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A NEUROPSYCHOLOGICAL EVALUATION OF COGNITIVE AND BEHAVIORAL IMPAIRMENTS IN PARKINSON'S DISEASE: RELATIONSHIPS TO FRONTOSTRIATAL CIRCUITRY

by

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A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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Abstract

A NEUROPSYCHOLOGICAL EVALUATION OF COGNITIVE AND BEHAVIORAL IMPAIRMENTS IN PARKINSON'S DISEASE: RELATIONSHIPS TO FRONTOSTRIATAL CIRCUITRY

by

DENNIS J. ZGALJARDIC

Adviser: Professor Joan C. Borod

Parkinson's disease (PD) is a neurodegenerative hypokinetic movement disorder presenting with subcortical pathology. However, as is frequently reported in the literature, individuals with PD can exhibit cognitive and behavioral impairments, executive dysfunction and depression being the most prominent. Attention has been given to the involvement of the frontostriatal circuits connecting the frontal cortical regions and the basal ganglia (i.e., dorsolateral prefrontal [DLPFC], anterior cingulate [ACC], and orbitofrontal cortex [OFC]) and to how these circuits might mediate frontal/executive dysfunction in PD. Our objective, in this study was to ascertain how changes in frontostriatal circuitry might explain neuropsychological impairments exhibited in this patient population. Standardized executive neuropsychological tests and self-report behavioral scales, categorized by circuit function, were administered to 32

nondemented dopamine-alleviated PD patients and to 29 demographically matched, healthy control subjects. Our findings revealed significant group differences between all task circuit conditions, with the PD group performing worse relative to the control group. Calculated effect sizes revealed that the greatest magnitude of difference between subject groups occurred for tasks mediated by the DLPFC circuit. In the PD group, indices of impairment were greater for tasks mediated by the DLPFC circuit than by the ACC and OFC circuit. Furthermore, an index of DLPFC circuit performance was discovered to be the only significant predictor in discriminating between individuals with and without PD. Using factor analysis, overall task performance across groups did not load according to circuit, alluding to limited specificity of select executive measures. In conclusion, our findings suggest that frontal/executive impairments in our PD sample appear to predominantly reflect dysfunction of the DLPFC circuit.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative hypokinetic movement disorder presenting with subcortical pathology. The prevalence of PD in individuals over age 65 in the general population is about 1%. The mean age of clinical onset is approximately 60 years. Disease onset before age 25 is uncommon. Previous work has suggested that PD may arise from either one or a combination of several different etiological factors including environmental toxins, free radical production, mitochondrial abnormalities, genetic predisposition, and aging (for review, see Barbosa, Limongi, & Cummings, 1997). The motor impairments characteristic of PD include the clinical triad of resting tremor, bradykinesia (slowness or retardation of movement), and rigidity, although other symptoms such as hypokinesia (impaired movement initiation), freezing phenomena (difficulty with congruent and sequential movements), and postural abnormalities are common (Ondo & Jankovic, 1998). These movement disturbances in PD, which disrupt thalamocortical projections and hinder the facilitation of motor programs, are the result of changes to phasic and tonic neuromodulatory influences upon output nuclei of the basal ganglia (substantia nigra pars compacta [SNc] and globus pallidus internal segment [GPi]) (for review, see Alexander & Crutcher, 1990; DeLong, 2000; Masterman & Cummings, 1997; Wichman & DeLong, 1996).

In spite of Parkinson's (1817) original claim that sensory and intellectual abilities are unaffected in patients with the disease that now bears his name, cognitive and behavioral impairments in this patient population have been well documented in the literature (for reviews, see Barbosa et al., 1997; Dubois & Pillon, 1997; Levin, Tomer, & Rey, 1992; Morriosn et al., 2000; Pahwa, Paolo, Tröster, & Koller, 1998; Raskin, Borod,

& Tweedy, 1990; Ridenour & Dean, 1999; Zgaljardic & Eidelberg, 2003). The cognitive and behavioral sequelae of PD may represent a manifestation of the disease separate from the pathology causing the characteristic motor symptoms (e.g., bradykinesia). Evidence for this comes from different modes of research. First, since the neuropathological hallmark of PD is a reduction of dopaminergic neurons in the substantia nigra, it was expected that increasing the amount of available dopamine would reverse cognitive and behavioral symptoms in addition to the triad of motor deficits. Nonetheless, the evidence has not been consistent, as cognitive and behavioral deficits are not typically alleviated after dopamine therapy (e.g., dopamine precursors [levodopa]) (e.g., Cooper et al., 1992; Gotham, Brown, & Marsden, 1988; Pahwa et al., 1998). In spite of a general focus on the dopaminergic system in describing the disease process of PD in the literature, other neurotransmitter systems (e.g., acetylcholine, norepinephrine, and serotonin) also appear to play a causal role in the etiology of deficits exhibited by these patients (Przuntek, 2000; Wolters, 2001). Second, findings from the literature have also suggested that different neuronal circuits connecting regions of the frontal cortex and the basal ganglia (i.e., frontostriatal circuits) may be implicated in the cognitive and behavioral sequelae of PD (e.g., Alexander, DeLong, & Strick, 1986; Lichter & Cummings, 2000; Middleton & Strick, 2000). As similar impairments are exhibited by patients with PD and by those with focal frontal system lesions (e.g., Starkstein & Kremer, 2000; Starkstein & Robinson, 1993; Taylor, Saint-Cyr, & Lang, 1986), some researchers suggest that the cognitive and behavioral profile in PD may be mediated by frontostriatal circuit dysfunction (e.g., Cummings, 1993; Gotham et al., 1988; Raskin et al., 1990; Richards, Cote, & Stern, 1993; Taylor et al., 1986).

Alexander et al. (1986) proposed the existence of five "closed loop" frontostriatal cortical circuits, which reportedly mediate motor, cognitive, and behavioral programs within the brain. They are grouped into "motor" and "complex" circuits. There are two "motor" circuits (i.e., the motor circuit and occulomotor circuit) and three "complex" (i.e., non-motor) circuits. The latter originate from the (a) dorsolateral prefrontal cortex [DLPFC], (b) anterior cingulate cortex [ACC], and the (c) orbitofrontal cortex [OFC] of the frontal lobe. The three complex circuits appear to be particularly applicable to the non-motor profile of PD. Each circuit projects to specific striatal regions (via excitatory glutaminergic transmission) in a topographical fashion and remains segregated throughout the basal ganglia and thalamus, allowing other areas of the brain to communicate with each circuit along their respective pathways (Alexander et al., 1986; Middleton & Strick, 2000). All circuits eventually return to the portion of the frontal cortex via the thalamus from which they originated (Delong, 2000). The frontostriatal circuits receive inputs from dopaminergic, noradrenergic, serotonergic, and cholinergic cell groups that modulate information processing (Tekin & Cummings, 2002).

The frontostriatal circuitry maintains direct and indirect pathways. In the direct pathway (modulated by the substantia nigra [pars compacta] via D1 receptor subtype transmission), neural information projects from the striatum (i.e., caudate, putamen, and ventral striatum) directly to the globus pallidus (internal segment) and substantia nigra (pars reticulata) creating a positive feedback loop. This projection is mediated by the neuromodulators GABA and substance P, which create inhibitory synapses. The indirect pathway (modulated by the substantia nigra [pars compacta] via D2 receptor subtype transmission), also originating from the striatum, synapses with the globus pallidus

(external segment). This pathway consists of both GABA-ergic and enkephalin projections and also creates inhibitory synapses (Delong, 2000; Masterman & Cummings, 1997; Tekin & Cummings, 2002). Under normal conditions, the direct pathway reduces inhibitory basal ganglia output to the thalamic target neurons, whereas the indirect pathway increases this output (DeLong, 2000; Wichmann & DeLong, 1996). The neuropathology resulting from PD leads to overactivity of the indirect pathway and decreased activity of the direct pathway.

The neuroanatomical model of cognitive and behavioral deficits in PD implicates disruption to each of the three complex frontostriatal circuits as contributing to the specific frontal/executive impairments found in PD (Cummings, 1993; Green et al., 2002; Lichter, 2000; Lichter & Cummings, 2000; Tamaru, 1997). Here, by frontal/executive impairments we mean both cognitive and behavioral deficits. Previous work evaluating brain-damaged individuals, normal control (NC) subjects, and non-human subjects (e.g., primates) has proposed the following associations between the three prefrontal cortical regions and cognitive and behavioral functions: (a) the ACC is believed to be involved in attentional processes such as response initiation, intention, inhibition, and conflict monitoring (Cummings, 1993; MacDonald, Cohen, Stenger, & Carter, 2000; Pardo, Pardo, Janer, & Raichle, 1990; Stuss, Floden, Alexander, Levine, & Katz, 2001); (b) the DLPFC reportedly mediates executive cognitive functions, such as set-shifting, complex problem solving, activation of remote memories, organizational strategies, and working memory (e.g., Cummings, 1993; D'Esposito et al., 1995; Frith, Friston, Liddle, & Frackowiak, 1991; Jonides et al., 1993; Nagahama et al., 1998; Stuss et al., 1998); (c) the OFC has been associated with frontal monitoring of the limbic system such as

disinhibition, circumstances where decisions are made based upon a reinforcement/reward schedule required to maintain a behavioral set, impulse control, perseveration, and mood and personality (e.g., Bechara, Tranel, Damasio, & Damasio, 1996; Cummings, 1993; Passingham, 1972; Upton & Thompson, 1999).

In sum, there is mounting evidence in the literature suggesting that many neuropsychological tasks and behavioral presentations can be organized according to specifically impaired subsystems in PD. The objective of this study is to delineate how the frontostriatal circuitry can be applied to cognitive and behavioral impairments in PD using clinical standardized frontal/executive neuropsychological tests. Frontostriatal circuit dysfunction in PD will be addressed in the current study with the development of a neuropsychological test battery that will incorporate findings from the PD, brain-damaged, animal (primate), and neuroimaging literatures. The standardized clinical neuropsychological tests administered to both PD patients and NCs will have each been shown to highlight impairment or function in one of the three previously described frontostriatal circuits. In so doing, we hope to gain a better understanding of the relationships between specific frontal/executive dysfunction in PD and the frontostriatal circuitry. To our knowledge, this has not been systematically studied in this manner with individuals with PD. In addition, direct evidence associating frontal/executive standardized neuropsychological task performance and underlying circuitry in PD is limited. The proposed test battery may be of use as a comprehensive assessment of frontal/executive abilities (categorized by circuit) in PD patients in the clinical setting. Our study will address cognitive and behavioral deficits in nondemented PD patients (NDPD) since the majority of individuals with PD do not manifest dementia.

