5%
DZ	3552 : 850 : 102	11.70%	19.4%
OS	3478 : 818 : 63	10.83%	13.3%

[a]MZ = monozygotic twins, DZ = same-sexed dizygotic twins, OS = opposite-sexed twins.
[b]Mild depressive symptoms = CESD-I score $\geq$ 4.
[c]Moderate-severe depressive symptoms = CESD-I score $\geq$ 9.

Table 5
Within-Trait Tetrachoric Correlations

	PD	(N)	Mild Dep. Symptoms[b]	(N)	Moderate-Severe Dep. Symptoms[c]	(N)
Zygosity[a]						
MZ	0.59	(3334)	0.36	(3191)	0.30	(3191)
DZ	0.54	(4790)	0.20	(4504)	0.17	(4504)
OS	NA	(4579)	0.11	(4359)	0.09	(4359)

[a] MZ = monozygotic twins, DZ = same-sexed dizygotic twins, OS = opposite-sexed twins.
[b] Mild depressive symptoms = CESD-I score ≥ 4.
[c] Moderate-severe depressive symptoms = CESD-I score ≥ 9.

Table 6

Cross-Twin Cross-Trait Tetrachoric Correlations

	PD & Moderate-Severe Dep. Symptoms[b]	PD & Mild Dep. Symptoms[c]	(N)
Zygosity[a]			
MZ	-0.08	0.06	(6445)
DZ	-0.11	0.04	(9181)
OS	-0.17	-0.10	(8847)

[a] MZ = monozygotic twins, DZ = same-sexed dizygotic twins, OS = opposite-sexed twins.
[b] Moderate-severe depressive symptoms = CESD-I score $\geq$ 9.
[c] Mild depressive symptoms = CESD-I score $\geq$ 4.

Table 7

Case control and co-twin control analyses predicting risk of moderate-severe depressive symptoms (CESD-I ≥ 9)

Case control

	Cases (cesd ≥9) (N = 3861)	Controls (N = 29,612)	OR (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)
PD	23	73	2.37(1.34, 4.20)	2.64 (1.45, 4.78)	3.23(1.77, 5.89)
No-PD	3838	29,539			

Co-twin control (N = 1395 monozygotic and dizygotic pairs)

	Cases (cesd ≥9)	Co-twin	OR (95% CI)	OR[c] (95% CI)
PD	8	3	2.31 (1.29, 4.12)	3.15 (1.74, 5.67)
No-PD	1344	1376		

Co-twin control monozygotic twins only (N = 545 monozygotic pairs)

	Cases (cesd ≥9)	Co-twin	OR (95% CI)	OR[c] (95% CI)
PD	4	1	2.71 (0.97, 7.54)	3.43 (1.20, 9.82)
No-PD	523	537		

[a] Odds ratio controlling for age and sex.
[b] Odds ratio controlling for age, sex, and prior history of major depression.
[c] Odds ratio controlling for prior history of major depression.

Table 8

Case control and co-twin control analyses predicting risk of mild depressive symptoms (CESD-I ≥ 4)

Case control

	Cases (cesd ≥4) (N = 12,455)	Controls (N = 21,018)	OR (95% CI)	OR[a] (95% CI)	OR[b] (95% CI)
PD	61	35	2.96 (1.76, 4.99)	3.16 (1.87, 5.33)	3.11 (1.82, 5.31)
No-PD	12,394	20,983			

Co-twin control (N = 3089 monozygotic and dizygotic pairs)

	Cases (cesd ≥4)	Co-twin	OR (95% CI)	OR[c] (95% CI)
PD	15	9	3.02 (1.81, 5.04)	3.22 (1.91, 5.41)
No-PD	3017	3061		

Co-twin control monozygotic twins only (N = 1205 monozygotic pairs)

	Cases (cesd ≥4)	Co-twin	OR (95% CI)	OR[c] (95% CI)
PD	4	4	1.56 (0.63, 3.85)	1.50 (0.59, 3.84)
No-PD	1179	1190		

[a] Odds ratio controlling for age and sex.
[b] Odds ratio controlling for age, sex, and prior history of major depression.
[c] Odds ratio controlling for prior history of major depression.

Table 9

Presence of Individual Depressive Symptoms in Participants with and without PD

CESD-I Item	Model[a] F (df)	PD status F (p)
1. Depressed	4500.91 ** (4, 16785)	0.02 ($p = .89$)
2. Lonely	2580.33 ** (4, 16797)	0.07 ($p = .79$)
3. Sad	4251.85 ** (4, 16758)	4.93 ($p = .03$) *
4. Appetite	1160.29** (4, 16800)	2.55 ($p = .11$)
5. Effort	4188.64** (4, 16794)	0.18 ($p = .67$)
6. Slept fitfully	2242.65** (4, 16788)	1.16 ($p = .28$)
7. Couldn't "get going"	2039.86** (4, 16747)	6.83 ($p = .01$) *
8. Happy	2614.86** (4, 16304)	2.07 ($p = .15$)
9. Enjoyed life	3119.40** (4, 16730)	3.51 ($p = .06$)
10. Unfriendly	579.61** (4, 16796)	3.58 ($p = .06$)
11. Disliked	576.11** (4, 16719)	0.21 ($p = .65$)

