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

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

Disease

by

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ABSTRACT

Depression and anxiety are common psychiatric disturbances in Parkinson's disease (PD). Past studies have demonstrated a relationship between depression and cognitive decline in PD; however, the unique influence of anxiety has not been well studied. The objective of the present study was to differentiate the unique influences of depression and anxiety on cognitive functioning in PD. Sixty-eight cognitively intact PD patients with mild to moderate motor disease severity completed self-report questionnaires and neuropsychological tests. Two hierarchical regression analyses were conducted with executive functioning performance as the criterion variable, and two additional hierarchical regression analyses were conducted with memory performance as the criterion variable. Depression and anxiety, as measured by the Depression Anxiety and Stress Scales (DASS), served as predictors for all analyses. Each set of analyses examined the amount of added, unique variance accounted for by anxiety when depression was entered as the first predictor, and also examined the amount of added, unique variance accounted for by depression when anxiety was entered as the first predictor.

It was found that depression significantly predicted delayed recall memory performance when entered as the first and second predictor. In contrast, anxiety did not

significantly predict performance on any of the cognitive measures. Two DASS subscales

assess for the physical symptoms of anxiety, and these subscales were not significantly

correlated with any cognitive variables. However, the DASS subscales tapping into non-

physical aspects of anxiety were significantly associated with several cognitive variables.

Patients may have endorsed physical symptoms of anxiety due to the symptoms

associated with PD, and not as a result of the genuine presence of anxiety. This could

have masked a potential relationship between anxiety and cognitive functioning in PD,

and suggests that specific components of anxiety may be associated with cognition in PD.

Future adaptation of the DASS may be necessary to differentiate the unique influences of

depression and anxiety in PD patients.

Introduction

Evidence from neuropsychological and neuroimaging studies indicate that emotional regulation is clearly linked to various aspects of cognitive processing. One method of understanding these connections is by studying clinical populations with mood disorders and cognitive deficits. Patients with Parkinson's disease (PD) are well suited for this type of investigation because they often perform deficiently on tasks of executive function and memory, in addition to commonly experiencing affective difficulties. It is well documented that depression is the most common psychiatric disturbance in PD. A number of studies have demonstrated a relationship between depression and cognitive decline in this population. Although there is a high degree of overlap between depression and anxiety, the additive influence of anxiety on cognitive function has not been well studied and will be the focus of the current investigation.

This paper will first provide information about PD, including a review of the main deficits, the course of progression, and the neurological pathways affected. Next, the characteristic pattern of cognitive impairments will be outlined. The discussion will mainly focus on patterns of executive functioning and memory deficits. Then, the emphasis will shift to a review of the literature on anxiety, depression, and comorbidity in PD. Also, the few studies that have examined relationships between psychiatric features and cognitive functioning with PD patients will be described.

Parkinson's Disease: Overview

PD is one of the most common degenerative neurological disorders afflicting individuals in middle and later stages of life, impacting approximately 1% of the population after age 50 (Li et al., 1985). It is characterized by the deterioration of dopaminergic neurons primarily within the substantia nigra. The reduction in dopamine interferes with the nigrastriatal pathway in the basal ganglia, resulting in movement disturbance (Gibb, 1992).

Alterations in dopamine levels result in an abnormal increase in muscle tone as well as extreme poverty of movement (Bradshaw & Mattingly, 1995). Tremor is greatest at rest and decreases with voluntary movement. Muscular rigidity also occurs and can transfer rapidly between states of relaxation and tension, called cogwheeling. In particular, disturbances in facial muscles can create a lack of facial expression, flat vocal intonations, and dysarthria. PD can also create conditions such as postural disturbance and shuffling gait (Cummings, 1992).

The severity of these symptoms and the progression vary by individual, but usually progress over the course of about 10-20 years (Langston, 1990). The disease can be divided into three predominant stages: early, nonfluctuating, and fluctuating (Manyam, 1997). In the early stage, the patient develops minor symptoms that do not result in significant disability. Sometimes these symptoms are initially expressed unilaterally. The nonfluctuating stage is characterized by prominent symptoms and use of medication is generally required and patients normally respond well to it. At the fluctuating stage, the medications usually cause side effects and the medication is effective for shorter periods of time. Abrupt shifts in motor abilities, often called "on/off"

periods, afflict about half of PD patients after five years of levadopa therapy (Miyawaki et al., 1997). On/off fluctuations have no apparent pattern, and impairments that interfere with lifestyle may surface at this stage.

Neuropathology

PD is considered to be the most common disorder affecting the basal ganglia (Middleton & Strick, 1994). The basal ganglia are a group of subcortical structures that play a critical role in initiating voluntary movement and planning and adjusting the force of subsequent motor output. The motor system operates in a hierarchical manner, so control of functioning is distributed over various levels. The cortical regions are at the highest level and are involved in the planning and selection of various actions. The spinal cord is at the lowest level and is responsible for the execution of simple reflexes. The basal ganglia provide a middle linkage of these levels by connecting the general commands from the cortex with the specific execution of motor output.

The basal ganglia are comprised of five separate regions that communicate in a network: the caudate, putamen, globus pallidus, subthalamic nucleus, and substantia nigra. The caudate and putamen are similar in nature and are generally referred to as a single structure, the striatum. An important pathway that involves the basal ganglia is known as the striato-pallido-thalamic loop. This loop is thought to prepare information for cortical processing by integrating information from multiple brain regions. Dopamine is an important neurotransmitter in this pathway because it can serve to reinforce actions and can make it more likely that a certain response will occur in the future.

In PD, there is a pronounced reduction in the dopaminergic neurons of the substantia nigra (Gibb, 1992). As a result, dopaminergic projections to the striatum are

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reduced and this disrupts the entire basal ganglia system. The end result is decreased motor excitation to the motor cortex. The basal ganglia are no longer able to provide an appropriate linkage from the cortex to the motor effectors, resulting in movement disturbance.

In addition to the influence of dopamine, there is considerable evidence to suggest that cholinergic, noradrenergic, and serotonergic neurotransmitter systems may also be damaged as a result of the disease (Mayeux, Stern, Cote, & Williams, 1984).

Cognitive Impairments in PD

The nigrastriatal dopaminergic pathway projects to several cortical regions that are implicated in cognitive and behavioral functioning. There are also changes that occur in the mesolimbic dopaminergic pathway. Thus, in addition to prominent decline in motor functioning, many PD patients also are afflicted with other various complications, such as hallucinations, sleep disturbance, autonomic dysfunction, and psychiatric difficulties (Mackin, 2000).

One such complication is that many PD patients tend to perform below average on tests of neuropsychological functioning. It has been estimated that as many as 80% of PD patients demonstrate some type of cognitive impairment and around 20% of PD patients qualify for a diagnosis of dementia (Brown & Marsden, 1990). Also, Portin & Rinne (1987) found that over 70% of patients display a gradual cognitive deterioration over time.

Cognitive impairment is an important aspect to consider because it appears to be related to significant declines in the daily functioning of PD patients (Mayeux & Stern,

1983). It has also been found to be related to other factors, such as severity of the movement dysfunction and the duration of the disorder (Hietanen & Teravainen, 1986).

Deficits are generally observed on measures of visuospatial abilities, memory, and executive functioning (Grant & Adams, 1996). Pervasive visuoperceptual and visuoconstructional deficits are commonly reported. In terms of memory, recall of recent material is generally found to be impaired, while recognition abilities are relatively intact. Executive deficits begin to appear early in the progression of PD, particularly in set shifting tasks. Attention and language skills are relatively spared in comparison to these other domains. Patients with unilateral symptoms of PD commonly display more pronounced cognitive deficits in relation to the affected hemisphere (Starkstein, Leiguarda, Gershanik, & Berthier, 1987). Overall, the pattern of impairment is similar to the deficits of frontal lobe patients (Owen et al., 1992).

Executive functioning

Impairment in executive functioning is a defining characteristic in the spectrum of cognitive dysfunction in PD (Dalrymple-Alford, Kalders, Jones, & Watson, 1994). Executive functioning involves a set of complex abilities that can be implemented in solving sophisticated problems and guiding purposeful behavior (Marie et al., 1999). It is associated with activation in the frontal lobes and involves a diversity of specific skills, including processes such as abstract reasoning, sequencing chains of events, inhibiting irrelevant tasks, altering behavior in response to changing environmental conditions, and simultaneously modulating between competing demands (Smith & Jonides, 1999).

Tasks that rely on executive abilities generally deteriorate early in the progression of PD and appear to be more vulnerable than other areas of cognitive performance

(Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003). Furthermore, one longitudinal study found that performance on several executive measures was predictive of the subsequent onset of dementia (Levy et al., 2002).

There is evidence that the level of executive dysfunction is related to the severity of motor impairment in PD (Alevriadou, Katsarou, Bostantjopoulou, Kiosseoglou, & Mentenopoulos, 1999) and also to dopaminergic levels in the basal ganglia (Marie et al., 1999). This suggests that the basal ganglia play a role in higher levels of cognition. In fact, it appears that the frontal lobes and basal ganglia are connected through parallel and segregated frontal-subcortical circuits (Alexander, DeLong, & Strick, 1986). Strong evidence has accumulated to confirm the interconnectivity between these two regions (Middleton & Strick, 1994).

In contrast to the relatively consistent structural evidence, the neuropsychological evidence investigating executive processes derives a picture that is not quite as clear. The definition of executive functioning is lacking in focus and specificity, which creates inconsistencies when experimentally testing this concept (Stuss, 1993). For instance, a variety of measures have been used to test different aspects of executive functioning in PD, including the Object Alternation Task, the Wisconsin Card Sorting Test, verbal fluency, the Odd Man Out Test, the Stroop Task, the Trail Making test, and the go no-go task. Thus, it is important to examine executive deficits in PD with respect to specific subcategories. Namely, PD patients have demonstrated difficulties on executive tasks that involve set shifting, planning, and working memory.

Set shifting. The inflexibility of behavior in response to changing environmental contingencies is one of the most prominent cognitive alterations in PD and has received a

large amount of attention in the literature (Richards, Cote, & Stern, 1993). PD patients have pronounced difficulties performing on experimental measures that test their ability to shift set or inhibit inappropriate alternatives (Van Spaendonck, Berger, Horstink, Borm, & Cools, 1995). This type of cognitive limitation is evident even during the earliest stages of the illness (Cools, Barker, Sahakian, & Robbins, 2001).

Although impaired performance on tests of set shifting in PD has been reasonably well established, the mechanisms responsible for this deficiency are not yet distinctly understood. Cools, van den Bercken, Horstink, van Spaendonck, and Berger (1984) suggest that an overriding set-shifting dysfunction in PD influences abilities in both cognitive and motor realms. Flowers and Robertson (1985) found that errors appeared across all portions of a discrimination task, reflecting a pattern of impairment that is not restricted to points at which a shift in set occurs. They propose that PD patients experience difficulties maintaining set when competing information is present. Another possibility to account for poor set-shifting performance is that PD patients fail to consider a previously unrewarded category that becomes the current category of interest, a concept called learned irrelevance (Owen et al., 1993). Taylor, Saint-Cyr, and Lang (1986a) has addressed the set-shifting impairment by suggesting that PD patients may have problems in activities that call upon the execution of internally generated planning strategies. In support of this idea, Brown and Marsden (1988) found that PD patients provided with external cues displayed no difficulties in switching between activities as opposed to when they were required to rely upon self-directed cues.

Planning. Research tends to show that PD patients are impaired on tasks that involve planning (Morris et al., 1988). While set-shifting impairment appears early and

consistently throughout the course of illness, planning deficits vary by disease stage (Lees and Smith, 1983). Owen et al. (1992) demonstrated that only medicated PD patients with severe clinical presentations were significantly less accurate at solving planning problems. Morris et al. (1988) found that although solution accuracy did not change, patients with mild to moderate symptoms took significantly longer to solve the problems.

Working memory. A number of recent studies have examined the role of working memory in contributing to the observed deficits in executive functioning in PD (Cooper, Sagar, & Sullivan, 1993; Owen et al., 1993). Several studies have shown that working memory impairments become prominent in later stages of the disease (Morris et al., 1988; Owen et al., 1992). Moreover, PD patients have particular difficulties in tasks that require the manipulation of information in working memory (Lewis et al., 2003; Owen et al., 1993).