The following review of the literature will first outline the cognitive and behavioral deficits afflicting patients with PD. Next, since the frontostriatal circuits receive inputs from dopaminergic, serotonergic, noradrenergic, and cholinergic cell groups that modulate information processing, we will discuss potential disruption to these neurotransmitter systems in PD, as well as the effects of neurochemical therapy. In the latter portion of the review, we will provide a summary of findings from both the non-PD (i.e., brain-lesioned, non-human, and healthy normal control [NC]) and PD literatures in order to better link frontal/executive functions to specific frontal regions, thus providing a framework in the development of an experimental neuropsychological test battery for the current study.

COGNITIVE AND BEHAVIORAL SEQUELAE IN PD

Dementia Severity in PD

Dementia occurs in approximately one-third of patients with PD; however prevalence rates tend to vary considerably across studies ranging from 4% to 93% (for reviews, see Aarsland & Karlsen, 1999; Barbosa et al., 1997; Dubois, Boller, Pillon, & Agid, 1991; Lichter, 2000; Mahler & Cummings, 1990; Nordberg, 2002; Pahwa et al., 1998). The disparity among the reported findings may be attributed to methodological differences across studies (for review, see Pahwa et al., 1998). Factors shown to predict the onset of dementia in PD have been age at disease onset (>60 years), as well as substandard performance on neuropsychological measures that assess visuospatial skills, response interference, and word-list generation (e.g., Mahieux et al., 1998; Palazzini et al., 1995).

Cognitive and behavioral deficits in PD patients with dementia (DPD) such as impaired learning, aphasia, and/or apraxia may result from cortical pathology indicative of Alzheimer's disease (AD) and/or Lewy Body dementia (LBD) (McKeith & Burn, 2000). DPD patients predominantly exhibit impairments of declarative memory (with fairly intact recognition), executive functions (e.g., set-shifting), visuospatial skills, speech and language (e.g., sentence processing and motor speech output) and mood (e.g., depression), although these findings typically vary across studies due to the multiplicity of patient samples (e.g., disease severity).

It is still unclear whether NDPD patients simply exhibit a milder neuropsychological profile compared to those patients with dementia (Zakzanis & Freedman, 1999). In one study, 93% of PD patients (demented and nondemented)

performed worse than demographically matched normal control subjects on select neuropsychological tasks (Pirozzolo, Hansch, Mortimer, Webster, & Kuskowski, 1982). Of those patients who were nondemented, 60% demonstrated cognitive deficits. The cognitive impairments exhibited by NDPD patients typically resemble a dysexecutive syndrome with secondary memory and visuospatial processing difficulties (Barbosa et al., 1997; Brown & Marsden, 1990; Green et al., 2002); however, select deficits have been documented in most areas of cognition (for review, see Raskin et al., 1990). There has been speculation in the literature as to whether these "secondary" deficits may be either directly credited to PD or secondary to executive deficits associated with the disease process (Mahieux et al., 1998; Pahwa et al., 1998; Raskin, Borod, & Tweedy, 1992; Taylor et al., 1986; Taylor & Saint-Cyr, 1995).

Executive Functions

Executive functions, which include numerous abilities (for review, see Stuss & Benson, 1986), are relatively compromised in PD and are regarded as the primary cognitive sequelae in this disease. PD patients (demented or nondemented) have been reported, for example, to exhibit impairments in working memory (e.g. Owen, Iddon, Hodges, Summers, & Robbins, 1997), trial-and-error learning (e.g., Postle, Locasio, Corkin, & Growdon, 1997), planning (e.g., Owen et al., 1995), response-monitoring (e.g., Cooper, Sagar, Tidswell, & Jordan, 1994), set-shifting (e.g., Hsieh, Lee, & Tai, 1995; Owen et al., 1992; Raskin et al., 1992; Richards et al., 1993), and attentional control (e.g., Brown & Marsden, 1988). In general, executive impairments in PD have been defined in terms of the difficulties patients may experience in developing their own plan of action or initiating goal-directed behavior, as well as maintaining adequate levels of processing

resources, which are necessary for self-monitoring behavior (Brown & Marsden, 1990; Taylor & Saint-Cyr, 1995). In order to appropriately separate out the abundance of neuronal processes underlying these executive abilities in humans, different theoretical models have been employed to describe the cognitive deficits experienced by PD patients. In the current section, we will provide a brief summary of two popular theoretical models.

The Supervisory Attentional System (SAS; Shallice, 1982; Shallice, 1988) describes executive impairments in terms of the difficulties patients may experience in developing their own plan of action or initiating goal-directed behavior, as well as maintaining adequate levels of processing resources, which are necessary for self-monitoring behavior. The SAS, in theory, is a mechanism within the frontal cortex, which distributes mental resources according to processing demands so as to govern non-routine behaviors (Shallice, 1988; Taylor & Saint-Cyr, 1995). The SAS model describes a system in which a single central component oversees and regulates the functions of several other subordinate components. The SAS influences inhibitory resources allowing for the suppression of routine behaviors in favor of more goal-appropriate ones. Here, frontal brain-damaged patients, for instance, may exhibit normal behavior in familiar settings, but may find it difficult to adapt when confronted with a novel environment or scenario. SAS dysfunction has been observed in individuals with frontal lobe injury specific to the DLPFC (e.g., Norman & Shallice, 1980; Shallice, 1988), and is also believed to result from reduced dopamine availability (Brown & Marsden, 1990; Taylor & Saint-Cyr, 1995).

Patients with PD have also been noted to exhibit impaired performance on neuropsychological tasks shown to assess SAS function (e.g., planning [Andres & van der Linden, 2001], response inhibition [Brown & Marsden, 1988], and set-shifting [Fimm, Bartl, Zimmermann, & Wallesch, 1994]). For instance, Brown and Marsden (1988) suggested that poor performance demonstrated by PD patients in their study was the result of imposing greater resource demands (i.e., relying heavily on internally generated information and exceeding already available resources), thus preventing efficient strategy formation via the central executive. In general, PD patients may present with difficulties in suppressing competing mental programs due to an increase in background noise or interference within the system (Robbins & Brown, 1990; Taylor & Saint-Cyr, 1995). In other words, due to SAS dysfunction, individuals with PD may find it difficult to inhibit other nonrelevant resources while performing a task, which may lead to excessive cognitive load. This may, in turn, decrease cognitive processing speed and potentially result in an inability to select and execute mental strategies efficiently.

The Working Memory model (Baddeley, 1986; Baddeley & Della Sala, 1998), on the other hand, describes a system that enables an individual to store, integrate, and update information, especially during multi-tasking, and subsequently utilize that information to appropriately guide action. Like the SAS model, decreased dopamine availability may also hamper working memory processes (Lichter, 2000). However, unlike the SAS model, the working memory model is not solely dependent upon a single central executive; instead, it incorporates a tripartite model consisting of a central executive (adapted from the SAS model, Norman & Shallice, 1980) and two subordinate systems (e.g., phonological loop [verbal] & visual-spatial sketchpad [nonverbal]).

Evidence supporting the utility of the working memory model in PD has been provided in the literature. Dalrymple-Alford, Kalders, Jones, and Watson (1994), for instance, compared performance differences between PD and NC groups on two concurrent tasks that assessed visuospatial tracking and verbal processing. When administered separately, task performance was comparable between groups; however, when subjects were administered a dual task paradigm, conducting both tasks simultaneously, PD subject group performance suffered. Their findings suggest that the central executive in PD is more susceptible to cognitive load relative to NC subjects. However, unlike Brown and Marsden (1988), Dalrymple et al., (1994) support Baddeley's (1986) working memory model in that excessive cognitive load will only take place in PD once both slave systems have been exhausted.

Despite arguments debating the utility of a specific model in describing frontal/executive impairments in PD, the general consensus from the two models presented above agree on the existence of a central executive as the core feature within their respective models. Both models appear to appreciate the DLPFC to be an integral contributor to this "central" mechanism with dopamine functioning as a facilitator by gating or disinhibiting task-relevant information via frontostriatal projections (Braver & Cohen, 2000; Cohen & Servan-Schrieber, 1993; Cools, Barker, Sahakian, & Robbins, 2001; Gerfen, 1992; Mirenowicz & Schultz, 1996). Therefore, massive degeneration of the nigrostriatal dopaminergic system in PD, leading to demodulation of frontostriatal circuitry and subsequently depletion of dopamine within specified prefrontal areas (e.g., DLPFC) might contribute to the frontal/executive impairments in PD, thus lending support to the model of Alexander et al. (1986).

Visuospatial Functions

Visuospatial deficits are frequently reported in PD. However, the literature maintains that NDPD patients may not necessarily exhibit a pure visuospatial deficit (e.g., line orientation and distance, judgment of direction, and visual analysis and synthesis), although task performance may be compromised if tests are timed and/or incorporate either a motor and/or executive component (Brown & Marsden, 1988; Lichter, 2000; Pahwa et al., 1998; Raskin et al., 1992). DPD patients tend to exhibit impaired visuospatial performance when compared to NDPD patients and NC subjects on tasks that do not incorporate a timed, motor, and/or executive component (Huber, Shuttleworth, & Freidenberg, 1989; Levin et al., 1991; Raskin, Borod, Wasserstein, et al., 1990).

Taylor et al. (1986) investigated allocentric, egocentric, and right-left orientation visuospatial functions in patients with NDPD and NC subjects. While PD patients' response accuracy across tasks was comparable to NC subjects, their reaction times (RTs) were significantly prolonged. The increase in RT found was attributed to impaired visual scanning and not to a decrease in cognitive processing speed (i.e., bradyphrenia), executive dysfunction, or a pure visuospatial deficit. Raskin et al. (1992) compared visuospatial and executive task performance in NDPD patients and NC subjects. These authors administered tasks of spatial orientation without a set-shifting component and set-shifting tasks without a spatial orientation component. Their findings indicated that patients with PD performed comparable to NC subjects on visuospatial tasks, but were significantly worse on select executive tasks. Moreover, Mahieux et al. (1998) credited poor performance on the Picture Completion subset of the Wechsler Adult Intelligence

Test – Revised to deficits related to frontal/executive function, such as sustained attention, response monitoring, and strategy development. Similarly, Bondi, Kasniak, Bayles, and Vance (1993) reported that deficits in visuospatial tasks demonstrated by patients with PD failed to reach statistical significance after controlling for the influence of executive demands.