[a] Modeling PD status, with age, sex, and overall level of depressive symptoms as covariates
* = $p < .05$
* = $p < .001$

Figure 1 *Study design*

SALT 1998 – 2002
(Pilot 1996)

SALT Population 50-65 years

SALT Population 65+ years

SALT PD First Screening:

49,814 Eligible (< 50 yrs)
    406 = died between selection and screening
    8086 = refused
    5125 = other non-participants (e.g., not interviewable)

36,197 = participated
    (Participation rate 73.2%)

Self- or proxy-reported PD = 154
PD symptoms endorsed (suspects) = 577

Dementia suspects
and co-twins,
controls and co-twins

**Study of Dementia in
Swedish Twins (HARMONY)**
[Diagnostic Work-up for Dementia]

1,557 = Dementia suspects with
       diagnostic work-up

60 = PD suspects identified through
     SALT and screened through
     dementia work-up
    53 = Excluded as PD suspects
       through the HARMONY
       neurological exam

34 = Additional PD suspects identified
     by dementia work-up

N = 577 PD suspects

PD Second Screening Phase:
Second telephone interview to exclude obvious non-PD

577 PD suspects identified
    68 = Dead or not willing to be contacted again
    57 = Not contacted due to an administrative error

452 = contacted for this phase
    103 = Did not participate

349 participated (Participation rate = 77.2%)
    182 = excluded directly by the exclusion algorithm
    21 = excluded after review by study physician

146 not excluded

N = 154 self- or
proxy-reported PD
in first screening

N = 7 PD suspects
evaluated in
HARMONY

N = 34 PD suspects
from HARMONY

N = 146 PD suspects

PD Third Screening Phase:
Somatic Exam & Medical Record Review

153 = eligible for this phase (146 from second
    screening + 7 from HARMONY)

136 participated in this diagnostic work-up
    19 = Did not participate;
      11 = refused
      7 = died after the second screening interview
      1 = not worked up due to logistical difficulties

66

PD Third Screening Phase: Medical
Record Review
N = 188 (154 self- or proxy-reported PD
    + 34 PD suspects from HARMONY)
6 = excluded because diagnosis could not be
    assigned due to insufficient info. (e.g., med.
    records could not be obtained)

Final PD Diagnosis
132 = PD cases identified (99 cases probable PD, 33 cases
possible PD)
125 = PD cases with PD onset before SALT
    7 = excluded because PD onset was after SALT

Appendix A

Center for Epidemiologic Studies – Depression Scale Items

Participants were asked how often they experienced each of the following symptoms during the last week. Responses were scored on a four-point scale:

0 = *Rarely / None (Less than one day)*

1 = *Some / A little (1 to 2 days)*

2 = *Occasionally (3 to 4 days)*

3 = *Most / All the time (5 to 7 days)*

1. I felt depressed.

2. I felt lonely.

3. I felt sad.

4. I didn't feel like eating; I had a bad appetite.

5. Everything I did was an effort.

6. I slept fitfully.

7. I couldn't "get going."

8. I was happy.

9. I enjoyed life.

10. People were unfriendly.

11. I felt that people disliked me.

Appendix B

Diagnostic Form for Parkinson's Disease

(Y=yes, N=no, U=uncertain, IM=information missing)

NINDS Group A Features:
   1. resting tremor (CAPIT)   Y   N   U   IM
   2. bradykinesia (CAPIT)   Y   N   U   IM
   3. rigidity (CAPIT)   Y   N   U   IM
   4. asymmetric onset   Y   N   U   IM

NINDS Group B Features (Atypical Findings):   Y   N   U   IM
   1. Features unusual early in the clinical course
      a. Prominent postural instability in the first three years after symptom onset
      b. Freezing phenomenon in the first three years
      c. Hallucinations unrelated to medications in the first three years
      d. Dementia preceding motor symptoms or in the first year
   2. Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
   3. Severe, symptomatic dysautonomia unrelated to medications
   4. Documentation of condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past six months)

   If U or Y : state finding _____

O Probable PD

        A. At least three of the four features in Group A are present
  and
        B. None of the features in Group B is present (NOTE: symptom duration of at least three years is necessary to meet this requirement)
  and
        C. Substantial and sustained response to levodopa or a dopamine agonist has been documented.

O Possible PD

        A. At least two of the four features in Group A are present; at least one of these is tremor or bradykinesia
  and
        B. Either   1. None of the features in Group B is present
            Or   2. Symptoms have been present for less than three years and none of the features in Group B is present to date
  and
        C. Either   1. Substantial and sustained response to levodopa or a dopamine agonist has been documented
            Or   2. Patient has not had adequate trial of levodopa or a dopamine agonist.

O Not PD