A working memory deficit may be at the core of other executive problems such as set shifting and planning. For instance, Brown and Marsden (1990) suggest that PD patients become reliant on external cues during set-shifting tasks due to depletion in working memory resources. Furthermore, Gabrieli (1996) found that the damaged working memory abilities of PD patients were related to impairments on numerous other executive tasks. According to these findings, it seems that problems only become apparent when cognitively challenging tasks surpass the capability of the working memory system.

In summary, it is well established that PD patients have executive functioning deficiencies, particularly in the areas of set shifting, planning, and working memory.

However, the exact mechanisms that drive these difficulties still remain as a substantial research question.

Memory

PD patients characteristically perform poorly on free recall tasks but tend to demonstrate near normal functioning on cued recall tasks and recognition tasks (Breen, 1993). This suggests that the information has been sufficiently encoded but PD patients have difficulty with retrieval. For instance, Sagar, Cohen, Sullivan, Corkin, and Growdon (1988a) showed that PD patients had an impaired ability to remember the dates of famous public events. However, they could still recognize the events when they were presented. This deficit not only applies to remote memories, but to new learning as well. Sagar, Sullivan, Gabrieli, Corkin, and Growdon (1988b) gave PD patients a verbal recency discrimination task that examined their ability to determine the order in which new information is presented. This study found that PD patients were impaired at this task while recognition remained intact.

PD patients seem to display relatively better performance on delayed tasks compared to immediate tasks. For instance, Sagar et al. (1988b) found that patients had difficulties in recognition memory only at the shortest intervals between stimulus presentation and testing. An overall slowing in processing speed may explain this pattern of performance, often called bradyphrenia. Another possible explanation for this pattern of performance is that PD patients have difficulty manipulating multiple pieces of information in short-term memory (Baddeley, 2003). In addition, deficits could be attributed to cognitive akinesia, which describes delays in initiation of encoding. Although there is no clear answer yet, the fact that memory abilities improve when PD

patients are given adequate time demonstrates that memory problems may be an indirect result of a more fundamental problem (Taylor, Saint-Cyr, & Lang, 1990).

It seems that deficits in memory may stem partially from problems in creating internal strategies (Van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1996). Buytenhuijs, Berger, Van Spaendonck, and Horstink (1994) administered a memory task that requires an internally directed strategy of semantic organization for optimal performance. PD patients tended to rely on external strategies and recite the words in the order in which they were presented.

Executive dysfunction could be the underlying cause of PD memory problems (Cooper et al., 1993; Taylor, Saint-Cyr, & Lang, 1990). Research has demonstrated that there seems to be an association between executive functioning and memory in PD patients (Bondi, Kaszniak, Bayles, & Vance, 1993). Specific memory difficulties such as this may be an indirect consequence of a broader deficit in executive functioning.

Psychiatric symptoms in PD: Comorbidity

Starkstein & Mayberg (1993) reported that psychiatric symptoms are present in as high as 90% of PD patients. Some studies have found that approximately half of PD patients suffer from affective illness that meets DSM-IV criteria (Starkstein, Preziosi, & Bolduc, 1990). Depression and anxiety appear to be particularly prevalent and it seems that there is a unique association between these constructs in PD patients. For instance, it is more likely that PD patients will experience comorbid anxiety and depression than elderly individuals that do not suffer from this neurologic disorder (Flint, 1994). Henderson, Kurlan, Kersun, and Como (1992) found that 20% of PD patients reported symptoms of both depression and anxiety on an "at least weekly" basis. Also, it appears

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that the association between depression and anxiety is stronger in PD than in other groups with neurological impairment.

Depression in PD

Depression is regarded as the most frequently occurring psychiatric symptom in PD (Stocchi & Brusa, 2000). Across studies, the mean frequency of depression has been found to be approximately 40% (Cummings, 1992). Gotham, Brown, and Marsden (1986) observed that depression was more common in PD subjects than controls and some researchers have noted that PD patients have significantly higher rates of depression than other patient populations possessing similar levels of functional disabilities (Ehmann, Beninger, Gawel, & Riopelle, 1990).

Increased interest has recently been directed toward depression as a factor that significantly affects outcome of patients with PD. Several studies found depression to be the most important component in decreasing the quality of life of PD patients (Schrag, Jahanshahi, & Quinn, 2000; Slawek, Derejko, & Lass, 2005). Importantly, depression was even more influential in contributing to quality of life factors than PD motor dysfunction.

Depression in PD can be differentiated from other depressive disorders because PD patients tend to experience greater anxiety and less self-punitive thinking patterns (Cummings, 1992). Also, suicide has been found to be more rare in the PD population than in normal depressed individuals (Cummings, 1992). Classic characteristics of depression in PD include apathy, decreased self-directed planning capabilities, psychomotor retardation, a mood that is strongly dependent on environmental circumstances, and a decrease in concentration (Brown, Marsden, Quinn, & Wyke,

1984). In addition, periods of negative mood states tend to accompany the worsening of PD motor symptoms (Taylor, Saint-Cyr, Lang, & Kenny, 1986b).

Despite the demonstrated impact of depression in patients' lives, many aspects of the disorder are poorly understood. For instance, estimations of prevalence rates vary drastically, ranging from 7% to 70% (Yamamoto, 2001). In part, the inconsistency between studies may be due to a failure to distinguish between patients that meet criteria for major depression and those that experience subsyndromal depressive symptoms. Tandberg, Larsen, Aarsland, and Cummings (1996) found that rates of major depression range from only 3-8%, yet about half of PD patients suffer from depressive symptoms). Tandberg et al. (1996) also highlighted the fact that prior estimates may be inflated due to sampling differences since the rates of depression in this study were found to be much lower in a community sample.

Another issue is that it is challenging to determine the presence of a depressive disorder because some signs of depression are also core features of PD, such as fatigue, lack of concentration, motor retardation, and sleep disturbance (Allain, Schuck, & Mauduit, 2000). Difficulties in establishing diagnostic criteria are also a potential cause of the large variation in prevalence reports (Cummings, 1992). There are not adequate provisions in the DSM-IV to properly identify individuals who seemed depressed but also have a neurological disorder (Yamamoto, 2001). In order to establish improved diagnostic criteria, the etiology of depression in PD must be better understood.

The severity of depressive symptoms is another point of contention in the PD literature. It is still not evident whether the nature of PD depression can be characterized more as major depression or dysthymic disorder (Yamamoto, 2001). PD patients have

been found to have a low rate of suicidal and guilt ideation, which suggests that perhaps depression in this population is less severe in nature than major depressive disorder (Poewe & Luginger, 1999).

Causal Factors

The origins of depression in PD are not clearly outlined, but much of the evidence suggests that endogenous factors may play an important role in the origins of depression. Most studies have found a lack of association between level of depression and the stage of PD, suggesting that depression in PD could be more than a psychological reaction to the severity of the illness (Brown & Jahanshahi, 1995). A number of studies have even reported that the symptoms of depression often precede the diagnosis of PD (Leentjens, Van den Akker, Metsemakers, Lousberg, & Verhey, 2003; Nilsson, Kessing, & Bolwig, 2001).

Several researchers support the viewpoint that both psychological and endogenous factors could be responsible for depression in PD (Brown and Jahanshahi, 1995; Cummings & Masterman, 1999). Serra-Mestres and Ring (2002) offers a model that accounts for both of these factors, suggesting that PD patients are more vulnerable to psychosocial stressors because of their biological predisposition, and therefore develop depression more often than normal individuals.

Neurochemical features

The dopamine depletion in PD could play a role in the expression of depressive symptoms. Although the majority of dopaminergic destruction in PD occurs in the nigrastriatal pathway, damage to other dopamine pathways might be involved in depression. For instance, it has been proposed that affective disturbance in PD may be

associated with reduced activity of the mesolimbic pathway. This pathway is thought to play a role in the induction of pleasurable mood states in response to rewarding stimuli (Mayberg & Solomon, 1995). Torack and Morris (1988) found that PD patients with affective disturbance and cognitive impairment tend to have more pronounced dopamine depletion in the ventral tegmental area. Mayberg et al. (1990) indicated that a positive correlation exists between PD depression and decreased glucose metabolism in frontal areas that receive dopaminergic projections from the ventral tegmentum.

There is evidence to suggest that abnormal levels of serotonin also exacerbate mood difficulties. Mayeux, Stern, Cote, & Williams (1984) found a reduction in a serotonin metabolite in the cerebrospinal fluid of depressed PD patients, as found with individuals with major depressive disorder. Mayberg and Solomon (1995) proposed a model to explain how serotonergic depletion could be implicated in the development of depression. According to this model, depletion of dopamine in the ventral tegmental area disrupts the orbitofrontal cortex and prefrontal cortex, which influences serotonergic levels in the dorsal raphae nucleus. Indeed, Paulus and Jellinger (1991) indicated that serotonergic depletion of the dorsal raphae nucleus was more dramatic in PD depressed patients compared to PD patients that were not depressed.

Depression and Cognition

A number of studies provide support for a relation between primary depression and cognitive impairment in the absence of neurological illness. However, the findings in this area have been inconsistent and difficult to characterize due to differences across studies on variables such as depression subtype, treatment setting, severity of depression,

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age, medication, and differences in memory assessment measures and rating scales for depression (Burt, Zembar, & Niederehe, 1995; Elliott, 1998).

Some studies have claimed that depressed individuals demonstrate global impairment in functioning that spans across various neuropsychological domains (Ravnkilde et al., 2002). In a meta-analytic review of the existing literature, Veiel (1997) describes the deficits as "global-diffuse impairment of brain functions with particular involvement of the frontal lobes". Veiel (1997) speculates that the pattern could be similar to that observed in patients with moderately severe traumatic brain injury.

Other studies have focused on selective impairments in particular neuropsychological domains, such as episodic memory (Airaksinen, Larsson, Lundberg, & Forsell, 2004), sustained attention (Weiland-Fiedler et al., 2004), free recall memory (Ilsley, Moffoot, & O'Carroll, 1995), psychomotor speed (Brebion, Smith, & Widlocher, 1997), and executive functioning (Channon, 1996). Overall, impairments have been consistently identified in a broad range of areas, but there are discrepancies in the pattern of deficits that are reported from study to study.

A number of theories have been proposed in an attempt to account for the factors that could explain these findings from the neuropsychological literature. In particular, Hasher and Zacks (1979) hypothesized that depressed patients may have more difficulty on effortful tasks compared to automatic tasks. Depressed patients may lack the motivation to sustain effortful activity, or it is possible that they are unable to maintain attention long enough to complete a challenging task (Cohen, Weingartner, Smallberg, Pickar, & Murphy, 1982). This hypothesis has been supported by some studies that examine differences in performance between explicit, or effortful, and implicit, or

automatic, memory tasks (Danion et al., 1991; Denny & Hunt, 1992; Bazin, Perruchet,

De Bonis, & Feline, 1994). According to this theory, executive functioning should also

be impacted by depression. Executive functioning tasks are considered particularly

effortful in that they require the individual to independently structure activities, and also

respond appropriately to changing environmental conditions with little external guidance.

Indeed, there is compelling neuropsychological evidence to indicate that executive

functioning tasks are sensitive to depression, and neuroimaging evidence also indicates

that frontal lobe dysfunction is linked to depression (Goodwin, 1997).

PD Depression and Cognitive Impairment

There is ample evidence to suggest that a relationship also exists between

depression and cognitive impairment in the presence of a diagnosis of PD. Mayeux,

Stern, Rosen, and Leventhal (1981) first discovered this in a study intended to determine

the prevalence of depression in PD. Subjects with higher levels of depression achieved

lower scores on the Mini Mental Status Examination (MMSE), suggesting a significant

negative relationship between depression and overall cognitive ability. However, factors

such as age, education, and severity of motor disability were not controlled for and could

have contributed to this relationship. Starkstein, Preziosi, Berthier, Bolduc, Mayberg, and

Robinson (1989) controlled for age, education, stage of disease, and severity of PD

symptoms, and still found that there was a significant relationship between MMSE scores

and depression.