Memory

Memory deficits exhibited by patients with PD are characterized by impairments of delayed recall, temporal ordering, and conditional associate learning (Lichter, 2000). PD patients tend to maintain normal rates of decay, have preserved encoding of information and recognition, and benefit from external cueing (Brown & Marsden, 1988; Cummings, 1986; Levin et al., 1992). This profile contrasts with that of patients with Alzheimer's disease (AD) (Huber et al., 1989; Mahler & Cummings, 1990) who tend to exhibit increased forgetting, due to impaired encoding, poor recognition, and an inability to benefit from external cueing (Cummings, 1986).

Poor performance on memory tasks exhibited by patients with PD has also been attributed to executive deficits (e.g., Taylor et al., 1986). Impaired delayed recall appears to reflect inefficient retrieval of information and not an encoding deficit as reported in AD patients (Raskin et al., 1990; Taylor & Saint-Cyr, 1995; Zakzanis & Freedman, 1999). It has been suggested that the dopaminergic system, compromised in PD, would normally activate relevant responses or strategies within the brain as opposed to non-relevant ones via a mechanism in the frontal cortex (Taylor & Saint-Cyr, 1995). Since a particular stimulus may evoke multiple response options, it is necessary for an individual to be able to monitor, integrate, and retrieve the optimal response with a certain degree of

efficiency and speed. PD patients may have difficulties in initiating and maintaining search strategies effectively, despite relatively preserved encoding and recognition. This particular series of functions is reportedly mediated by the DLPFC (for review, see Lichter, 2000), thus supporting the notion that memory impairments described in PD most likely reflect an executive deficit possibly indicative of select frontostriatal circuit disruption.

Speech and Language

Patients with PD often demonstrate deficits in the motor aspects of speech (for review, see Raskin et al., 1990). On testing, deficits in speech output, especially for DPD patients, have been attributed to vocal-motor deficits such as dysarthria, which involves a reduction of speech volume and pitch (for review, see Levin et al., 1992). DPD patients are usually more likely than NDPD patients to exhibit impairments of speech intonation, length of utterance, and spontaneity (Cummings, Darkins, Mendez, Hill, & Benson, 1988).

Patients with PD have exhibited select impairments in linguistic ability. Confrontation naming performance was reportedly reduced in DPD patients in comparison to NCs and NDPD patients, albeit significantly better than performances of other demented neurodegenerative patient groups (e.g., Frank, McDade, & Scott, 1996). Word-list generation, using semantic and/or phonemic cueing has been found to be impaired in PD patients with and without dementia (Bayles, Trosset, Tomoeda, Montgomery, & Wilson, 1993; Raskin et al., 1992; Tröster et al., 1998), although this has usually been credited to a executive deficit (e.g., set-shifting or strategy initiation) and not to a breakdown of lexical stores, per se, as reported in patients with AD (Pahwa et al.,

1998; Troyer, Moscovitch, Winocur, Leach, & Freedman, 1998). More specifically, NDPD patients have demonstrated impairments on tasks assessing complex comprehension and grammar relative to NCs (Cummings et al., 1988). Similarly, evidence also suggests that patients with PD can demonstrate sentence-processing deficits (for review, see Grossman, 1999). This particular deficit may be attributed to dysfunctional attentional mechanisms (potentially situated within the ACC) necessary to attend to sentence structure (Grossman, Crino, Reivich, Stern, & Hurtig, 1992). These authors indicate that the ACC may play a role in modulating attention to subtle grammatical features of a sentence. Moreover, the sentence processing deficits reportedly demonstrated in PD may not necessarily be related to alterations in dopamine levels and/or deficits in working memory (e.g., Skeel et al, 2001). On the contrary, recent findings using functional magnetic resonance imaging (fMRI) (e.g., Grossman et al., 2003) revealed that NDPD patients had reduced recruitment of striatal regions (possibly via changes in frontostriatal circuitry output) in comparison to normal controls when asked to process sentences with high demands on working memory. The authors suggest that impaired syntactic performance in PD may, in part, be attributed to cognitive resource limitations (i.e., working memory and information processing speed). In order to maintain equivalent levels of sentence comprehension as NC subjects, the PD group exhibited greater recruitment of other cortical regions to compensate for depleted working memory resources.

Attention

There have been mixed findings regarding attentional deficits in PD in the literature. There is some indication that select areas of attention are better preserved than

others. Digit span, representative of vigilance or sustained attention, remains fairly intact, while performance on attentional tasks that demand speeded cognitive processing or require the patient to internally guide their attentional resources appear to be impaired (for reviews, see Pahwa et al., 1998; Raskin et al., 1990; Ridenour & Dean, 1999). Patients with PD may also be impaired on tasks of covert attention. Rafal, Posner, Walker, and Friedrich (1984) administered a task of visual (nonverbal) covert orienting of attention to NDPD patients. Subjects were their own controls and were tested both while on and off dopamine therapy as a way to assess the involvement of striatal structures in mediating attentional processes. PD patients, either on or off dopamine therapy, performed similarly across conditions. However, when patients were off medication, their RTs were prolonged, although this finding was not significant. The authors concluded that patients with PD maintain preserved attentional set-shifting within the visual (nonverbal) modality. In divided tasks, patients with PD have more difficulty filtering out non-salient information. For instance, in a verbal dichotic listening task, Claus and Mohr (1996) asked subjects to attend to selective right or left ear stimuli and recall information from the unattended ear. NDPD patients were comparable to NCs on the free recall condition, while DPD patients performed similarly to demented patients with Huntington's disease (HD) and AD. However, when asked to recall information from the attended ear, PD patients (with or without dementia) performed significantly better than the other demented groups and as well as NCs. Sharpe (1992) has also suggested that PD patients are compromised in their ability to resist interference, as indicated by their poor ability to ignore targets, which are presented in the unattended ear in a dichotic task. PD impaired performance on several types of directed attention tasks

(i.e. covert and divided tasks) appears to be secondary to impaired inhibitory and response monitoring mechanisms (see Anterior Cingulate Cortex section).

Mood

Depression is fairly common in patients with PD. Prevalence rates of depression are approximately 40%, with some studies reporting rates as low as 4% and some as high as 90% (for reviews, see Aarsland & Karlsen, 1999; Barbosa et al., 1997; Cummings, Diaz, Levy, Binetti, & Litvan, 1996; Lichter, 2000; Raskin et al., 1990; Starkstein & Kremer, 2000). Hantz, Caradoc, Caradoc, Weatherall, and Dixon (1994) reported that the prevalence of depression in a group of PD patients was no different than in a group of age-matched physically disabled patients, whereas Menza and Mark (1994) reported a greater prevalence of depression in patients with PD relative to NC subjects with equivalent levels of physical disability. The inconsistencies reported in the literature may be attributed, in part, to poor diagnostic validity and reliability of clinical psychiatric measures used in assessing depression in PD. In several cases, false positive results are obtained because motor symptoms related to PD tend to resemble clinically depressed symptomatology (Aarsland & Karlsen, 1999; Levin, Llabre, & Weiner, 1988; Mayberg & Solomon, 1995; Starkstein & Kremer, 2000) or are masked by deficits in emotional processing (for review, see Zgaljardic, Borod, Foldi, & Mattis, 2003). For instance, similar to clinically depressed patients, individuals with PD may also display motor retardation, insomnia, a lack of energy, early morning awakenings, fatigue, and weight loss (Ondo & Jankovic, 1998).

Reports have also provided some evidence that there may be performance differences on neuropsychological tasks between PD patients with and without

depression (Kuzis, Sabe, Tiberti, Leiguarda, & Starkstein, 1997; Starkstein & Kremer, 2000; Wertman et al., 1993). For instance, Kuzis et al. (1997) assessed the cognitive profiles of PD patients with and without depression, depressed patients without PD, and a group of NC subjects. First, NC subjects and non-depressed PD patients did not demonstrate any significant differences on task performance. Second, both PD patients with depression and depressed patients without PD had similar impairments on tasks of word-list generation and auditory attention. Finally, PD patients with depression alone demonstrated the greatest impairment on tasks designed to measure executive functions (i.e., Wisconsin Card Sorting Test [WCST] and Raven Progressive Matrices [RPM]). Tröster, Stalp, Paolo, Fields, and Koller (1995) raised the concern that overall clinical severity may account for such findings; the authors did not report any significant group differences when depressed and non-depressed PD patients were matched on this factor. These findings suggest that for those patients with PD and depression, task performance appears to be considerably impaired, especially within the executive domain. This can be attributed to greater frontostriatal circuit disruption in depressed patients with PD as opposed to non-depressed patients with PD and depressed individuals without PD (Kremer & Starkstein, 2000; Mayberg, 2000; Wertman et al., 1993). Depression in PD is typically associated with decreased activation of the OFC (for reviews, see Cummings, 1993; Masterman & Cummings, 1997; Mayberg et al., 1990), whereas some reports to the contrary (e.g., Ring et al, 1994) have credited the medial frontal region including the ACC.

Apathy, on the other hand, is characterized as having indifference to environmental, emotional, and physical states (for reviews, see Devinsky, Morrell, &

Vogt, 1995; Lichter, 2000; Marin, 1991; Stuss, van Reekum, & Murphy, 2000) and is reportedly a consequence of ACC dysfunction (for review, see Cummings, 1993). Reported prevalence estimates of apathy in PD currently range from 16.5% to 42% (Aarsland & Karlsen, 1999; Czernecki et al., 2002; Pluck & Brown, 2002). Due to reports indicating a greater prevalence of depression than apathy in PD (e.g., Starkstein et al., 1992), it has been speculated that this patient population may exhibit greater disruption to the OFC than ACC frontal region.

The etiology of apathy in PD has not yet been systematically assessed, although studies have shown that individuals with PD do exhibit greater levels of apathy in comparison to age-matched physically disabled patients. Pluck and Brown (2002) not only discovered that PD patients were more apathetic than age-matched patients with osteoarthritis, but that a comparison of high versus low apathetic PD patients showed no significant differences in depression scores. In addition, no relationships were found between apathy and depression scores. In all, their findings suggest that depression and apathy may employ separate processes, possibly related to differential frontostriatal circuit involvement (i.e., ACC vs. OFC). In terms of the influence of dopamine on apathy levels in NDPD, one study has reported a decline in subjective complaints of apathy for dopamine-alleviated patients (Czernecki et al., 2002).

NEUROCEMICAL CHANGES AND CELLULAR DEGENERATION

The hallmark of PD is a reduction (up to 90%) of neurons in the substantia nigra, accompanied by subcortical Lewy body inclusions (Barbosa et al., 1997; McKeith & Burn, 2000; Savage, 1997). The pigmented substantia nigra neurons are dopaminergic and modulate cortical afferents in order to facilitate motor programs via direct and indirect striato-cortical pathways. The substantia nigra is part of a larger group of subcortical structures, collectively known as the basal ganglia, which include the substantia nigra (pars compacta and pars reticulata), corpus striatum (putamen, caudate, and ventral striatum), globus pallidus (internal and external segments), and subthalamic nucleus (DeLong, 2000). Dopamine therapy (e.g., levodopa) is the most effective treatment to date in alleviating motor symptoms, although improvements can be complicated with side effects (e.g., dyskinesias, motor fluctuations, and visual/auditory hallucinations) (Jankovic, 2000). In addition, other neurotransmitter systems are directly and indirectly compromised in PD, which may also elicit the need for further development of additional types of neurochemical therapies.

Dopamine Therapy and Cognitive/Behavioral Symptomatology in PD

Since the neuropathological hallmark of PD is a reduction of dopaminergic neurons in the substantia nigra, it would be expected that increasing the amount of available dopamine therapeutically might reverse potential cognitive and behavioral symptomatology. However, the research evidence demonstrates that dopamine therapy has not consistently been shown to alleviate cognitive and behavioral symptoms concomitant to PD. In fact, the relationship between dopamine and cognitive and behavioral changes is complex and inconsistent. Dopamine withdrawal in a sample of

patients with PD, for instance, demonstrated impaired performance on executive neuropsychological tests (Lange, Paul, Robbins, & Marsden, 1993; Lange et al., 1992). Brozoski, Brown, Rosvold, and Goldman (1979) discovered that depletion of prefrontal regional dopamine in rhesus monkeys resulted in impaired performance on a spatial delayed alternation task. The impairment found was just as severe as if the corresponding area was surgically ablated. Moreover, the depression exhibited when patients with PD are taken off dopamine therapy has been shown to resolve after being alleviated with dopamine (e.g., Maricle, Valentine, Carter, & Nutt, 1998; Quinn, 1998). In light of these findings, dopamine might not be directly associated with non-motor dysfunction, but may be operative in an indirect fashion. The cognitive and behavioral deficits reported in PD might result (at least partially) from disruption to other neurotransmitter systems (e.g., cholinergic) that are either directly or indirectly attributed to PD neuropathology (Briley, 1993; Dubois, Ruberg, Javoy-Agid, Ploska, & Agid, 1983; Growdon et al., 1998; Mayberg, 2000).

Growdon et al. (1998) assessed the effects of chronic dopamine administration on motor and cognitive performance in NDPD patients with mild-to-moderate clinical severity over a 6-month period. As predicted, patients demonstrated an improvement in motor symptomatology. Significant improvements were also detected on tests of executive functions, but were dissociable from memory and visuospatial performance, suggesting that the dopaminergic system may have a role in mediating select aspects of cognitive functioning, although other nondopaminergic systems were presumed to be involved. Similarly, Kulisevesky et al. (2000) reported that PD patients did improve on various neuropsychological measures after chronic dopamine therapy, but the effect was

short lasting and decrements in performance on most tasks were noted after 12-18 months. Furthermore, Pillon et al. (1989) correlated cognitive task performance with motor symptoms in 120 medication-withdrawn NDPD patients. According to their findings, motor symptoms that responded well to dopamine therapy (e.g., rigidity, hypokinesia, and/or bradykinesia) did not correlate significantly with cognitive performance, while those that did not respond well to dopamine therapy (e.g., gait disorder and dysarthria) did correlate. The common denominator drawn from these studies suggests that dopamine alone might not ameliorate all PD-related cognitive and behavioral deficits.

For neuropsychiatric disturbances concomitant to PD (e.g., depression, hallucinations, and/or delusions) (for reviews, see Aarsland & Karlsen, 1999; Kremer & Starkstein, 2000; Mayberg, 2000; Starkstein & Robinson, 1993), clinical evidence has shown that these symptoms do not typically subside after dopamine therapy and in some cases may be exacerbated by them (e.g., Aarsland & Karlsen, 1999; Jankovic, 2000; Mayberg, 2000; Nordberg, 2002; Saint-Cyr, Taylor, & Lang, 1993). Instead, PD patients with mood disturbance tend to benefit from tricyclic antidepressants and selective serotonin re-uptake inhibitors (for reviews, see Aarsland & Karlsen, 1999; Barbosa et al., 1997; Kremer & Starkstein, 2000).

Dopaminergic pathways (e.g., meso-cortical limbic [ventral tegmental area -- VTA]), which project to the OFC, may have an indirect impact on serotonergic systems in the basal temporal lobe which have predominately been found to be disrupted in depressed patients without PD (Kuzis et al., 1997; Mayberg & Solomon, 1995). This is supported by evidence indicating that PD patients with depression, in comparison to non-

depressed PD patients, (1) exhibit greater neuronal loss in the dorsal raphe (serotonergic) nuclei, (2) have decreases in serotonin receptor binding sites in the frontal cortex and basal ganglia (for review, see Litvan, 2000), and (3) show significantly lower levels of the serotonin metabolite 5-HIAA in the cerebrospinal fluid (CSF) (Mayeux, Stern, Sano, Williams, & Cote, 1988). Consequently, low CSF levels of homovanillic acid (dopamine metabolite) are not associated with depression in PD (Lichter, 2000). Furthermore, PD patients with greater VTA disruption are more likely to exhibit depression than those patients without extensive VTA disruption (Mayberg, 2000).

Acetylcholine Therapy and Cognitive/Behavioral Symptomatology in PD

Post-mortem, pharmacological, and neuropsychological studies have generated a great deal of interest into the possibility of the existence of a cholinergic system deficit in PD (Dubois et al., 1983; Hutchinson & Fazzini, 1996; Ott & Lannon, 1992; Perry et al., 1985; Rogers, Brogan, & Mirra, 1985). Losses of ascending cholinergic projections from the basal forebrain (e.g., substantia inominata and nucleus basalis of Meynert), muscarinic receptor hypersensitivity in the frontal cortex, and reductions of neurotransmitter specific metabolites such as choline acetyltransferase (CAT) have been reported in PD patients (Asahina et al., 1998; Aubert et al., 1992; Nakano & Hirano, 1984; Perry et al., 1985; Rinne, Myllykyla, Lonnberg, & Marjamaki, 1991; Shinotoh et al., 1999; Whitehouse et al., 1987). Cholinergic modulation is necessary for learning, memory, and visuospatial performance in both humans and animals (Everitt & Robbins, 1997). Hence, impaired cognitive functioning in PD patients may involve a decline in cholinergic activity in specified regions of the brain. Moreover, the extent of cognitive impairment in patients with PD has been shown to correlate with a reduction of

cholinergic modulators (Dubois et al., 1983; Perry et al., 1985; Rinne et al., 1991). In addition, these reported depletions, at least in NDPD patients, do not appear to be occurring in conjunction with cortical Lewy bodies, plaques, or tangles usually associated with AD or Lewy body disease (LBD). In fact, it has been reported that NDPD patients demonstrate a 50% reduction in CAT activity and an average of a 17% reduction in nucleus basalis of Meynert neurons (Perry et al., 1985). Despite these extensive neuronal and neurochemical losses reported in NDPD patients, the development of a dementia may occur in the later stages of the disease due to the formation of extensive Lewy bodies, plaques, and/or neurofibrillary tangles.

Dubois et al. (1987) administered subthreshold doses of a cholinergic antagonist (scopolamine) to NDPD patients and NC subjects. The dose was considered "subthreshold" because it did not produce central or peripheral side effects in subjects (e.g., nausea or dry mouth). Here, NDPD patients performed significantly worse than NC subjects on a recognition test for meaningless drawings. In another study, PD patients taking an anticholinergic (trihexyphenidyl) performed worse on tasks of executive function (e.g., Wisconsin Card Sorting Test) than those patients who did not receive the drug (Dubois, Pillon, Sternic, Lhermitte, & Agid, 1990). Groups were matched for clinical severity and dopamine therapy regimens. Consequently, there were no group differences on tasks of memory, intellectual function, or visuospatial skills. More recent replications of these findings have been conducted (e.g., Bedard et al., 1999).

The availability of anticholinesterase medication (which promotes increased acetylcholine availability within the brain) has led to numerous studies conducted over the past couple of decades attempting to assess the potential for cognitive improvement in

patients with AD (e.g., Greenberg et al., 2000; Mega, Masterman, O'Connor, Barclay, & Cummings, 1999), LBD (e.g., McKeith & Burn, 2000), traumatic brain injury (e.g., Taverni, Seliger, & Lichtman, 1998), multiple sclerosis (e.g., Greene et al., 2000), epilepsy (e.g., Bortz et al., 2000), and progressive supranuclear palsy [PSP] (e.g., Litvan et al., 2001). Systematic studies published focusing on anticholinesterase therapy in PD are few, but remain an important area of research. Preliminary work has demonstrated improvements in cognitive functioning, using basic mental status measures, after anticholinesterase therapy (e.g., Hutchinson & Fazini, 1996; Korczyn, 2001). Asahina et al. (1998) reported that in comparison to patients with PSP, those with PD (with and without dementia) had greater muscarinic receptor binding in the frontal cortex, suggesting more extensive cholinergic/frontal pathology related to cognitive dysfunction. Thus, the drug's potential in benefiting PD patients with cognitive complaints, especially within the executive domain, appears to be promising.

Norepinephrine Therapy and Cognitive/Behavioral Symptomatology in PD

Symptoms such as depression, dementia, olfactory disruption, and orthostatic hypotension have been associated with disruption of the noradrenergic system in PD (Briley, 1993; Duyckaerts, Gaspar, Costa, Bonnet, & Hauw, 1993; Gaspar, Duyckaerts, Alvarez, Javoy-Agid, & Berger, 1991). There are two main norepinephrine systems in humans: (1) neurons in the medulla oblongata, and (2) neurons in the locus ceruleus. The former system is reportedly mildly impacted in PD, whereas the latter is considerably impacted (Bertrand, Lechowicz, Szpak, & Dymecki, 1997; Briley, 1993; Soldani & Fornai, 1999). The locus ceruleus is an area within the tegmentum (i.e., pons) of the midbrain. The distributions of adrenoreceptors (which receive projections from the locus

coeruleus) within the cortex are particularly concentrated in the ACC (Jones, Hoyer, & Palacios, 1990). The extent of the neuronal loss with the locus ceruleus in PD appears to be proportional to the severity of cognitive dysfunction (Zweig, Cardillo, Cohen, Giere, & Hedreen, 1993).