Several longitudinal studies have also demonstrated that the presence of

depression in PD is an important predictor of subsequent intellectual decline. Starkstein,

Bolduc, Mayberg, Preziosi, and Robinson (1990) followed a sample of PD patients for a

3-4 year period and found that depressed patients had experienced more rapid cognitive decline compared to patients without depression. In another longitudinal study, Starkstein, Mayberg, Leiguardia, Preziosi, & Robinson (1992) recorded outcome after twelve months and observed that PD patients with major depression at initial evaluation subsequently exhibited more extreme cognitive deterioration as compared to patients with no depression.

Some studies have distinguished between levels of severity of depressive symptoms. Using DSM-III diagnostic criteria, Starkstein, Preziosi, Bolduc, & Robinson (1990) demonstrated that patients with major depression obtained significantly lower MMSE scores than those diagnosed with minor depression. Starkstein, Preziosi, Berthier, Bolduc, Mayberg, & Robinson (1989) conducted a more thorough neuropsychological assessment and concluded that in general, minor depression does not create intellectual difficulties in PD. However, the minor depressed group did score significantly lower than the non-depressed group on an executive measure. This finding reflects the proposition of Mayeux et al. (1981) that a graded association may exist between severity of depression and cognitive functioning. Starkstein, Mayberg, Leiguardia, Preziosi, & Robinson (1992) showed that there was significantly greater cognitive decline over time in major depressed PD patients compared to those with minor depression.

It appears that other specific characteristics such as stage of illness, time of illness onset, and side of PD symptoms may influence the relationship between depression and cognition. Starkstein, Bolduc, Preziosi, & Robinson (1989) demonstrated an interactive relationship between stage of PD and diagnosis of depression. The individuals that were in the late stage of PD and also had depression demonstrated the worst cognitive

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performance, particularly on executive tasks. Starkstein, Berthier, Bolduc, Preziosi, and Robinson (1989) found a significant relationship between scores on a depression measure and cognitive ability in an early-onset group but not in a late-onset group. Finally, Starkstein, Preziosi, Bolduc, and Robinson (1990) indicated that patients with predominantly right-sided symptoms had higher rates of depression and lower scores on a global cognitive measure than patients with left sided symptoms.

More recent studies have administered comprehensive neuropsychological assessments to identify specific deficits in addition to examining overall cognitive functioning. Starkstein, Bolduc, Preziosi, and Robinson (1989) observed that depressed PD patients have more pronounced impairment on tests that assess executive functioning compared to non-depressed PD subjects. In fact, Starkstein et al. (1989) found that of all areas of cognitive ability, depressed PD subjects had the most extreme deficits on tests of executive function. According to these authors, depressed PD patients exhibited greater levels of perseveration, more difficulties with shifting sets and putting information in order, and decreased verbal fluency and visual scanning abilities.

Several studies obtained similar findings, but included a group of individuals with primary depression (Kuzis, Sabe, Tiberti, Leiguarda, & Starkstein, 1997; Wertman, Speedie, Shemesh, & Gilon, 1993). It was found that depressed PD patients exhibited greater impairment on set shifting and verbal fluency tasks than non-depressed PD patients and individuals with primary depression only. Kuzis et al. (1997) suggested that while depression alone accounts for some cognitive decrements in depressed PD patients, difficulties on executive tasks may be associated with the unique pathological alterations that occur with PD and depression combined.

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It has been proposed that depression also exacerbates memory impairments in PD patients. Troster et al. (1995a) found that PD individuals with and without depression both had significant impairments compared to normal controls on tests measuring conceptualization and perseveration. However, memory abilities were significantly impaired relative to controls only in depressed PD patients. To further support this finding, Starkstein, Rabins, Berthier, Cohen, Folstein, and Robinson (1989) demonstrated that delayed recall memory was negatively affected in depressed PD patients, depressed stroke patients, and individuals with functional depression. This study found that the severity of depression was the same across groups, implying that depression itself has a strong influence on memory ability in patients with primary and secondary depression.

Troster, Stalp, Paolo, Fields, & Koller (1995b) compared the overall patterns of cognitive impairment for groups of PD patients with and without depression. According to their findings, the general pattern of impairment remains the same in both groups. However, Troster et al. (1995b) concluded that depressed individuals display more severe impairment in the vulnerable areas.

Although the majority of studies have demonstrated a clear relationship, it should be noted that a few studies have failed to show a significant association between cognitive impairment and depression in PD patients. Despite the fact that it is fairly well established that individuals with major depression experience deficits in short-term memory, Taylor et al. (1986b) found no significant differences between depressed and non-depressed PD patients on measures of short-term memory. Starkstein, Preziosi, Berthier, Bolduc, Mayberg, and Robinson (1989) provide a possible explanation for this by pointing out that the depressed PD group in the Taylor et al. (1986b) study scored

relatively low on the BDI. Thus, it may be more accurate to assert that *minor* depression does not create short-term memory impairments.

Huber, Paulson, & Shuttleworth (1988) found a significant relationship between severity of motor difficulties and cognitive impairment in PD patients. However, depression did not appear to be significantly related to general cognitive impairment. Ryder et al. (2002) also failed to find significant relationship between cognitive functioning and depression. However, executive functions were not measured in this study, overlooking an important area of cognitive ability in PD. Bieliauskas and Glantz (1989) found that depression in PD was not related to diagnosis of dementia, an overall measure of memory, or measures of executive functioning. Troster et al. (1995) suggests that differing definitions of depression, thresholds for identification of mood disorders, assessment strategies, small sample sizes and confounds of age at disease onset, disease duration, and disease severity could account for discrepancies in findings.

Anxiety in PD

Anxiety is another common psychiatric symptom associated with PD, however, it has been vastly neglected compared to depression. Similar to the pattern observed with depression, there is a wide variation in reported prevalence of anxiety disorders in patients with PD, ranging from 5.3% to 40% (Starkstein, Robinson, & Leiguardia, & Preziosi, 1993). The incidence of anxiety disorders in the general population is estimated in the range of 5%-15% (Myers et al., 1984) and about 11% in patients with chronic medical problems (Wells, Golding, & Burnam, 1988).

PD patients with anxiety represent a substantial and unique subgroup. First, anxiety in PD patients is more common than in elderly controls (Gotham, Brown, &

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Marsden, 1986; Richard, Schiffer, & Kurlan, 1996) and these patients also have higher rates of anxiety than other neurological samples (Schiffer, Kurlan, Rubin, & Boer, 1988). Second, anxiety disorders tend to occur less often in elderly individuals compared to younger adults (Regier et al., 1988). Considering that the PD population tends to consist of older individuals, this makes the common occurrence of anxiety particularly unusual.

Generalized anxiety disorder, social phobia, and panic disorder have been reported to be the most prevalent types of anxiety disorders manifested in PD patients (Richard, Schiffer, & Kurlan, 1996). However, a recent study found that panic disorder occurs in conjunction with PD more often than generalized anxiety disorder (Lauterbach, Freeman, & Vogel, 2003).

Stein, Heuser, Juncos, & Uhde (1990) found that PD patients with anxiety disorders did not have higher levels of disability, suggesting that anxiety is not simply a psychological response to the seriousness of the disease. Alternatively, anxiety could be associated with the biological changes of PD. Shiba et al. (2000) suggested that anxiety disorders may be the earliest sign of the subsequent development of PD. This study found that anxiety disorders significantly predict PD when examining psychiatric disorders that existed in PD patients 20 or more years before they were diagnosed with PD. Furthermore, Richard, Szegethy, Lichter, Schiffer, & Kurlan (1999) found that PD patients are as susceptible to yohimbine-induced panic attacks as patients with panic disorder. Lauterbach et al. (2003) proposed that the relationship between panic attacks and PD could be influenced by dysfunction of the locus coeruleus. Indeed, there is evidence of disturbance in the dorsal ascending noradrenergic pathway in PD, a pathway that begins in the locus coeruleus (Weiner & Lang, 1995). Dopaminergic deficits may

exist in mesolimbic regions of the brain in addition to depletion in the basal ganglia,

providing a viable explanation for the high rates of anxiety symptoms (Agid et al., 1989).

Anxiety and Cognition

Eysenck (1979) theorized that task-irrelevant activity related to anxiety impairs

cognitive performance. According to this assertion, task-irrelevant activity, such as

worry, detracts from working memory performance by taking up space in the processing

system. Indeed, subjects with anxiety have been shown to have greater problems on tasks

of working memory than non-anxious subjects (Firetto & Davey, 1971). There is also

experimental evidence of task distraction due to a state of anxiety (Deffenbacher, 1978).

Some researchers examining the association between anxiety and

neuropsychological performance suggest that the detrimental effects of anxiety may

extend beyond problems with working memory and distraction. Indeed, patients with

diagnosed anxiety disorders, such as panic disorder and obsessive-compulsive disorder,

have displayed evidence of impaired intellectual performance on measures of attention,

motor speed, verbal fluency, and memory (Orsillo & McCaffrey, 1992). In addition,

Vasterling, Brailey, Constans, & Sutker (1998) found a pattern of neuropsychological

impairment suggestive of difficulty filtering irrelevant information and executive

dysfunction in PTSD subjects.

Differentiating the Effects of Depression and Anxiety: The Tripartite Model

There is compelling evidence that a strong association exists between depression

and anxiety. Clark and Watson (1990) determined that among a range of clinical and non-

clinical samples, correlations between self-report scales of depression and anxiety range

from .40 to.70. It has been argued that these two constructs conceptually overlap to such

a degree that essentially, they could be considered different aspects of the same broad disorder (Foa & Foa, 1982).

Alternatively, it has been argued that real differences may exist, but many current measurement tools are limited in their assessment of the constructs. Several researchers propose that while these psychological states do overlap considerably, there are also distinct components that differentiate depression and anxiety. Clark and Watson (1991) proposed the Tripartite Model to account for these distinctions. According to this model, depression is uniquely associated with low levels of positive affect and anxiety is uniquely associated with autonomic arousal. The high correlation between depression and anxiety is driven by a shared construct of general distress, which describes an overall vulnerability to experience a range of negative feelings. Clark and Watson's (1991) theory has been tested and these studies provide strong evidence to support the model (Joiner, 1996; Brown, Chorpita, & Barlow, 1998; Keogh & Reidy, 2000).

Beuke, Fischer, & McDowall (2003) highlight the methodological limitations of studies that fail to examine both constructs. Given the strong overlap between depression and anxiety, a study that finds an effect between depression and cognitive functioning must also measure anxiety to rule it out as a possible explanation for the finding. Despite the clear importance of this recommendation, anxiety and depression are still commonly studied in isolation and the measurement of both constructs has not become a uniformly adopted procedure in the literature. Most studies of PD patients that examine the influence of affect on cognitive performance include measures of depression, but not anxiety (e.g., Huber et al., 1988; Mayeux et al., 1981; Taylor et al.,1986; Troster et al., 1995).

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Differentiating the Effects of Depression and Anxiety in PD

Only two studies have been found that examine how anxiety and depression both are independently related to cognitive functioning in PD (Hanna, 2006; Ryder et al., 2002). In an unpublished dissertation study, Hanna (2006) used the BAI and BDI to assess for depression and anxiety in 30 individuals with PD. Cognitive functioning was assessed in the domains of executive functioning, processing speed, visuospatial ability, and memory using an extensive battery of neuropsychologial tests. Correlational analyses revealed that anxious symptoms were significantly and negatively correlated with a measure of working memory (Digit Span Forward), processing speed (Digit Symbol), and memory (CVLT Long Delay Free Recall). These effects remained after applying Bonferroni's correction and after controlling for depression using partial correlation analyses. However, the interpretation of these findings is limited in that regression analyses were not conducted and the sample size was compromised. The 30 participants did not complete the full battery of neuropsychological tests, so the sample size for each group ranged from 15 to 29.

Ryder et al. (2002) assessed 27 male subjects with idiopathic PD using the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), the Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1995), and the State-Trait Anxiety Inventory (STAI; Spielberger, 1983). Neuropsychological measures consisted of the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), a measure of overall cognitive status, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), a brief battery assessing language, attention, visuospatial perception, and memory. Stepwise and hierarchical

regression analyses were performed to determine the contribution of depression and anxiety on cognitive functioning. Neither measure of cognitive functioning was significantly associated with depression, but anxiety accounted for a significant portion of the variance in all RBANS indices except for Attention. These authors suggest that anxiety could be a more accurate predictor of cognitive functioning than depression in PD patients.

Although raising important theoretical questions, the Ryder et al. (2002) study was limited in several ways. First, the BDI-II includes items that assess somatic symptoms of depression, and may not be ideally suited for the PD population. Taylor, Lovibond, Nicholas, Cayley, & Wilson (2005) underscore two drawbacks of including somatic items to assess depressed patients with medical illness. First, these patients may experience somatic symptoms due to disturbances unrelated to depression. Thus, scores on depression measures may become inaccurately inflated. Second, recent work suggests that somatic items may not be specific indicators of depression and that these symptoms are also common in anxious patients (Watson, Clark, & Weber, 1995).

Another limitation of the Ryder et al. (2002) study is that the BDI-II and STAI were not specifically designed to discriminate between depression and anxiety and may have overlapping items. Also, this study primarily assessed Caucasian males, limiting the generalizability of the results. Finally, the authors did not examine executive functioning. Given that there is considerable evidence of executive impairments early in the course of PD, and depressed and anxious individuals are also sensitive to executive dysfunction, future research in this area should include an executive measure.

Summary

It is well established that patients with PD suffer from a variety of cognitive impairments. PD patients demonstrate a pattern of pronounced difficulties on tasks involving executive functioning and memory abilities. In addition, it is common for individuals with PD to experience psychiatric complications. The relationship between depression, anxiety, and cognitive functioning in PD patients has not yet been adequately established. A sizable amount of research suggests that PD depression is related to overall cognitive impairment. Some studies have employed comprehensive neuropsychological batteries and indicate that depression augments preexisting cognitive dysfunction in PD patients. To date, only a few studies have examined the unique impact of anxiety in relation to cognitive impairments in PD. The focus of the present study is to reexamine the unique influences that depression and anxiety each contribute to cognitive impairment in PD patients.

It is possible that the established relationship between depression and cognition could be influenced by a third variable. It has been established that there is a high degree of overlap between depression and anxiety in patients with PD. The comorbidity of depressive and anxious symptoms appears to be quite common, even in normal populations, but is particularly prevalent in PD patients. In addition, many studies have indicated that anxiety can have a negative impact on cognition in other populations.

Despite the high rate of comorbidity and the demonstrated influence of anxiety on cognitive functioning, most studies of PD patients have neglected to separate out the unique effects of depression and anxiety. In fact, only one study of this nature has been uncovered in the PD literature. Ryder et al. (2002) concluded that depression is not

significantly related to cognition in PD patients and instead that anxiety is negatively

correlated with cognitive performance. Anxiety was a significant predictor of decrements

on memory, visuospatial, and language tasks. However, Ryder et al. (2002) did not

examine executive functioning and the mood measures employed may have been limited

in properly discriminating between depression and anxiety in PD subjects.

The present study seeks to extend the findings of Ryder et al. (2002). The

proposed project aims to address the inconsistencies in the literature regarding depression

and cognition by examining the independent influence of depression on memory and

executive functioning in PD. This project will also examine the independent effect of

anxiety on memory and executive functioning using a mood measure designed to

maximally discriminate between depression and anxiety.

Hypotheses and Predictions

The level of depressive symptoms in idiopathic PD patients will be measured. It is

hypothesized that depressive symptoms will influence executive functioning and memory

performance. It is predicted that patients who report higher levels of depressive

symptoms will experience greater decrements in executive functioning and memory. This

prediction is based on the results of several studies finding that patients with PD and

major depression had significantly more pronounced impairment in tasks related to

executive functioning (Kuzis et al., 1997; Starkstein et al., 1989; Wertman et al., 1993).

In addition, numerous studies have found a linkage between severity of depression and

tasks related to memory performance in PD patients (Mayeux et al., 1981; Troster et al,

1995a; Troster et al., 1995).

The level of anxious symptoms in idiopathic PD patients will be measured. It is hypothesized that anxiety will also influence performance on measures of executive functioning and memory. It is predicted that high anxiety levels will be significantly related to greater impairment on measures of executive functioning and memory. This prediction is partially supported by the findings of Ryder et al. (2002), who reported that anxiety is a significant predictor of difficulties in immediate and delayed memory functioning in PD patients. Past studies have suggested that anxiety is linked to diminished working memory and attentional capacities in subjects without neurological illness (Eysenck and Calvo, 1992). Given that memory and attention are fundamental components of higher-order processes such as executive functioning, it also predicted that anxiety- related deficits would be observed within this domain.

Method

Participants

The sample consisted of 68 individuals diagnosed with idiopathic PD. An a priori power analysis was conducted to determine the number of participants in the sample required for adequate power. A medium effect size (d = .15) was assumed for this study. Power analysis using the G-Power computer program (Faul & Erdfelder, 1992) revealed that 68 participants yield a power of .80 given an effect size of d = .15.

The primary investigator excluded patients with a history of stroke, a history of drug and alcohol abuse, psychiatric diagnoses other than anxiety and depression, patients receiving chemotherapy treatment for a diagnosis of cancer, uncontrolled diabetes, seizures, and PD due to environmental exposure to toxins. One patient indicated that there was some possible, but questionable, manganese exposure and one patient had experienced mercury poisoning. Patients were excluded if they had experienced head trauma involving loss of consciousness lasting longer than 10 minutes. Three patients reported a remote history of head injury but there were no lasting cognitive changes. Patients were excluded if the treating neurologist indicated that clinical signs of atypical PD were present and if the patient had not responded well to levadopa therapy. One patient that was included had some atypical signs, but responded well to medication.

Subjects were also excluded if they were unable to speak English fluently. Several participants spoke English as a second language; three individuals spoke Spanish as their first language, one participant spoke Russian as a first language, and one participant

spoke Polish as a first language. An attempt was made to exclude individuals with early-onset PD, defined as age of onset less than or equal to 50 years of age (Marder et al., 2003). Due to recruitment difficulties, five individuals that were diagnosed before age 50 were included in the sample. Patients with a history of myocardial infarction were excluded if the treating neurologist, or the medical record, indicated that the event impacted cognition. Three individuals in the sample had experienced a heart attack in the past and two participants had experienced a transient ischemic attack. Patients with a history of other neurological conditions or neurosurgical surgery to alleviate PD symptoms were generally excluded, although one patient with a deep brain stimulator implant was allowed to participate and one patient had bilateral grafts of fetal cells implanted into the striatum and substantia nigra.

The inclusion criteria for age spanned from 55 to 85 years to cover the normal age range of patients with PD. The final sample ranged in age from 56 to 82 years old (M = 69.85, SD = 6.99) and consisted of 45 (33.8%) males and 23 (66.2%) females. Sixty-three (92.6%) subjects were Caucasian, four (5.9%) were Hispanic, and one (1.5%) was African-American. Years of education ranged from 12-22 years (M = 15.60, SD = 2.58). Age at diagnosis ranged from 39-78 (M = 63.22, SD = 9.11). Disease duration (from the time of diagnosis to the time of testing) ranged from less than one year since diagnosis to 24 years since diagnosis (M = 6.78, SD = 5.07). Thirty-two patients reported that motor symptoms began on the left side of their body. Thirty-two patients reported that symptoms originated on the right side and four patients did not report this information. Fifteen (22.1 %) patients were classified in Stage I of the disease, meaning that motor symptoms were mild and unilateral. Thirty-two (47.1%) patients were classified in Stage

II, meaning that symptoms were bilateral but posture was not yet affected. Nine patients

(13.2%) were classified in Stage III, meaning that balance and postural difficulties had

begun but the patient remained functionally independent. Staging data was not reported

for twelve participants. There were no patients included from the most advanced disease

stages (Stage IV and Stage V).

Scores on the Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh,

1975) ranged from 24-30 ($M = 28.13$, $SD = 1.67$). Folstein et al. (1975) has suggested

that a score of less than 24 on the MMSE indicates the possibility that dementia is

present. Subjects enrolled in the study were screened based on their MMSE score, with a

cutoff of 24, to exclude any patients with possible dementia.

Medications that patients were taking were recorded at the time of testing, and

medications that could be associated with changes in cognitive functioning were

examined for group differences. Fourteen patients were taking antidepressants, 4 patients

received acetylcholinesterase inhibitors to prevent the progression of cognitive decline,

and 8 patients were taking anxiolytics (benzodiazepines). Five patients were given

anticholinergics, 12 patients were taking selegiline, 14 patients received amantadine, and

3 patients were taking seroquel to control hallucinations. Fifty-three patients were taking

direct dopamine agonists to control the motor symptoms associated with PD.

To prevent the occurrence of Type 1 error rates, only the HVLT Delayed Recall

Index was included in the analyses examining the influence of medication on cognition.

T-test analyses were conducted and no significant cognitive differences were found to be

associated with the use of antidepressants, acetylcholinesterate inhibitors, anxiolytics,

selegiline, amantadine, seroquel, or direct dopamine agonists.

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The difference in group means for patients taking anticholinergics was approaching significance ($M = 9.20 \pm 2.17$ vs. $M = 7.06 \pm 2.37$, $t(67) = 1.95$, $p = .06$). The group mean of patients receiving anticholinergics was higher, and a higher score on the HVLT is associated with better memory performance. One of the side effects of anticholinergics is memory impairment, so the direction of group differences is unexpected. The patient subgroups did not differ in stage of disease, age, education, disease duration, or levels of depression and anxiety.

Materials and Procedure

Participants were recruited from the Department of Neurology at the University of South Florida, the Movement Disorders Clinic at Tampa General Hospital, local support groups, and seminars. Most of the patients were invited to participate during regular patient visits, either by their treating neurologist or by the primary investigator. Information on patient characteristics and medical history was initially gathered through chart review. Board-certified neurologists had previously determined diagnosis and staging of PD and this history was recorded from the patient's medical chart. To ensure that the information was current and accurate, the researcher confirmed the staging classification and the diagnosis of idiopathic PD by consulting with the treating neurologist at the time of the appointment. Patients were also asked to self-report on any additional information that was needed.

After giving informed consent, participants were screened with the MMSE to ensure that they met basic cognitive requirements. Next, subjects were asked to fill out a self-report measure to determine their affective status. Following this, cognitive

functioning was examined through tests of memory and executive functioning. The memory measure was administered first followed by the executive measure.

Measures

The MMSE is a brief screening measure that can be used to evaluate general cognitive status. Tasks that the patient is required to perform fall into eleven categories: orientation to time, orientation to place, registration, attention, recall, naming, repetition, comprehension, reading, writing, and drawing. Patients can be classified into one of four categories of cognitive performance based on scores: normal, mild cognitive impairment, moderate cognitive impairment, and severe cognitive impairment.

The Depression Anxiety Stress Scales (DASS) is a self-rating scale developed by Lovibond & Lovibond (1995a) in an attempt to maximally discriminate between the constructs of depression, anxiety, and stress. The instrument consists of 42 total items on a 4-point scale, 14 items belonging to the anxiety scale (DASS-A), 14 items on the depression scale (DASS-D), and 14 items on the stress scale (DASS-S). In addition, the DASS contains various subscales, making it possible to measure specific components of anxiety, depression, and stress. The DASS-D includes subscales of Dysphoria, Hopelessness, Devaluation of Life, Self-Deprecation, Lack of Interest/Involvement, Anhedonia, and Inertia. The DASS-A contains subscales of Autonomic Arousal, Skeletal Muscular Effects, Situational Anxiety, and Subjective Experiences of Anxious Affect. The DASS-S contains subscales of Difficulty Relaxing, Nervous Arousal, Easily Upset/Agitated, Irritable/Overreactive, and Impatient.

Factor analytic studies indicate that the DASS adequately discriminates between these emotional states and supports the theoretical underpinnings of the tripartite model

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(Antony, Bieling, Cox, Enns, & Swinson, 1998; Lovibond, 1998). The DASS-D only contains features that are unique to depression, focusing on a lack of positive affect. The DASS-A assesses symptoms that are unique to anxiety that deal with autonomic arousal. The DASS-S examines symptoms that are common to both depression and anxiety and these items focus on a general negative irritability.

All three scales of the DASS have demonstrated satisfactory reliability in both clinical and non-clinical samples. The internal consistency for the Depression, Anxiety, and Stress scales is reported to be .91, .84, and .90 in a normal sample (Lovibond & Lovibond, 1995b). In a clinical sample, it is reported to be .96, .89, and .93, respectively (Brown, Chorpita, Korotitsch, & Barlow, 1997). Lovibond and Lovibond (1995b) reported that the DASS demonstrates adequate convergent validity. In a student sample, the DASS-A and BAI were highly correlated ($r = .81$), and the DASS-D and BDI were also highly correlated ($r = .74$). The DASS demonstrated adequate discriminant validity as well. Comparatively, the correlations were lower between the DASS-D and BAI ($r = .54$), and the DASS-A and BDI ($r = .58$).