In comparing postmortem brains of individuals with AD and PD, Zarow, Lyness, Mortimer, and Chui (2003) discovered that the greatest amount of neuronal loss in both patient populations occurred in the locus ceruleus relative to the substantia nigra and nucleus basalis of Meynert. For PD (N = 19), the greatest neuronal loss occurred within the locus ceruleus, with secondary losses in the substantia nigra and the nucleus basalis of Meynert respectively. It was not entirely clear in their study if the PD patients were demented or not, which may help explain the unexpected findings (i.e., substantia nigra less than locus ceruleus neuronal loss). Moreover, the extent of locus ceruleus and substantia nigra neuronal loss in patients with PD did not correlate, suggesting that these particular patterns of neurodegeneration may not share similar underlying susceptibility in the disease process.

Noradrenergic depletion appears to compromise attentional processes in humans and may be implicated in some aspect of frontal/executive dysfunction as described in patients with PD. This dysfunction could be explained by a difficulty in directing attentional resources to a task at hand that may be resulting from heightened levels of distractibility in individuals with PD (e.g., Sharpe, 1992). In other words, noradrenergic projections to the frontal cortex that would normally enhance signal-to-noise ratios may be impaired in PD (Everitt, Robbins, & Seldon, 1990). In an attempt to relate the attentional deficits in PD with disruption of the noradrenergic system, Bedard et al.

(1998) administered a selective noradrenergic agonist to nine nondemented patients with PD. A neuropsychological test battery including tests of attention and other executive functions was administered. The selected tasks required one to disengage their attention from a familiar sequence of behaviors and re-engage it toward a novel set of behaviors. In comparison to a placebo group, PD subjects taking a noradrenergic agonist improved on select executive tests such as the Odd Man Out Test and the Stroop Color/Word interference test. In the same study, EEG (electroencephalogram) evoked potentials associated with attentional processes improved in PD subjects receiving the noradrenergic agonist.

FRONTOSTRIATAL CORTICAL CIRCUITRY

In the upcoming sections, a review of the literature (predominantly non-PD lesion and neuroimaging data) will be provided in an attempt to delineate specific frontal/executive functions and neuropsychological tasks across the three previously described complex frontostriatal circuits (i.e., ACC, DLPFC, and OFC). PD reportedly disrupts the circuits connecting the prefrontal cortical regions and striatum that may contribute to the cognitive and behavioral deficits found in these patients (Lichter & Cummings, 2000). Research detailing the severity of this disruption and the extent to which individual circuits are impaired based upon neuropsychological task performance in PD is limited. For this reason, we incorporated the following section into the review as a means to better conceptualize and categorize frontal/executive neuropsychological deficits by circuit and attempt to relay them to the non-motor PD profile. In other words, this newer approach may allow us to appreciate the link between task performance and neuroanatomy in this particular patient population especially during the development of our experimental test battery.

Anterior Cingulate Cortex

In the most extreme case, bilateral lesion of the ACC can result in akinetic mutism (Masterman & Cummings, 1997). This behavioral syndrome is characterized by profound apathy and a lack of impulse for speech, action, and psychic initiative (Lichter & Cummings, 2000). In addition to associating ACC disruption with affective and behavioral alterations (i.e., apathy; see Mood section above), there is ample evidence to suggest that the ACC also mediates cognitive functions (e.g., in cingulotomy patients [Cohen, Kaplan, Moser, Jenjins, & Wilkinson, 1999] and in PD patients [Grossman et al.,

1992]). In these studies, impairment generally reflects deficits in attention, such as response intention, sustained attention, spontaneous response production, and response monitoring, particularly the processes of intention and response selection and control. "Intention" refers to attention to action, which influences the propensity to respond via behavioral readiness, anticipation, and response maintenance. ACC disruption appears not to have a circumscribed effect on tasks assessing sensory selective attention, attention span, and working memory. Learning and memory performances also appear to be preserved with ACC disruption (e.g., Cohen et al. 1999).

The ACC is intricately connected to cortical, limbic, and subcortical structures via afferent pathways from the lateral frontal and parietal regions as well as efferent pathways to the amygdala, nucleus accumbens, septi, and basal ganglia (Alexander et al., 1986; Cohen et al., 1999; Morecraft, Geula, Mesulam, 1993). Overlapping projections from the anterior and posterior cingulate with other limbic system nuclei, and the lateral frontal and parietal cortices, along with efferent projections from the ACC to frontal subsystems, may account for the role of the ACC in attentional, cognitive, and behavioral processes.

Recent investigations provide evidence for a pattern of ACC disruption in patients with PD. Schroeder et al. (2002) reported ACC activation changes during performance on the incongruent trial of the Stroop task in PD patients using regional cerebral blood flow (rCBF) as a clinical marker. PD patients in their study had previously been implanted with subthalamic nucleus (STN) deep brain stimulators for treatment of their motor symptoms. Task performance was impaired (i.e., prolonged reaction times) while patients' stimulators were on. Decreased activation was noted in the right ACC and right

ventral striatum (i.e., ACC circuit). Their findings provide direct support for a disruption in the ACC circuit in individuals with PD. In spite of this recent finding, neuropsychological investigations specifically pinpointing ACC disruption in PD are limited. Thus, in the current section we will provide evidence linking ACC disruption (primarily via studies using frontal-brain damaged patients) and neuropsychological task impairments.

Perret (1974) evaluated the performance of 118 unilateral brain-damaged patients using the Stroop Color-Word Interference Test and a test of word-list generation. A subset of patients with left frontal lesions performed significantly worse in comparison to other brain-damaged groups. Perret (1974) claimed that the common denominator for normal performance on both tasks was the ability to suppress the usual tendency of analyzing words (i.e., phonetically or semantically) in order to solely attend to either the color in which they are printed or the initial letter presented. Research work suggests that patients with ACC dysfunction exhibit impairments in response selection, performance monitoring, spontaneity, resolution of cognitive conflict, and willed action (Carter et al., 1998; Cohen et al., 1999; Frith et al., 1991; Pardo et al., 1990; Raichle et al., 1994; Smith & Jonides, 1999; Stuss et al., 2001), possibly indicative (although speculative) of the types of impaired task performance exhibited by patients in the study by Perret (1974). Consequently, PD patients with high levels of apathy (typically associated with ACC disruption) were discovered to perform worse on measures of executive function involving willed action and response monitoring in comparison to a group of PD patients with reportedly lower levels of apathy (Pluck & Brown, 2002).

Stuss and colleagues (1998, 2001) utilized similar neuropsychological measures as in the study by Perret (1974) to index frontal lobe activation. On a task of phonemic and semantic word-list generation, Stuss et al. (1998) evaluated 74 brain-damaged patients, as well as a comparison group of age-matched NC subjects. Patients with superior medial frontal lesions (including the ACC), both alone or in conjunction with other cortical lesions, were moderately impaired on word-list generation (phoneme-cued) and produced significantly fewer words during the initial 15 seconds than did NCs. The authors suggested that lesions to the ACC might impair a patient's ability to initiate word-list generation. This complements findings from previous work associating ACC function with response intention and initiation on tasks involving spontaneous verb generation, design fluency, and object construction (Cohen et al., 1999; Frith et al., 1991; Petersen, Fox, Posner, Mintum, & Raichle, 1988). Stuss et al. (2001) administered a modified version of the Stroop Color-Word Interference Task (blocked format) to brain-damaged patients and NC subjects. For incongruent color-naming performance (interference condition), increased RT and number of errors were associated with lesions to the superior medial region of the frontal lobe. This particular region is implicated in maintaining the strength of response intention and competition (i.e., to name colors and not words) indicative of DLPFC function. In their study, specific damage to the ACC did not correlate with poor performance during the interference condition. In spite of its reported role in response monitoring and conflict resolution, ACC activation in their study may have been partially obscured due to a blocked presentation format that minimized response competition.

In support of ACC involvement during Stroop task performance, MacDonald et al. (2000), using event-related fMRI with NC subjects, reported on the existence of an association between specific Stroop task performance and cortical activation. Their findings suggested that the ACC was not activated during the implementation of task instructions (i.e., to name the color but not the word). Instead, this function is contingent upon intact working memory abilities dependent upon the DLPFC. The ACC was significantly activated during instances of conflict monitoring (i.e., response competition). In other words, according to their findings, the ACC is not characterized as providing a system to hold task-relevant information on-line (i.e., top-down control), but rather may be crucial for maintaining the attentional demands of the task by providing a system capable of monitoring errors during instances of conflicting responses, which appears to be independent of working memory (Pardo et al., 1990). Pardo et al., 1990 investigated the regions of the brain that mediated the processing selection in the Stroop paradigm by indexing rCBF, as measured by PET. Results indicated that the greatest neuronal activity occurred in the right ACC during the incongruent condition. The vigorous activity, during the incongruent condition, in the ACC argued for this region's involvement in the anterior attentional system.

Dorsolateral Prefrontal Cortex

The DLPFC is an area that is considered central to frontal/executive functions in humans (for review, see Cummings, 1993; Masterman & Cummings, 1997). The DLPFC mediates several functions, such as organizing a behavioral response to solve a complex problem, activate remote memories, maintain and shift behavioral sets, generate motor programs, strategy generation, and use of verbal skills and internal cues to guide behavior

(Cummings, 1993; Stuss & Alexander, 2000; Taylor et al., 1986; Taylor & Saint-Cyr, 1995). As for specific neuropsychological tests, performances on verbal and design fluency, alternating and reciprocal sequences, problem solving tasks (e.g., Tower of London), conditional associate learning, and self-monitoring (e.g., Wisconsin Card Sorting Test) all depend on functions mediated by the DLPFC (Cummings, 1995). DLPFC functions in the context of executive operations in PD have been extensively reviewed (e.g., Brown & Marsden, 1990; Dubois et al., 1991; Taylor & Saint-Cyr, 1995). Since deficits of executive "cognitive" functions have been frequently observed in PD patients, it is believed that the DLPFC is significantly disrupted in this patient population (e.g., Green et al., 2002). Both clinical and experimental research implicates impaired dopaminergic neurotransmission in the specific cognitive deficits of PD, particularly those related to DLPFC functions. The executive deficits observed in NDPD are likely the consequence of DLPFC circuit dysfunction at the level of the caudate nucleus, resulting from a lesion of the nigrostriatal dopaminergic pathway (Lichter, 2000).

The DLPFC has been aptly labeled the "central executive" for reasons that its activation tends to overlap with that of the ACC and OFC by maintaining a role in working memory and top-down control (D'Esposito et al., 1995; Elliot, Rees, & Dolan, 1999; MacDonald et al., 2000; Shallice, 1988). For instance, as previously mentioned, MacDonald et al. (2000) maintained that the DLPFC and the ACC mediate separate functions necessary to successfully complete the Stroop task. In their study, the DLPFC was activated during both the congruent and incongruent color-naming trials suggestive of its role in working memory (whether or not response monitoring is necessary). Similarly, while administering the Stroop task and a task of word-list generation to brain-

damaged patients, Stuss and colleagues (1998, 2001) suggested that the DLPFC governed working memory processes via articulatory rehearsal throughout the duration of the task (e.g., holding task instructions on-line).

The DLPFC is critical for new learning when working memory (D'Esposito et al., 1995; Goldman-Rakic, 1987; Jonides et al., 1993; Jueptner et al., 1997), set-shifting (Nagahama et al., 1998), and attention to action are necessary (Lichter, 2000). Set-shifting deficits in patients with PD, for instance, are well documented in the literature (Brown & Marsden, 1990; Cools, van der Berken, Horstink, van Spaendonck, & Berger, 1984; Raskin et al., 1992; Richards et al., 1993). For example, Cronin-Golomb, Corkin, and Growdon (1994) administered separate tests of set-shifting, concept formation, and problem-solving to a group of NDPD patients. Their findings revealed that performance on the two latter tasks was relatively preserved in PD, while set-shifting ability (assessed using an experimental task) was significantly impaired in comparison to NC subjects. They attributed impaired set-shifting in PD to an inability of appropriately inhibiting responses presumably resulting from DLPFC disruption. In support of this claim, Nagahama et al. (1998), using an experimental card-sorting task, discovered that the DLPFC in NC subjects was activated significantly during set-shifting performance.

The consensus from the literature suggests that the DLPFC is considerably disrupted in PD. Recent work has demonstrated that executive impairments either within the verbal or nonverbal domain are most likely related to metabolic changes in the DLPFC region in PD patients (e.g., Cools, Stefanova, Barker, Robbins, & Owen, 2002; Lewis et al., 2003). Neuroradiologic findings have suggested that disrupted striatal outflow to the DLPFC may underlie cognitive deficits found in PD. Owen, Doyon,

Dagher, Sadikot, and Evans (1998) administered an experimental spatial working memory task to NDPD patients (medication withdrawn) and NC subjects. Using rCBF as a clinical metabolic marker, they discovered significant decreases of blood flow in the right globus pallidus (internal segment) in the PD group without corresponding declines in the DLPFC region suggesting that striatal dysfunction (resulting from dopamine depletion) leads to executive deficits by indirect interruption of the frontostriatal circuitry. By contrast, Cools et al. (2002) revealed that when patients with PD were dopamine-alleviated, rCBF levels obtained while performing a planning and a spatial working memory task separately (relative to performing a control task) were normalized in the right DLPFC region. These latter findings suggest that dopamine may modulate executive deficits in PD by having a direct effect on the DLPFC.

Orbitofrontal Cortex

Previous work using non-human subjects (e.g., primates) suggests that the OFC might not mediate cognitive functions as the ACC and DLPFC, instead lesions to this region have been associated with changes in eating (i.e., visceral functions) and social behavior patterns with altered emotional reactions to environmental changes (Starkstein & Kremer, 2000). This is not necessarily surprising since the OFC has strong neural connections with sensory (olfactory and taste) and limbic (emotional) brain structures (Elliott, Dolan, & Frith, 2000; Lichter & Cummings, 2000). Despite these claims, cognitive-like deficits have been noted in non-human subjects and usually entail errors of perseveration and impaired response inhibition (e.g., Iversen & Mishkin, 1970; Passingham, 1972). However, these reported cognitive-like deficits in brain-lesioned animals might instead result from the subjects' inability to appropriately process reward-

punishment contingencies since food (i.e., reward) is usually related to desired task performance in several of these studies. Here, non-human subjects respond to a stimulus associated with food, but in later trials, find it difficult to extinguish that response even when food is no longer presented with the stimulus. Studies have suggested that damage to the DLPFC in primates results in impaired "cognitive" inhibitory control (i.e., disinhibition) in attentional selection, whereas disruption of the OFC may result in reduced inhibitory control in affective processing (i.e., emotional/behavioral contingencies; e.g., Dias, Robbins, & Roberts, 1996). This cognitive and behavioral dichotomy using neuroradiologic methods has been demonstrated in studies using human subjects as well (e.g., Nagahama et al., 1998).

In humans, OFC disruption can lead to emotional instability (e.g., disinhibition, depression, and obsessive-compulsive disorder) due to a dissociation of frontal monitoring systems from limbic input (for reviews, see Eslinger & Damasio, 1985; Lichter, 2000; Masterman & Cummings, 1997). Patients may exhibit social and behavioral deficits such as euphoria, diminished affect, impulsivity, social irresponsibility, poor reasoning and decision-making abilities with relatively preserved intellect (Damasio, 1994; Rahman, Sahakian, Cardinal, Rogers, & Robbins, 2001; Rolls, 2000; Stuss et al., 1982; Stuss et al., 1983; Upton & Thompson, 1999). For instance, Bechara and colleagues (1994, 1996) described the performance of OFC brain-damaged patients on an experimental gambling task. This task was designed to assess and quantify decision-making abilities by having subjects attempt to maximize their profits (using fake money) during a card game (using reinforcement contingency schedules). Here, OFC patients tended to profit from short-term rewards at the expense of long-term

consequences. Interestingly, when asked about the task, patients were able to accurately describe the reinforcement contingencies of the task, but were unable to implement this knowledge in an attempt to earn more money. Furthermore, Bechara et al. (1996) discovered that in comparison to NC subjects, OFC patients demonstrated a decreased galvanic skin response prior to the execution of a high-risk response on the gambling task. The authors suggested that the OFC is important in triggering autonomic reactions while anticipating a reward or punishment, which may explain why OFC patients perform poorly when decision-making abilities are required.

Similarly, Upton and Thompson (1996, 1999) administered a decision-making task (Twenty Questions Test; Klouda & Cooper, 1990) to epilepsy patients with frontal lobe foci. This task is similar to the gambling task in that it requires abstract decision-making and hypothesis-testing capabilities. Their findings revealed that patients with considerable OFC disruption exhibited the greatest impairment on a measure associated with impulsivity. Hence, this led the authors to conclude that OFC patients may have a tendency to present with reduced impulse control prior to appropriate strategy formation, thus, allowing them to frequently guess prematurely in comparison to patients with DLPFC and ACC disruption. The relationship between OFC dysfunction and reduced impulse control is supported from earlier work (e.g., Crowe, 1992; Duffy & Campbell, 1994; Fuster, 1989; Luria, 1966; Malloy & Duffy, 1992; Stuss et al., 1983).

Cools et al. (2001) demonstrated that PD patients who were dopamine-alleviated performed poorly on a probabilistic reversal-learning task (stimulus-reward shifting task) that had been previously associated with OFC function in normal control subjects (Rolls, 1999). Reversal learning is another example of shift learning in which discriminative

stimuli remain the same, but identity of the reinforced stimulus (or object) is switched. Thus, the subject has to desist responding to the previously non-reinforced stimulus in order to gain a reward. The subject must learn which stimulus is now rewarded. This is different than set-shifting typically associated with DLPFC function. By contrast, the same patients, after medication withdrawal, had difficulties on a letter/number set-shifting task typically associated with DLPFC function, but demonstrated improvements on the probabilistic reversal-learning task. During the dopamine-alleviated condition, positron emission tomography (PET) findings indicated OFC hypometabolism while PD patients were performing the latter task. The authors concluded that dopamine therapy could either benefit or impair performance depending on the nature of the task administered and the basal level of dopamine in the associated frontostriatal circuitry. These findings have strong implications for differential involvement and/or impairment of the frontostriatal circuitry in PD.

FRONTAL/EXECUTIVE NEUROPSYCHOLOGICAL TESTING IN PD

The array of neuropsychological tests used to evaluate patients with PD should reflect the frontal/executive impairments outlined in this review. Inconsistencies in assessment may have contributed to some of the cognitive impairments reported in PD across studies. Previous work has shown that frontal/executive measures vary in their ability to assess cognition in patients with PD and NC subjects (e.g., Gotham et al., 1988; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1996). This may be attributed to the fact that neuropsychological tests are usually constructed to elicit function and not define neuroanatomy. Some neuropsychological measures are multi-faceted and lack a defined unitary frontal/executive function (Stuss, 1993; Stuss & Alexander, 2000). Moreover, cortical regions other than the frontal lobes also contribute to performance on select frontal/executive measures (Duffy & Campbell, 1994; Goldenberg, Podreka, Muller, Deecke, 1989; Stuss & Alexander, 2000; Stuss, Stethem, Hugenholtz, & Picton, 1995) and the extent and focus of the cortical damage may vary from patient to patient. Findings of this sort may help explain the low correlations and/or performance inconsistencies reported across frontal lobe assessment measures (Stuss & Alexander, 2000). In order to help validate neuropsychological performance in PD patients, it is important that the neuroanatomical correlates (e.g., frontostriatal circuits) underlying specific task functions be clearly understood.