All subjects were given the Wisconsin Card Sorting Test-64 Card Version (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2000). The WCST-64 is a shortened version of the Wisconsin Card Sorting Test, Revised and Expanded (WCST; Heaton, Chelune, Talley, Kay, and Curtiss, 1993), one of the most widely used measures of executive functioning. The WCST-64 was administered to reduce administration time. This test is identical in content to the WCST except that 64 cards are administered instead of 128 cards.

The test provides detailed feedback regarding specific aspects of problem-solving abilities, such as inefficient initial conceptualization, perseveration, failure to maintain a cognitive set, and inefficient learning. Separate scoring indices can be calculated for each of these concepts. Evidence suggests that WCST scores provide a sensitive measure of brain dysfunction, particularly executive dysfunction (Robinson, Heaton, Lehman, & Stilson, 1980).

Materials consist of one deck of 64 response cards and four stimulus cards for each deck. The form, color, and number of figures printed on the stimulus cards and response cards can vary. Subjects must match each of the response cards to one of the four stimulus cards and the examiner gives feedback regarding whether the match is correct. Correct responses are based on a sorting principle of form, color or, number. The participant is not informed of the sorting principle and must figure this out based on feedback from the examiner. The examiner changes the sorting principle when the subject has achieved ten correct consecutive responses. The subject is also not informed of the change in sorting rule.

Axelrod, Goldman, and Woodard (1992) examined reliability of the standard version of the WCST, and found that interscorer reliability was between .88 and .93, while intrascorer reliability was between .91 and .96. However, test-retest reliability was found to be moderate, ranging from .39 to .72 (mean .57, median .60). Perseverative Responses and Percent Perseverative Errors subscales had lower reliability estimates. Normative data have also been developed for use with the short form of the WCST (Kongs, et al., 2000). It has been found that reliability and validity estimates for the WCST-64 are comparable to that of the original WCST (Greve, 2001)

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The test has been found to be valid in many different clinical populations, including patients with PD (Bowen, Kamienny, Burns, & Yahr, 1975; Pillon, Dubois, Lhermitte, & Agid, 1986). In particular, PD patients have been shown to have difficulty with set maintenance and perseveration on the WCST (Taylor, Saint-Cyr, & Lang, 1986a). Furthermore, Paolo, Axelrod, Troster, Blackwell, and Koller (1996) found that the WCST-64 version was also sensitive to the executive impairments of PD patients without dementia.

The Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretlen, Groninger, Brandt, 1998) is a verbal learning and memory test that consists of a list of 12 words, each belonging to one of three semantic categories. There are three immediate memory trials, one delayed recall, and a recognition trial. For the immediate memory trials, the same list of words is read and the patient is prompted to immediately recall as many words as possible. The patient is also asked to recall as many words from the list as they are able to after a delay of 20-25 minutes. Finally, a list of 24 words is read and the individual is asked to indicate whether these words had appeared on the prior list. Total Recall, Delayed Recall, Retention %, and Recognition Discrimination scores are calculated to measure performance. Six different forms of the test are available. An alternate form was administered in this study to safeguard against the possibility that subjects have taken the HVLT before.

Benedict et al. (1998) tested a sample of elderly adults and found that test-retest reliability was .74 for Total Recall, .66 for Delayed Recall, and .40 for Recognition Discrimination. Benedict and Zgaljardic (1998) found that practice effects are minimal when alternate forms of the HVLT-R are utilized. In addition, it appears that the HVLT-

R is a valid measure for use with elderly subjects with cognitive difficulties (Shapiro, Benedict, Schretlen, & Brandt, 1999). The HVLT-R was found to correlate highly with comparable indices from the Logical Memory and Visual Reproductions subtests of the WMS-R, demonstrating adequate construct validity.

Data Analyses

Four separate hierarchical regression analyses were performed with scores from the WCST-64 (Total Number of Categories Completed) and HVLT-R (Total Raw Score Trials 1-5) as criterion variables. DASS-D (Depression scale) and DASS-A (Anxiety scale) served as predictors for all analyses. In the first two analyses, executive functioning performance (as measured by the WCST-64) served as the dependent variable. The Number of Categories Completed index of the WCST-64 was selected as the dependent variable because it reflects the ability to shift set from one activity to the next. Past research shows that PD patients are particularly sensitive to this type of task (e.g., Cools et al., 2001). Two separate hierarchical regression analyses were conducted to examine the amount of added, unique variance accounted for by anxiety when depression is entered as the first predictor, and also to examine the amount of added, unique variance accounted for by depression when anxiety is entered as the first predictor.

Memory performance (as measured by the HVLT-R) served as the dependent variable in two additional hierarchical regression analyses. The Total Recall score of the HVLT-R was selected as the dependent variable because prior research has shown that PD patients have, in general, more pronounced impairments on immediate memory tasks compared to delayed memory tasks (Sagar et al., 1988a). Two hierarchical regression

analyses were conducted to examine the amount of added, unique variance accounted for by anxiety when depression is entered as the first predictor, and also to examine the amount of added, unique variance accounted for by depression when anxiety is entered as the first predictor.

It was hypothesized that patients who report higher levels of depressive symptoms would receive lower scores on tests of executive functioning and memory. Second, it was hypothesized that patients who report higher anxiety levels would receive lower scores on measures of executive functioning and memory.

Results

Data Check

　　The dataset was checked for errors and missing scores and seven cases were found to have missing data. The missing scores were from the DASS and six participants skipped one item as they were filling in the self-report measure. One participant skipped three items. Each missing item was filled in by substituting the participant's mean score of the subscale for that particular item.

Descriptives of Cognitive and Behavioral Variables

　　Table 1 reveals the descriptive statistics for the DASS, HVLT, and WCST using untransformed scores. The DASS Depression, Anxiety, and Stress scores from the PD sample were compared to a normative sample of 2914 healthy adults, ranging in age from 17 to 69 years (Lovibond & Lovibond, 1995a; see Table 9, Table 10). Although scores from the normative sample were stratified by gender and age, the overall sample mean and standard deviation were used to calculate T-scores. Lovibond and Lovibond (1995a) indicated that gender and age differences in the normative sample are small. In addition, age stratification of the normative sample was only conducted up to age 59, and the PD sample in this study extends to age 85. According to the DASS severity ratings, the Depression T-score mean of 48.88 falls within normal ranges (46th percentile), as well as the Anxiety T-score mean of 54.95 (69th percentile), and the Stress T-score mean of 46.64 (38th percentile). The Anxiety Raw Score mean of 7.13 is at the cutoff point between

normal and mild levels of anxiety. The Depression Raw Score mean of 5.56 and the

Stress Raw Score mean of 7.46 fall well within the normal range.

The WCST Perseverative Errors scores and WCST Categories Completed scores

from the PD sample were compared to a normative sample of 899 healthy adults, 20

through 89 years of age (Heaton et al., 1993; see Appendix C). The T-scores for the

Perseverative Errors Index were calculated by adjusting for age and education. The

Perseverative Errors T-score mean of 47.88 was in the Average Range (42nd percentile).

The T-scores for the Categories Completed Index were calculated by adjusting for age.

The Categories Completed T-score mean of 38.63 was in the Low Normal Range (14th

percentile).

The HVLT Total Recall and Delayed Recall scores from the PD sample were

compared to a normative sample of 1,179 healthy adults ranging in age from 16 to 92

years. For each PD patient, a T-score was calculated, adjusting for age and education.

The Total Recall T-score mean of 43.25 fell within the Low Normal Range (24th

percentile). The Delayed Recall T-score mean of 43.32 also fell within the Low Normal

Range (24th percentile).

Table 2 shows the percentage of patients in the normal, mild, moderate, severe,

and extremely severe ranges on the DASS scales. Using raw scores, Table 3 shows the

correlations between the DASS scales and cognitive variables. Table 4 reports the

correlations between demographic variables (age, years of education, and disease

duration) and cognitive variables (raw scores). Table 5 shows the correlations between

the demographic variables and the raw scores of the DASS. Table 6 shows how the

DASS scales (DASS-D, DASS-A, and DASS-S) correlate with each other using raw

scores. Pearson correlations are reported as logarithmic transformation was conducted on variables with skewed distributions to meet parametric assumptions. This data transformation is explained in more detail below.

Regression Analyses

The dataset was screened to determine if the assumptions of regression had been met. Collinearity statistics were calculated in SPSS (tolerance = .72, VIF = 1.39), and multicollinearity did not appear to be a problem in this dataset. Skewness and kurtosis appeared to be present in the distributions of several variables by examining histograms and boxplots. The distributions for DASS-D, DASS-A, DASS-S, and WCST Perseverative Errors were positively skewed. The skewness test statistic for DASS-D was 1.45 ($SE = .29, z = 4.97, p < .001$), and the kurtosis test statistic was 1.21($SE = .57, z = 2.10, p < .05$). The skewness test statistic for DASS-A was 1.14 ($SE = .29, z = 3.93, p < .001$). The skewness test statistic for DASS-S was .71 ($SE = .29, z = 2.43, p < .05$). The skewness test statistic for WCST Perseverative Errors was 1.29 ($SE = .29, z = 4.43, p < .001$). The kurtosis test statistic for WCST Categories Completed was –1.24 ($SE = .57, z = -2.16, p < .05$).

A logarithmic data transformation was conducted on the skewed and kurtotic variables to reduce the influence of the outliers. With the transformation, the DASS-D skewness test statistic was reduced to .07 ($SE = .29, z = .24$), and kurtosis test statistic was reduced to -.833 ($SE = .57, z = -1.46$). The logarithmic transformation changed the DASS-A skewness test statistic to -.01 ($SE = .29, z = -.05$), the DASS-S skewness test statistic changed to -.48 ($SE = .29, z = -1.65$), and the WCST Perseverative Errors test statistic changed to .18 ($SE = .29, z = .62$). For WCST Categories Completed, the kurtosis

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test statistic of −1.22 (SE = .57, z = -2.14, p < .05) was similar in magnitude to the original test statistic, so the variable was not transformed. Through examination of histograms and boxplots, all variables appeared to be normally distributed, with the exception of the mild kurtosis on the WCST Categories Completed Index.

The logarithmic transformation of DASS-D, DASS-A, DASS-S, and WCST Perseverative Errors were used in all regression analyses. HVLT Total Recall, HVLT Delayed Recall, and WCST Categories Completed were not transformed in the regression analyses.

Finally, scores on the cognitive measures were adjusted to account for age and education by conversion from raw scores to T-scores, as reported above and listed in Table 1. There were no significant differences in the regression findings based on age and education adjustment, so the raw scores are reported for all hierarchical regression analyses.

HVLT-R Total Recall. Linear regression analyses were performed to investigate how depression and anxiety scores predict performance on the HVLT-R Total Recall Index. The predictor variables were entered into the regression equation hierarchically. See Table 7 and Table 8 for a summary of the regression findings.

In the first analysis, depression was the first predictor entered and anxiety was entered second. Depression did not significantly predict HVLT-R Total Recall scores, β = -.23, $t(66)$ = -1.60, p = .11. The proportion of variance explained by depression was not significant, R^2 = .03, $F(1, 67)$ = 2.15, p = .15. Anxiety also did not significantly predict HVLT-R Total Recall scores, β = .10, $t(66)$ = .69, p = .49. The proportion of variance explained by anxiety was not significant, R^2 = .01, $F(1, 66)$ = .48, p = .49.

In the second analysis, anxiety was the first predictor entered and depression was entered second. Anxiety did not significantly predict HVLT-R Total Recall scores, $\beta = -.13$, $t(66) = .93$, $p = .35$. The proportion of variance explained by anxiety was not significant, $R^2 = .002$, $F(1, 67) = .16$, $p = .69$. Depression also did not significantly predict HVLT Total Recall scores, $\beta = -.16$, $t(66) = -1.10$, $p = .28$. The proportion of variance explained by depression was not significant, $R^2 = .018$, $F(1, 66) = 1.21$, $p = .28$.

WCST-64 Categories Completed. Linear regression analyses were conducted to examine how depression and anxiety scores predict performance on the WCST-64 Categories Completed Index. The predictor variables were entered into the regression equation hierarchically. See Table 9 and Table 10 for a summary of the regression findings.

In the first analysis, depression was the first predictor entered and anxiety was entered second. Depression did not significantly predict WCST-64 Categories Completed scores, but there was a trend toward significance, $\beta = -.25$, $t(66) = -1.78$, $p = .08$. The proportion of variance explained by depression approached significance, $R^2 = .05$, $F(1, 67) = 3.58$, $p = .06$. Anxiety did not significantly predict WCST-64 Categories Completed scores, $\beta = .05$, $t(66) = .35$, $p = .73$. The proportion of variance explained by anxiety was not significant, $R^2 = .002$, $F(1, 66) = .12$, $p = .73$.

In the second analysis, anxiety was the first predictor entered and depression was entered second. Anxiety did not significantly predict WCST-64 Categories Completed scores, $\beta = .05$, $t(66) = .35$, $p = .73$. The proportion of variance explained by anxiety was not significant, $R^2 = .01$, $F(1, 67) = .48$, $p = .49$. Depression did not significantly predict WCST-64 Categories Completed scores, but there was a trend toward significance, $\beta = -$

.25, $t(66)$ = -1.78, p = .08. The proportion of variance explained by depression

approached significance, R^2 = .05, $F(1, 66)$ = 3.16, p = .08.

Ancillary Analyses

The original hypotheses and predictions were not supported; therefore, further

exploration of the data was performed. The influence of depression and anxiety on the

Delayed Recall Index of the HVLT-R was examined. See Table 11 and Table 12 for a

summary of the regression findings. The effect of depression and anxiety on the

Perseverative Errors Index of the WCST-64 was also investigated. See Table 13 and

Table 14 for a summary of the regression findings.

HVLT-R Delayed Recall. It appears that depression may exert its greatest

influence at a later point in memory during delayed recall. In the first analysis, depression

was the first predictor entered and anxiety was entered second. Depression significantly

predicted HVLT-R Delayed Recall scores, β = -.33, $t(66)$ = -2.39, p <.05. Depression also

explained a significant proportion of variance in HVLT-R Delayed Recall scores, R^2 =

.10, $F(1, 67)$ = 7.06, p < .05. Anxiety did not significantly predict HVLT-R Delayed

Recall scores, β = .04, $t(66)$ = .30, p = .77. The proportion of variance explained by

anxiety was not significant, R^2 = .001, $F(1, 66)$ = .09, p = .77.

In the second analysis, anxiety was the first predictor entered and depression was

entered second. Anxiety did not significantly predict HVLT-R Delayed Recall scores, β =

.04, $t(66)$ = .30, p = .77. The proportion of variance explained by anxiety was not

significant, R^2 = .02, $F(1, 67)$ = 1.24, p = .27. Depression significantly predicted HVLT-R

Delayed Recall scores, β = -.33, $t(66)$ = -2.39, p < .05. Depression also explained a

significant proportion of the variance in HVLT-R Delayed Recall scores, $R^2 = .078$, $F(1, 66) = 5.73$, $p < .05$.

WCST-64 Perseverative Errors. In the first analysis, depression was the first predictor entered and anxiety was entered second. Depression did not significantly predict WCST Perseverative Errors scores, $\beta = .14$, $t(66) = .10$, $p = .32$. The proportion of variance explained by depression was not significant, $R^2 = .01$, $F(1, 67) = .98$, $p = .33$. Anxiety also did not significantly predict WCST Perseverative Errors scores, $\beta = -.04$, $t(66) = -.31$, $p = .76$. The proportion of variance explained by anxiety was not significant, $R^2 = .001$, $F(1, 66) = .09$, $p = .76$.

In the second analysis, anxiety was the first predictor entered and depression was entered second. Anxiety did not significantly predict WCST Perseverative Errors scores, $\beta = -.04$, $t(66) = -.31$, $p = .76$. The proportion of variance explained by anxiety was not significant, $R^2 = .001$, $F(1, 67) = .07$, $p = .79$. Depression did not significantly predict WCST Perseverative Errors scores, $\beta = .14$, $t(66) = .10$, $p = .32$. The proportion of variance explained by depression was not significant, $R^2 = .02$, $F(1, 66) = .99$, $p = .32$.

Age Effects. Age effects on cognitive variables are well known in the literature, and therefore, the influence of this variable was examined in more detail. Age was significantly correlated with all four of the cognitive variables, so age was entered as a predictor into the regression model to examine the specific influence of age on each of the four cognitive variables in four separate hierarchical regressions. Entered alone, age significantly predicted HVLT-R Total Recall scores ($\beta = -.28$, $t(66) = -2.38$, $p < .05$), HVLT-R Delayed Recall scores ($\beta = -.35$, $t(66) = -3.07$, $p < .01$), WCST Perseverative

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Errors scores ($\beta = .38$, $t(66) = 3.38$, $p < .01$), and WCST Categories Completed scores ($\beta = -.34$, $t(66) = -2.91$, $p < .01$).

Another hierarchical regression analysis was conducted to determine if depression was a significant and unique predictor of HVLT-R Delayed Recall Scores, above and beyond the effects of age (see Table 15). Age was entered into the regression model as the first predictor, and depression was entered as the second predictor. Age significantly predicted HVLT-R Delayed Recall scores, $\beta = -.30$, $t(66) = -2.57$, $p < .05$. Age explained a significant proportion of variance in HVLT-R Delayed Recall scores, $R^2 = .12$, $F(1, 67) = 9.43$, $p < .01$. Depression significantly predicted HVLT-R Delayed Recall scores, $\beta = -.24$ $t(66) = -2.09$, $p < .05$. The proportion of variance explained by depression was significant, $R^2 = .05$, $F(1, 66) = 4.37$, $p < .05$.

Subscales. The DASS-D, DASS-S, and DASS-A subscales were examined for significant correlations with cognitive variables (see Table 16, Table 17, and Table 18). These analyses are considered to be purely exploratory, and therefore, a correction for experimenter-wise error was not implemented. Spearman's rho correlations were reported because the data was not transformed for each subscale and parametric assumptions may have been violated. See Appendix A, Appendix B, and Appendix C for a list of items in the Depression, Anxiety, Stress scales that are organized by subscale.

For the DASS-D, Hopelessness ($r = -.31$, $p < .05$), Devaluation of Life ($r = -.27$, $p < .05$), and Anhedonia ($r = -.28$, $p < .05$) were significantly correlated with HVLT-R Delayed Recall. The correlation between the Inertia subscale and HVLT-R Delayed Recall approached significance ($r = -.22$, $p = .07$). The Self-Deprecation subscale was significantly correlated with WCST Perseverative Errors ($r = .24$, $p < .05$) and the

correlation between the Hopelessness subscale and WCST Perseverative Errors approached significance ($r = .21, p = .09$). The correlation between the Self-Deprecation subscale and WCST Categories Completed approached significance ($r = -.21, p = .08$).

For DASS-A, the Subjective Experience of Anxious Affect subscale was significantly correlated with HVLT-R Delayed Recall ($r = -.25, p < .05$). The correlation between the Situational Anxiety subscale and HVLT-R Delayed Recall approached significance ($r = -.21, p = .09$). The Situational Anxiety subscale correlated significantly with WCST Categories Completed ($r = -.27, p < .05$). The correlation between the Subjective Experience of Anxious Affect subscale and WCST Categories Completed approached significance ($r = -.22, p = .08$). The Subjective Experience of Anxious Affect subscale correlated significantly with WCST Perseverative Errors ($r = .25, p < .05$).

For the DASS-S, Difficulty Relaxing ($r = -.27, p < .05$), Easily Upset/Agitated ($r = -.42, p < .0001$), Irritable/Overreactive ($r = -.29, p < .05$), and Impatience ($r = -.28, p < .05$) subscales were significantly correlated with HVLT-R Delayed Recall. Easily Upset/Agitated ($r = -.34, p < .01$) Irritable/Overreactive ($r = -.28, p < .05$), and Impatience ($r = -.24, p < .05$) subscales were significantly correlated with HVLT-R Total Recall. Easily upset/Agitated ($r = -.28, p < .05$) and Irritable/Overreactive ($r = -.33, p < .01$) subscales were significantly correlated with WCST Categories Completed.

Table 1. Descriptive Statistics

Measures	Min	Max	Mean(Raw)	SD(Raw)	Mean(T)	SD(T)
DASS						
Depression	0	26	5.56	6.22	48.88	8.92
Anxiety	1	22	7.13	5.05	54.95	10.29
Stress	0	23	7.46	6.13	46.64	7.76
HVLT						
Total Recall	8	33	21.28	5.83	43.25	10.92
Delayed Recall	1	12	7.19	2.41	43.32	9.49
WCST						
Categories Completed	0	5	2.06	1.71	38.63	9.86
Perseverative Errors	4	46	13.84	8.92	47.88	15.34

Table 2. Distribution of Patients in the DASS Severity Ranges

Scale	Percentage
Depression Scale	
Normal	80.9%
Mild	2.9%
Moderate	14.7%
Severe	1.5%
Extremely Severe	0.0%
Anxiety Scale	
Normal	63.2%
Mild	10.3%
Moderate	14.7%
Severe	8.9%
Extremely Severe	2.9%
Stress Scale	
Normal	85.3%
Mild	7.3%
Moderate	7.4%
Severe	0.0%
Extremely Severe	0.0%

Table 3. Correlations between DASS Scales and Cognitive Variables (Pearson)

	Total	Categories	Delayed	PersErrors
DASS-D	-.18	-.23	-.31**	.12
DASS-A	-.02	-.08	-.14	.03
DASS-S	-.20	-.19	-.28*	.09

Note. Total=HVLT Total Recall, Categories=WCST Categories Completed,
Delayed=HVLT Delayed Recall, PersErrors=WCST Perseverative Errors.
*$p < .05$, **$p < .01$.

Table 4. Correlations between Demographic and Cognitive Variables (Pearson)

	Total	Categories	Delayed	PersErrors
Age	-.28*	-.34**	-.35**	.38**
Education	-.03	-.02	.03	-.07
Disease Duration	.10	.12	.12	-.12
Stage of Disease	-.23	-.12	-.26*	.03
Gender	.34**	.02	.28*	.08
Race	-.18	-.06	-.11	.15
Side of Onset	.05	-.08	.07	.10
MMSE	.43**	.28*	.47**	-.34**

Note. Total=HVLT Total Recall, Categories=WCST Categories Completed,
     Delayed=HVLT Delayed Recall, PersErrors=WCST Perseverative Errors.
     $*p < .05, **p < .01$.

Table 5. Correlations between Demographic Variables and DASS (Pearson)

	DASS-D	DASS-A	DASS-S
Age	.23*	.16	.08
Years of Education	.18	.06	.10
Disease Duration	-.03	.13	.12
Stage of Disease	.31*	.33*	.24
Gender	-.19	-.13	-.16
Race	-.13	-.08	-.13
Side of Onset	-.02	-.17	.03
MMSE	-.10	-.04	.03

Note. *$p < .05$, **$p < .01$.

Table 6. Correlations between DASS-D, DASS-A, and DASS-S (Pearson)

	DASS-D	DASS-A	DASS-S
DASS-D	1.00	.53**	.47**
DASS-A	.53**	1.00	.58**
DASS-S	.47**	.58**	1.00

Note. *p < .05, **p < .01.