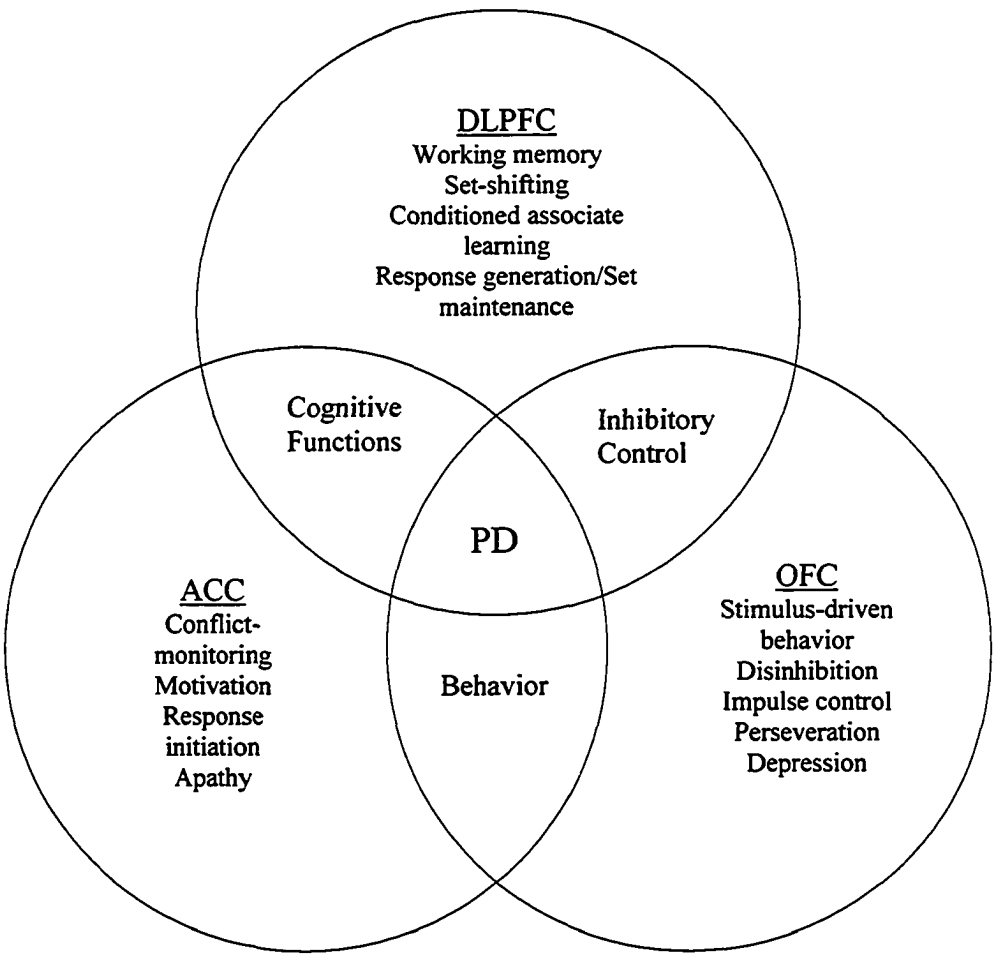
REVIEW SUMMARY AND STUDY HYPOTHESES

Frontostriatal circuitry dysfunction appears to have a profound effect on cognition and behavior in patients with PD. The changes in cognitive function were cited in a number of studies that reported poor or inconsistent performance on neuropsychological tasks assessing executive functions such as set-shifting, planning, organization, response monitoring, decision-making, and maintenance of cognitive set. Behavioral (i.e., non-cognitive) alterations in PD are prominently represented by depression and apathy. The prevalence of depression outweighs apathy, but the two syndromes appear to be dissociable and may involve separate processes.

The three complex frontostriatal circuits (e.g., DLPFC, ACC, and OFC) mediate a number of frontal/executive functions. Although previous research has shown that patients with PD exhibit impairments across several cognitive domains, it may be more plausible to assume that impaired executive abilities are responsible for the broad spectrum of cognitive and behavioral impairments based upon the evidence presented above. Individually, the three circuits described here delegate specific functions, with the DLPFC acting as a moderator (i.e., central executive) over the entire system. The DLPFC and ACC appear to mediate both cognitive and behavioral functions, while the OFC is more involved in aspects of non-cognitive behavior (e.g., depression and impulse control). Figure 1 offers one way to view cognitive and behavioral functions associated with each frontostriatal circuit, as well as their functional relationships. From our perspective, the ACC and DLPFC are related in terms of their respective contributions to cognition; the ACC and OFC are linked through their involvement in

Figure 1

Neuropsychological Functional Interrelationships between Frontostriatal Circuitry



behavior (e.g., mood); and the OFC and DLPFC are similar in regards to their functional contribution toward inhibitory control processes. Although not illustrated here, variations of this proposed integration might be that, the DLPFC may contribute more of its resources in comparison to the other two prefrontal regions in governing frontal/executive functions. Thus, greater impairment related to DLPFC function might be expected in PD (Lewis et al., 2003).

To our knowledge there have not been any systematic investigations evaluating the degree of frontostriatal circuit dysfunction in PD patients using standardized neuropsychological tests. PD neuropathology is characterized by a disruption of frontostriatal circuitry, and it is these pathways that are believed to mediate most non-motor deficits. The relationship between the severity of the cognitive and behavioral disruption and the extent of individual circuit impairment is still being explored via neuroradiologic and neurochemical studies. Furthermore, the PD literature has shown that inconsistencies in frontal/executive task performance do exist across measures. Evidence from the research literature indicates that (a) variable damage to frontostriatal circuits in PD may have differential effects on task performance, and (b) the construction of select neuropsychological tests may be too heterogeneous to measure underlying executive functions mediated by the specific neural circuitry.

Rationale and Hypotheses

In the current study, we administered standardized neuropsychological tests and self-report behavioral scales believed to tap functions mediated by the three frontostriatal cortical circuits to a group of nondemented Parkinson's disease patients and demographically-matched healthy normal control subjects. For example, performance on

a conditional associate learning task is reportedly mediated by the DLPFC (e.g., Levine, Stuss, & Milberg, 1997), behavioral alterations (e.g., depression) have been related to OFC dysfunction (e.g., Mayberg et al., 1990), whereas select performance on the Stroop Color-Word Interference test is reportedly impaired in patients with specific disruption to the ACC (MacDonald et al., 2000; Pardo et al., 1990; Stuss et al., 2001). Our neuropsychological test battery includes a variety of frontal/executive tasks. The standardized tasks were selected based upon evidence from the PD, human brain damage, animal, and neuroimaging research literatures presented above. Other neuropsychological tasks will be incorporated as screening measures to assess general cognitive status.

Questions that will be addressed in the current study are: (1) Do our findings support a segregation of frontal/executive task performance in PD patients (relative to NC subjects) along the lines drawn by the three different frontostriatal cortical circuits? (2) Since the literature maintains that patients with PD typically display a greater "cognitive based" executive dysfunction, will patients perform worse on DLPFC-related tasks in comparison to ACC or OFC-related tasks? (3) Which set of tasks, categorized by circuit, is the best predictor of group membership? (4) Does performance on tasks mediated by the same frontostiatal circuit (e.g., spatial working memory and conditioned associate learning [DLPFC]) correlate with each other? (5) Will low or non-existent correlations be found for tasks not purported to be mediated by the same circuit (e.g., depression [OFC] versus Apathy [ACC])?

METHODS

Subjects

Subjects were 61 right-handed adults, including 32 nondemented Parkinson's disease patients (59% men) and 29 healthy control subjects (48% men). The number of subjects was determined before initiation of the study by using a power analysis (Ramsey & Ramsey, 1997). This power analysis used the noncentrality variable (lambda) and the degrees of freedom from Richards et al. (1993), i.e., the study used to gage set-shifting (Odd Man Out Test) performance differences between PD and NC subjects groups for the current study. The critical F value was determined from alpha set at .05. Given these parameters, 60 subjects were required to obtain a power of .995.

Handedness was determined by self-report and confirmed by the Coren, Porac, and Duncan (1979) lateral preference inventory; there were no reported histories of converting from left-handedness. All subjects were native speakers of English (or had learned English by the age of seven); were between the ages of 50 and 79 (overall M = 66.8, SD = 7.0); had an overall mean education level of 15.8 years (SD = 2.5); and had an overall mean occupational level of 7.4 (SD = 1.5) on the Hollingshead Scale (Hollingshead, 1977), ranging from "1" (e.g., unskilled service worker) to "9" (e.g., major professional). In order to compare demographic characteristics of the two subject groups, we conducted independent samples t-tests. No significant group differences were found for age, t = -.102, p = .919; years of education, t = 1.24, p = .220; and occupational level, t = .587, p = .560. See Table 1 for subject group means and standard deviations.

Table 1

Between Group Comparisons for Demographic, Screening, and Comparison Variables

Variable	PD (Mean/SD) N=32	NC (Mean/SD) N=29	t value	p value
Age	66.88/8.13	66.69/5.73	-.102	.919
Education	15.38/2.73	16.17/2.24	1.239	.220
Hollingshead	7.25/1.68	7.48/1.38	.587	.560
Estimate IQ	113.56/7.39	115.38/4.98	1.114	.270
Purdue Pegboard (dominant hand)	9.28/2.99	12.79/1.93	5.389	.001*
Purdue Pegboard (nondominant hand)	9.06/2.20	12.21/1.50	6.460	.001*
Purdue Pegboard (both hands)	6.81/2.01	10.34/1.63	7.494	.001*
DRS	140.94/2.45	141.76/2.32	1.340	.185
BDI	7.72/5.97	5.52/4.49	-1.615	.112
BTA	17.06/1.85	17.83/1.26	1.871	.066
VFDT	30.59/1.56	30.48/1.43	-.288	.774

DRS = Dementia Rating Scale (total score); BDI = Beck Depression Inventory; BTA = Brief Test of Attention; VFDT = Visual Form Discrimination Test

* = $p < .001$

Inclusion criteria

A diagnosis of PD, as well as disease severity ratings (Hoehn and Yahr stages [0-5]); Hoehn & Yahr, 1967) were verified by a neurologist at the Movement Disorder Center of North Shore University Hospital as part of the patients' clinical visit. Clinical severity of PD was limited to mild/moderate levels (Hoehn & Yahr stages ranging from 1.5 to 3) for inclusion purposes in order to reduce confounding factors (e.g., incoherent speech and immobility). Stage 1.5 signifies "unilateral and axial involvement", stage 2 signifies "bilateral involvement without impairment of balance", stage 2.5 signifies "mild bilateral involvement with recovery on repulsion (pull) test without rater assistance", and stage 3 signifies "mild to moderate bilateral involvement; some postural instability but physically independent; needs assistance to recover from pull test". Our sample included five Stage 1.5 patients, fifteen Stage 2 patients, one Stage 2.5 patient, and eleven Stage 3 patients ($\underline{M} = 1.92$, $\underline{SD} = .99$).

Exclusion Criteria

Subjects deemed as having a dementia (Mattis-Dementia Rating Scale total score ≤ 123 [Montgomery & Costa, 1983] were excluded. The current study only enrolled nondemented PD patients to prevent potentially confounding variables associated with demented patients (e.g., Alzheimer's disease pathology). Although attempting to reduce confounding variables in a study such as this one can be justified, the potential bias in excluding demented patients with PD may also add to the inconsistent findings reported in the literature. Thus, the proposed procedures can only be justified by the fact that, to our knowledge, a systematic study evaluating the neuropsychological underpinnings of all three frontostriatal circuits in PD patients has not yet been employed.