Table 7. Main Analyses (IV's: Depression, Anxiety; DV: HVLT Total Recall)

Step 1	R^2	B	SE B	β	p
Constant		22.90	1.28		
Depression (DASS-D)	.03	-2.45	1.67	-.18	.15
Step 2	ΔR^2				
Constant		21.64	2.24		
Depression (DASS-D)		-3.18	1.98	-.23	.11
Anxiety (DASS-A)	.01	2.07	2.99	.10	.49

Note. For Step 1: $F = 2.15, p = .15$. For Step 2: $F = 1.31, p = .28$

Table 8. Main Analyses (IV's: Anxiety, Depression; DV: HVLT Total Recall)

Step 1	R^2	B	SE B	β	p
Constant		41.74	4.25		
Anxiety (DASS-A)	.002	1.95	4.81	.05	.69
Step 2	ΔR^2				
Constant		41.63	4.24		
Anxiety (DASS-A)		5.27	5.68	.13	.36
Depression (DASS-D)	.018	-4.13	3.76	-.16	.28

Note. For Step 1: $F = .16, p = .69$. For Step 2: $F = .69, p = .51$

Table 9. Main Analyses (IV's: Depression, Anxiety; DV: WCST Categories Completed)

Step 1	R^2	*B*	*SE B*	β	*p*
Constant		2.64	0.37		
Depression (DASS-D)	.051	-0.92	0.49	-.23	.06
Step 2	ΔR^2				
Constant		2.45	0.65		
Depression (DASS-D)		-1.03	0.58	-.25	.08
Anxiety (DASS-A)	.002	0.31	0.87	.05	.73

Note. For Step 1: $F = 3.58$, $p = .06$. For Step 2: $F = 1.83$, $p = .17$

Table 10. Main Analyses (IV's: Anxiety, Depression; DV: WCST Categories
Completed)

Step 1	R^2	B	SE B	β	p
Constant		2.48	0.66		
Anxiety (DASS-A)	.01	-0.52	0.75	-.08	.49
Step 2	ΔR^2				
Constant		2.45	0.65		
Anxiety (DASS-A)		0.31	0.87	.05	.73
Depression (DASS-D)	.05	-1.03	0.58	-.25	.08

Note. For Step 1: $F = .48$, $p = .49$. For Step 2: $F = 1.83$, $p = .17$

Table 11. Ancillary Analyses (IV's: Depression, Anxiety; DV: HVLT Delayed Recall)

Step 1	R^2	B	SE B	β	p
Constant		8.37	0.52		
Depression (DASS-D)	.095	-1.78	0.67	-.31	.01*
Step 2	ΔR^2				
Constant		8.15	0.90		
Depression (DASS-D)		-1.91	0.80	-.33	.02*
Anxiety (DASS-A)	.001	0.36	1.21	.04	.77

Note. For Step 1: $F = 7.06, p < .05$. For Step 2: $F = 3.53, p < .05$
*p < .05.

Table 12. Ancillary Analyses (IV's Anxiety, Depression; DV: HVLT Delayed Recall)

Step 1	R^2	B	SE B	β	p
Constant		8.20	0.93		
Anxiety (DASS-A)	.02	-1.18	1.06	-.14	.27
Step 2	ΔR^2				
Constant		8.15	0.90		
Anxiety (DASS-A)		0.36	1.21	.04	.77
Depression (DASS-D)	.08	-1.91	0.80	-.33	.02*

Note. For Step 1: $F = 1.24$, $p = .27$. For Step 2: $F = 3.53$, $p < .05$
*$p < .05$.

Table 13. Ancillary Analyses (IV's: Depression, Anxiety; DV: WCST Perseverative Errors)

Step 1	R^2	B	SE B	β	p
Constant		1.05	0.06		
Depression (DASS-D)	.014	0.07	0.07	.12	.33
Step 2	ΔR^2				
Constant		1.07	0.10		
Depression (DASS-D)		0.09	0.09	.14	.32
Anxiety (DASS-A)	.001	-0.40	0.13	-.04	.76

Note. For Step 1: $F = .98$, $p = .33$. For Step 2: $F = .53$, $p = .59$.

Table 14. Ancillary Analyses (IV's: Anxiety, Depression; DV: WCST Perseverative Errors)

Step 1	R^2	B	SE B	β	p
Constant		1.07	0.10		
Anxiety (DASS-A)	.001	0.03	0.11	.03	.79
Step 2	ΔR^2				
Constant		1.07	0.10		
Anxiety (DASS-A)		-0.04	0.13	-.04	.76
Depression (DASS-D)	.015	0.09	0.09	.14	.32

Note. For Step 1: $F = .07$, $p = .79$. For Step 2: $F = .53$, $p = .59$

Table 15. Ancillary Analyses (Age Effects on HVLT Delayed Recall)

Step 1	R^2	B	SE B	β	p
Constant		15.69	2.77		
Age	.12	-0.12	0.04	-.35	.003**
Step 2	ΔR^2				
Constant		15.24	2.71		
Age		-0.10	0.04	-.30	.012*
Depression (DASS-D)	.05	-1.39	0.66	-.24	.040*

Note. For Step 1: $F = 9.43$, $p < .01$. For Step 2: $F = 7.14$, $p < .01$.
     *$p < .05$, **$p < .01$.

Table 16. Correlations between DASS-D Subscales and Cognitive Variables (Spearman)

	Total	Categories	Delayed	PersErrors
Dysphoria	-.10	-.15	-.24	.20
Hopelessness	-.19	-.14	-.31*	.21
Devaluation of Life	-.10	-.12	-.27*	.20
Self-deprecation	-.13	-.21	-.18	.24*
Lack of interest	-.11	-.07	-.11	-.01
Anhedonia	-.17	-.08	-.28*	.04
Inertia	-.14	-.20	-.22	.11

Note. Total=HVLT Total Recall, Categories=WCST Categories Completed,
    Delayed=HVLT Delayed Recall, PersErrors=WCST Perseverative Errors.
    *$p < .05$.

Table 17. Correlations between DASS-A Subscales and Cognitive Variables (Spearman)

	Total	Categories	Delayed	PersErrors
Autonomic arousal	.04	.10	-.11	-.05
Skeletal musculature effects	.02	-.02	-.02	-.01
Situational anxiety	-.17	-.27*	-.21	.11
Subjective experience of anxious affect	-.14	-.22	-.25*	.25*

Note. Total=HVLT Total Recall, Categories=WCST Categories Completed,
    Delayed=HVLT Delayed Recall, PersErrors=WCST Perseverative Errors.
    *$p < .05$.

Table 18. Correlations between DASS-S Subscales and Cognitive Variables (Spearman)

	Total	Categories	Delayed	PersErrors
Difficulty Relaxing	-.13	-.07	-.27*	.06
Nervous Arousal	-.03	-.03	-.11	-.01
Easily Upset/Agitated	-.34**	-.28*	-.42**	.18
Irritable/Over-reactive	-.28*	-.33**	-.29*	.18
Impatient	-.24*	-.13	-.28*	.12

Note. Total=HVLT Total Recall, Categories=WCST Categories Completed,
     Delayed=HVLT Delayed Recall, PersErrors=WCST Perseverative Errors.
     *p < .05, **p < .01.

Discussion

The purpose of the current study was to extend the research findings investigating the influence of depression on cognitive functioning in PD. A high comorbidity exists between depression and anxiety in PD, and therefore, there is a need to examine the unique influences of these overlapping psychological states. Most prior studies have neglected to examine the unique influence that anxiety in PD may present, above and beyond depression, despite the evidence that anxiety has a detrimental impact on cognitive functioning in clinically anxious populations without PD. Furthermore, the few studies that have examined anxiety used self-report measures that poorly discriminate symptoms of anxiety from symptoms of depression. In addition, many of the past studies used measures of cognitive functioning that tested overall status, but these neuropsychological tests lacked sensitivity to common areas of cognitive vulnerability in PD. The present study attempted to clarify past findings by correcting for these various limitations.

It was hypothesized that higher levels of depression and anxiety would significantly predict impaired performance on a memory test of immediate recall, with both depression and anxiety exerting a unique influence. Also, it was hypothesized that depression and anxiety would both uniquely predict impairments on a measure of executive functioning that tests for ability to shift between sets (i.e. sorting strategies) with the changing demands of a card sorting task. Neither hypothesis was supported,

although there was a trend toward significance when depression was entered as a predictor on the WCST Categories Completed Index.

Ancillary analyses, however, did reveal that depression significantly predicted performance on a measure of delayed recall. This finding is generally consistent with the literature that shows a relationship between depression and memory in PD (Troster et al., 1995a; Starkstein et al., 1989). In contrast, anxiety was not a significant predictor of delayed recall when entered as either the first or second predictor. Finally, neither depression nor anxiety had a significant impact on the number of perseverative errors made on a task of executive functioning.

Depression Findings on HVLT

The original hypothesis that depression would predict performance on immediate recall was based on findings in three relevant areas; research on cognitive impairments primarily related to PD (Karayanidis, 1989; Sagar et al., 1988b; Scholz & Sastry, 1985), research regarding the impact of depression on cognition in PD patients (Burt et al., 1995), and also research related to the effects that depression has on memory in individuals with primary depressive disorder (Troster et al., 1995b).

Based on the prior literature from these three domains, the findings of the present study are somewhat surprising. Depression consistently predicted performance on delayed recall, but there was no significant depression effect found on immediate recall scores. This finding, although unexpected, appears to be in line with the theory that depressed patients exhibit more impairment on tasks that are effortful. Both immediate and delayed recall tasks may be considered somewhat effortful in that they both require the use of internally generated strategies and no cuing is provided. However, memory

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tasks that require a longer test-stimulus interval are generally considered to be more effortful than tasks with shorter test-stimulus intervals and have been proposed to be reflective of a motivational deficit (Cohen et al., 1982). Backman, Hill, and Forsell (1996) found that motivation-related symptoms of depression indeed are predictive of poorer recall performance, as compared to mood-related symptoms of depression.

It should also be noted that some studies in the literature are, in fact, somewhat consistent with the present findings. Starkstein, Rabins, Berthier, Cohen, Folstein, and Robinson (1989) compared performance on the MMSE between depressed patients with PD, depressed patients with cerebrovascular lesions, patient with depression and no neurological illness, and age-matched controls. All three depressed groups displayed significantly poorer performance on the delayed recall portion of the MMSE compared to the non-depressed group, and no other group differences were observed. Kindermann and Brown (1997) completed a meta-analysis of depression and memory in the elderly, and found larger effects for delayed versus immediate memory, although significance tests were unable to be conducted due to correlated observations. Contrary to the present findings, Cooper and Sagar (1993) did not find a significant relationship between depression and cognitive performance in PD patients, but did find that PD patients displayed more severe performance deficits on a task of delayed memory.

Depression Findings on WCST

Depression did not significantly predict performance on any indices of the WCST, although a trend toward significance did appear on the Categories Completed Index. According to the theory that depression predicts impairments on tasks that are effortful, one would expect that a measure of executive functioning would be particularly sensitive

to the impact of depression. However, the effect size of depression on cognitive functioning is generally considered to be small to moderate, so it is conceivable that the effect may have been masked due to particular characteristics of the sample.

First, the sample size may have been too small to detect the effect. A medium effect size (d = .15) was assumed for this study; however, more subjects would need to be included in the study to detect a small effect. Second, the WCST Categories Completed Index was the only variable that was entered into the analyses with significant kurtosis. The distribution was left untransformed because the data transformation did not improve the kurtotic shape. However, the unusual shape of the distribution may have contributed to the lack of significant findings.

Subscales of the DASS-D

The DASS-D subscales of Hopelessness, Devaluation of Life, and Anhedonia were significantly correlated with HVLT Delayed Recall. In particular, anhedonia, defined as an inability to experience pleasure, is considered to be a core component of depression. Studies have shown that reward processing is linked to dopaminergic pathways (Surguladze, Keedwell, & Phillips, 2003) and could explain why PD patients, for whom low levels of dopamine are a hallmark of the disease, display a loss of incentive. A disruption in reward processing may be linked to depression in PD, and also could explain why cognitive performance is compromised on tasks that require a high degree of initiative and effort.

Anxiety Findings on HVLT and WCST

Contrary to the proposed hypotheses, anxiety was not a significant predictor of any scores on the HVLT or the WCST. No trends approaching significance were

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identified and the R-squared values were small, ranging from .2% to 1.8%. The DASS-A scores were elevated in comparison to the DASS-D and DASS-S scores. The DASS-A mean T-score was at the high end of the cutoff for the Normal range, bordering between Normal and Mild levels of anxiety. The untransformed distribution of the DASS-A scores was positively skewed, although the DASS-A scores were more evenly distributed through the severity ranges compared to the DASS-D and DASS-S scores (see Table 2). Although addressed through data transformation, the restricted range of the depression and stress scores could have potentially limited their predictive ability. This is less likely to be the case for the anxiety scores, yet regardless, anxiety still failed to show significant influence when entered into the regression analyses.

One potential explanation for the relative elevation in anxiety scores is that two subscales of the DASS-A assess for the physical symptoms of anxiety. Lovibond and Lovibond (1995a) report that 36% of DASS-A items reflect autonomic nervous system symptoms, and 21% of the items involve the effects of anxiety on voluntary musculature. In particular, the Skeletal Muscle Effects subscale contains items that address shakiness and trembling. The Autonomic Arousal subscale contains an item that addresses difficulty in swallowing. While symptoms such as these are unique to anxious individuals in comparison to depressed individuals, they are common to patients with PD. It is possible that patients in this study may have endorsed items such as these due to the symptoms associated with PD, and not as a result of the genuine presence of anxiety. Higginson, Fields, Koller, and Troster (2001) suggest that overestimates of anxiety in PD are often a problem when using self-report questionnaires compared to clinical interview.

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If the DASS-A scores are artificially inflated because of physical complaints associated with PD, this could have masked a potential relationship between anxiety and cognitive functioning in PD. Examination of the DASS-A subscales reveals that the Skeletal Muscle Effects subscale and the Autonomic Arousal subscale were not significantly correlated with any cognitive variables. However, the DASS-A subscales tapping into non-physical aspects of anxiety (Situational Anxiety and Subjective Experience of Anxious Affect) were significantly associated with several cognitive variables, or approaching significance. This suggests that specific components of anxiety may be associated with cognition in PD, but this relationship did not appear in the regression analyses when using the total DASS-A score (which combines all subscales). It is difficult to draw firm conclusions regarding the influence of anxiety because patients in this study were not asked to identify their own causal attributions of symptoms being related to PD versus anxiety.

In a multipart dissertation study, Hanna (2006) argues that anxiety in PD is not simply a somatic artifact. A number of anxiety and depression instruments were administered containing varying levels of somatic items. The BAI and BDI both contain a high number of somatic items; so higher cutoff scores were used to determine clinically significant levels of anxiety and depression in PD, as suggested in the literature. The STAI-T and GDS have less emphasis on somatic items and were also administered. Non-somatic features of anxiety, such as pathological worry and the perception of stress, were identified and assessed using the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990) and Cohen's Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstain, 1983).

In this study, clinically significant levels of anxiety and depression were comparable regardless of the measure used. Also, BAI scores were significantly correlated with the PSWQ and the PSS after controlling for the effects of depression. Patients were divided into anxious and non-anxious groups based on BAI scores and a significant difference was found between these groups on the PSWQ and the PSS. Based on these findings, the author suggests that cognitive and affective components of anxiety are present and important to consider beyond the physical symptoms of PD. Studies finding that anxiety disorders predate the onset of the motor symptoms in PD (e.g., Shiba et al., 2000) also lend support to the interpretation that anxiety is an independent construct in PD.

Future adaptation of the DASS may be necessary to obtain a more precise measure of anxiety in PD, and to more accurately determine the relation of anxiety to cognitive functioning. There are several possible approaches for handling the issue of the somatic items on the anxiety scale. First, the subscales containing somatic items could be dropped and the remaining non-somatic subscales could be expanded and adapted for use with PD patients. However, this solution does not account for the possibility that some autonomic features of anxiety in PD may actually be caused by anxiety itself and not PD. This option would also omit fundamental features of anxiety that are important to consider in that they have been found to maximally discriminate from depression. Another possible consideration is to include all subscales and add a separate section for patients to self-report their own subjective attributions of their symptoms. Additionally, it may be possible to adjust the severity ranges of the DASS similar to the approach taken with the BAI and BDI. Higher cutoff scores to denote clinically significant anxiety and

depression are often used with these measures to account for overinflation of scores due to somatic items (Higginson, Fields, Troster, 2001; Leentjens, Verhey, Luijckx, & Troost, 2000). A final option is to revise the actual items of the Autonomic Arousal and Skeletal Muscle Effects subscales to more appropriately apply to PD patients. This approach, although feasible, may take considerable research efforts to develop.

It seems that it would be worth pursuing further adaptation of the DASS, given that these scales seem to provide the maximal amount of discrimination between depression and anxiety of the known measures in the literature. The BAI and BDI have also been noted to have good divergent validity, however, a different approach was taken in the development of these measures (Beck & Steer, 1990). The initial pool of items were taken from pre-existing scales and administered to a clinical sample. The BDI had already been developed and the BAI was developed to discriminate from this measure. The final selection of items for the BAI was based on consistency with items in the scale, high correlations with other anxiety measures and DSM criteria for an anxiety diagnosis, and low correlations with depression scales and DSM criteria for a depression diagnosis. In comparison, the DASS was developed using no external preexisting criteria to influence the scale construction.

In summary, there is still no consensus regarding the unique influence of anxiety on cognitive functioning. The finding of Ryder et al. (2002) demonstrating that anxiety had a unique influence on cognitive functioning was based on scores from the STAI-T and BDI. Although correlations between these measures were not reported in the Ryder study, Hanna (1996) administered these measures and found a high correlation between them ($r = .78, p < .01$). Lovibond and Lovibond (1995a) describe the STAI as wide in

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item content and note that several of the items are similar to items on the DASS-D and DASS-S scales. These measures do not appear to be ideal for entry into a regression analysis because they are highly correlated with content overlap. From this, it is difficult to tell whether symptoms related to cognitive functioning are better attributable to symptoms of depression or anxiety. However, the authors of the DASS do suggest that a correlation around .50 might be a minimum irreducible correlation between the constructs of depression and anxiety.

Future Research

Although trends have been identified, there is clearly also a great deal of variation across the literature examining depression and cognitive functioning in PD patients. Several factors that may add to the complication are that studies vary in terms of the subtypes of PD patients that are included (Lewis et al., 2005), staging of illness, and medications taken. Studies also differ in terms of the types of depressed patients that are included (major depression, minor depression, and dysthymia), which could potentially manifest their influence on cognition in different ways. Further, some studies diagnose patients according to DSM-IV criteria while others use self-report measures of depression. Finally, some researchers administer neuropsychological tests to pinpoint specific deficits while others use general cognitive measures. A meta-analysis in this area has not yet been conducted, and the field may benefit from this type of work, which may help to clarify the discrepant findings.

It may be useful to establish clinical severity levels for the DASS so that it can be used as a clinical instrument. The DASS was originally developed based on the concept that symptoms of depression and anxiety exist on a continuum, and has no ties to

categorical DSM-IV diagnoses. Although the measure is useful in maximally discriminating constructs, it is difficult to make clinical judgments based on the severity ranges provided in the manual. If clinically meaningful cutoffs are developed, a future research possibility could be to categorize patients into groups based on high or low levels of depression and anxiety. This could be useful for research on the influence of depression and anxiety on cognition. It would then be reasonable to examine the differences in how patients with comorbid depression and anxiety might perform cognitively, compared to individuals with high depression and low anxiety, or high anxiety and low depression.

Also, the psychometric characteristics of the DASS should be evaluated in PD patients. The discrimination of the measure has been tested in specialized populations, such heart attack patients and individuals with sleep disturbance, but no studies have been uncovered involving PD patients. Finally, another research possibility is to administer the BAI and the BDI and determine if the results from this study could be replicated using these instruments.

Clinical Implications

It is important for clinicians that make diagnostic and treatment decisions to have access to accurate information regarding cognitive functioning in PD patients with psychiatric difficulties. For instance, knowledge of the specific pattern of cognitive impairment associated with depression in PD could be of great assistance in making an early differential diagnosis between depression and other clinical conditions that could occur comorbidly with PD. It would be helpful to establish early clinical indicators of the

various diagnostic distinctions to direct treatment decisions and prevent further decline as much as possible.

Theoretical Implications

Until states of depression and anxiety in PD can be accurately characterized, there will be limitations to the strength of conclusions that can be drawn from research examining their effects on cognition. In 2003, the National Institute for Neurological Diseases and Stroke (NINDS) and the National Institute of Mental Health (NIMH) joined together to review the reliability and validity of current strategies for diagnosis of depression in PD (Marsh et al., 2006). It was agreed upon that the current DSM-IV criteria for diagnosing depression needed modification to fully address symptom overlap and improve the detection of depression in PD. At present, according to DSM-IV criteria, a diagnosis of depression cannot be made when symptoms can be accounted for by a general medical condition. With PD patients, it is often difficult to distinguish which symptoms can be explained by depression and which symptoms are expressed due to PD itself. Thus, the validity of a diagnosis of depression in PD according to DSM-IV criteria becomes questionable.

An alternative approach to using DSM-IV diagnostic criteria is to assess using self-report symptom checklists to provide an indicator of symptom severity and examine subsyndromal features of depression. With many such measures, there is a risk of overestimation of symptoms of depression as a result of the inclusion of somatic items that overlap with symptoms of PD and are not specific to depression. In this sense, the use of the DASS-D may hold an advantage in that the core features of depression are retained and the somatic items are not included. This type of specificity in measurement

may be necessary to adequately distinguish between features of comorbid depression and anxiety. However, the ultimate outcome should be carefully considered when selecting an appropriate measure to assess for anxiety and depression in PD. In the research context, specificity in the distinctions between syndromes may be a priority, while in a clinical setting, increased sensitivity to detection of symptoms can help to properly guide treatment choices. Marsh et al (2006) suggest several different approaches to symptom assessment in PD, and Schrag et al. (2007) discuss many rating scales that are commonly selected to assess depression in PD.

It is also important to consider the use of caregiver ratings in assessment of psychological symptoms in PD. This may be particularly important in PD patients with cognitive impairment, whose insight and ability to self-assess may be limited. Informants can be useful in providing additional details and describing the time course and patterns of various symptoms. (Schwenk, 2002)

There are currently no existing depression or anxiety rating scales specifically developed for use with PD patients. Schrag et al. (2007) discourages researchers from the development of new scales, and instead highlights the need for further study and adaptation of existing measures. Before anxiety and depression measures tailored to PD patients can be developed, the complexities of the fundamental theoretical issues must be better understood.

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Appendices

Appendix A. List of items on the DASS Depression subscale

Dysphoria:
> I felt down-hearted and blue.
> I felt sad and depressed.

Hopelessness:
> I could see nothing in the future to be hopeful about.
> I felt that I had nothing to look forward to.

Devaluation of Life:
> I felt that life was meaningless.
> I felt that life wasn't worthwhile.

Self-deprecation:
> I felt I was pretty worthless.
> I felt I wasn't worth much as a person.

Lack of interest/involvement:
> I felt that I had lost interest in just about everything.
> I was unable to become enthusiastic about anything.

Anhedonia:
> I couldn't seem to experience any positive feeling at all.
> I couldn't seem to get any enjoyment out of the things I did.

Inertia:
> I just couldn't seem to get going.
> I found it difficult to work up the initiative to do things.

Appendix B. List of items on the DASS Anxiety Subscale

_____

Autonomic arousal:

       I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat).

       I perspired noticeably (e.g., hands sweaty) in the absence of high temperature or physical exertion.

       I was aware of dryness of my mouth.

       I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion).

       I had difficulty in swallowing.

Skeletal musculature effects:

       I had a feeling of shakiness (e.g., legs going to give way).

       I experienced trembling (e.g., in the hands).

Situational anxiety:

       I was worried about situations in which I might panic and make a fool of myself.

       I found myself in situations which made me so anxious I was most relieved when they ended.

       I feared that I would be "thrown" by some trivial but unfamiliar task.

Subjective experience of anxious affect:

       I felt I was close to panic.

       I felt terrified.

       I felt scared without any good reason.

       I had a feeling of faintness.

_____

Appendix C. List of items on the DASS Stress Subscale
_____
Difficulty relaxing:

    I found it hard to wind down.

    I found it hard to calm down after something upset me.

    I found it difficult to relax.

Nervous arousal:

    I felt that I was using a lot of nervous energy.

    I was in a state of nervous tension.

Easily upset/agitated:

    I found myself getting upset rather easily.

    I found myself getting upset by quite trivial things.

    I found myself getting agitated.

Irritable/over-reactive:

    I tended to over-react to situations.

    I found that I was very irritable.

    I felt that I was rather touchy.

Impatient:

    I was intolerant of anything that kept me from getting on with what I was doing.

    I found myself getting impatient when I was delayed in any way (e.g., lifts, traffic lights, being kept waiting).

    I found it difficult to tolerate interruptions to what I was doing.
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