All relevant medical history and demographic information was obtained via subject medical record review and a structured interview. For PD patients, laterality of motor symptoms was not relevant since previous work (e.g., St. Clair, Borod, Sliwinski, Cote, & Stern, 1998) had revealed nonsignificant differences between patients with either left- or right-sided motor symptoms on measures of cognitive functioning. All patients were allowed to continue their usual PD drug regimens since cognitive changes resulting from dopamine therapy have not been clearly substantiated in patients with PD (e.g., Growden et al., 1998; Kulisevsky et al., 2000). Patients taking anticholinergic therapy for motor symptoms were excluded due to potential cognitive sequelae (e.g., memory decline). For NC subjects, only a structured interview was conducted.

Subjects were excluded if they (1) were severely depressed (Beck Depression Inventory of $\geq$ 30 [Spreen & Strauss, 1991]), (2) demented (criteria set above), (3) had undergone any surgical procedure for PD (e.g., pallidotomy), (4) had a history of any other neurological disorder, or head injury (involving a loss of consciousness), (5) presented with aphasia, myoclonus, apraxia, occulomotor abnormalities, ataxia, sensory loss, or any other cortically-based pathology [verified by a neurologist and medical records]), (6) were on anticholinergic therapy (e.g., Artane [trihexyphenidyl HCl]) for their PD motor symptoms, (7) were taking any other medication that may directly or indirectly impact cognitive functioning (e.g., sedatives, anti-convulsants, cholinesterase inhibitors, and/or neuroleptics), (8) presented with an estimated IQ below 1.5 standard deviations from the mean, and/or (9) indicated prior history of alcohol/drug dependence, psychiatric disorder, traumatic brain injury, and/or any other condition that might

adversely impact cognitive performance. All exclusionary criteria pertained to NC subjects as well.

Procedures

All subjects were administered one of three counter-balanced (randomly ordered) neuropsychological test batteries, consisting of standardized screening and frontal/executive measures. See Appendix A. The single testing session lasted approximately two hours. Subjects were recruited from the Movement Disorders Center at North Shore University Hospital and tested in a quiet room. Normal control subjects typically were spouses and/or caregivers of the included PD patients. Informed consent was obtained from all subjects prior to enrollment. Subjects were not monetarily reimbursed for their time or for transportation expenses.

Materials

Frontostriatal circuit dysfunction in PD was addressed with the development of a neuropsychological test battery that incorporated findings from the PD, brain-damaged, animal (primate), and neuroimaging research literatures. The standardized neuropsychological tests selected have each been shown to highlight impairment or function of one of the three previously described frontal cortical regions (i.e., ACC, DLPFC, and OFC). In order to compensate for PD motor symptomatology specific considerations were made in selecting the standardized tasks so as to minimize motor involvement and fatigue. The following section categorizes these neuropsychological tasks according to (1) comparison task (described below), (2) screening tasks, (3) DLPFC-related tasks, (4) ACC-related tasks, and (5) OFC-related tasks. A description of each investigational task includes test procedures, principal dependent variables, and a

brief explanation of how the measures relates to frontostriatal circuit function. The test battery incorporates *one* comparison measure, *five* screening measures, *six* DLPFC-related tasks, *three* ACC-related tasks, and *four* OFC-related tasks. Please see Appendix B and Appendix C for a list and brief description of the neuropsychological tasks and experimental dependent variables (with test score ranges) categorized by screening measures and frontostriatal circuit related tests.

Comparison Measure

The *Purdue Peg Board* (Tiffin, 1968) is a test of speeded motor dexterity. While PD motor severity was assessed using the Hoehn and Yahr scale, we wanted to incorporate an additional measure of motor functioning for both subject groups for the purposes of conducting exploratory comparisons between motor, cognitive, and behavioral task performance in our sample. The comparison measure was not utilized as a screening measure in this study.

The Purdue Pegboard test incorporates two parallel rows of 25 holes each with metal pegs located in four bins at the top end of the board. The pegs are approximately one inch long. In the three subtests utilized, the subject places as many pegs as possible into the holes, first with their dominant hand, then with their non-dominant hand, and finally with both hands simultaneously, each within a 30-second time period. To test the right-hand, the subject has to insert as many pegs as possible into the holes, starting at the bottom of the right-hand row. The left-hand is then tested using the left row. Lastly, both hands are used simultaneously to fill both rows from bottom to top (Spreen & Strauss, 1991). Mean cutoff scores (5^{th} percentile) for the test are as follows: (1) Dominant hand - males (age 50-59) = 10.3; females (age 50-59) = 10.7; males (age 60-

69) = 8.6; females (age 60-69) = 11.8; males (age 70+) = 7.4; females (age 70+) = 10.2, (2) Nondominant hand – males (age 50-59) = 10.4; females (age 50-59) = 9.8; males (age 60-69) = 8; females (age 60-69) = 9.2; males (age 70+) = 7.9; females (age 70+) = 8.6, (3) Both hands – males (age 50-59) = 8.3; females (age 50-59) = 8.3; males (age 60-69) = 8.7; females (age 60-69) = 7.7; males (age 70+) = 5.4; females (age 70+) = 6.2.

Screening Measures

The *Mattis Dementia Rating Scale* (MDRS; Mattis, 1988) is a comprehensive screening measure of dementia that was selected for this study as a means to exclude individuals presenting with a dementia. The subtests of the MDRS include: (1) attention, (2) initiation/perseveration, (3) construction, (4) conceptualization, and (5) memory. For the present study, a total score cutoff of 123 indicated the presence of a dementia (Mattis, 1988; Montgomery & Costa, 1983a).

An estimate of premorbid full scale IQ was calculated using the method of Barona, Reynolds, and Chastain (1984). This method was chosen for the current study, as opposed to the Wechsler Adult Intelligence Scale-III (Wechsler, 1997), since no administration procedures are required thus reducing total test administration time. This was important in the current study to minimize fatigue for the PD patient sample. Barona et al. (1984) established a regression formula based upon the WAIS-R (Wechsler, 1987) that incorporates a subject's (1) age [in years], (2) gender, (3) education level [in years], (4) ethnicity [black, white, other], (5) region of residence [southern, north central, western, or northeast], and (6) occupation [professional and technical, managerial, skilled workers, not in labor force, farmers, or unskilled workers]. Each variable is assigned a point value, which is incorporated into the following regression formula:

Estimated Full Scale IQ = 54.96 + .47 (age) + 1.76 (gender) + 5.02 (education) + 4.71 (ethnicity) + .59 (region) + 1.89 (occupation).

The *Benton Visual Form Discrimination Test* (VFDT; Benton, Hamsher, Varney, & Spreen, 1983) is a measure of basic visual perception. Subjects are shown 16 separate sets of abstract designs and were asked to choose the identical design out of a display with four choices. Two points are awarded for each correct item, only one point is awarded when a peripheral error is committed, and no credit is awarded for all other error types (e.g., distortion, rotation, and/or displacement), resulting in a possible total test score of 32. The cutoff score (5th percentile) is 25 (Benton et al., 1983).

The *Brief Test of Attention* (BTA; Schretlen, 1989) assesses gross attention and concentration beyond simple immediate auditory span (Lezak, 1995). The subject is asked to pay attention to a tape-recorded voice reading a sequence of numbers and letters. The sequence string increases after each successive test item. There are two trials. In one trial, the subject must account for all the numbers only read during the sequences, while on another trial, the subject must only pay attention to the letters only read. A score of 10 can be obtained on each trial for a total possible test score of 20. Cutoff scores for the BTA differ by age group. For subjects between and including the ages of 50-69, the cutoff score (5th percentile) is 10. For subjects between and including the ages of 70-79, the cutoff score (5th percentile) is 9. For subjects between and including the ages of 80-84, the cutoff score (5th percentile) is 8 (Schretlan, 1989).

The *Beck Depression Inventory* (BDI; Beck, 1987) contains 21 individual statements reflecting particular aspects of depressive symptomatology experienced over the past seven days, including the day of test administration (e.g., mood, sense of failure,

indecisiveness, work inhibition, and appetite). There has been concern that the somatic complaint items included in the BDI may be confounded in elderly patients and those with specific movement disorders such as PD (Lezak, 1995). However, Levin, Llabre, and Weiner (1988) reported that responses given by PD patients indicated that the somatic complaints were associated with the depression and not disease symptomatology, suggesting that the BDI is a valid measure in assessing depression in this patient population.

Each item has four choices indicating the level of severity in which one agrees with the presenting statement. For example, the range of statements under self-hate is "3 = I hate myself," "2 = I am disgusted in myself," "1 = I am disappointed in myself," "0 = I don't feel disappointed in myself." The highest score you can obtain for one item is 3 points. Classification of depression severity by BDI scores has been defined: as 10-15 = mild; 16-19 = mild/moderate; 20-29 = moderate/severe; 30+ = severe (Spreen & Strauss, 1991).

DLPFC Tasks

The DLPFC-related tasks selected reflect abilities associated with working memory (verbal & nonverbal), set shifting, conditioned associate learning (i.e., trial and error learning), and intrinsic response generation.

The *Odd Man Out Test* (OMOT; Flowers & Robertson, 1985; Richards et al., 1993) assesses aspects of cognitive set-shifting. The test was designed to eliminate the limitations imposed by the WCST. For instance, while the WSCT assesses concept formation, planning, and problem solving, in addition to set-shifting, the OMOT was specifically designed to solely assess the latter. The time needed to administer the

OMOT is substantially reduced in comparison to the WCST and has been useful in detecting set-shifting impairments in PD patients (e.g., Morrison et al., 2000; Raskin et al., 1990, 1992; Richards et al., 1993). Set-shifting abilities have also been associated with DLPFC function (e.g., Nagahama et al., 1998; Stuss et al., 1998).

The stimuli used for the OMOT consist of 3 X 5 inch index cards each with either three letters of the alphabet or three geometric designs. When presented to the subject, he/she is asked to indicate which two items is the "odd one out of the three". Once the response is made, the examiner instructs the subject to utilize that particular strategy throughout that trial (i.e., trial A- size strategy). Next, the subject is presented with a second set of index cards (i.e., trial B – form strategy) and is once again asked to indicate which is the "odd one out of the three", but they are instructed to use a different strategy than the one they used for trial A. After trial B is completed, the subject is presented with trial A and is asked to differentiate the designs again according to strategy used earlier during trial A only. Subsequently, this same procedure is repeated for trial B. This test is not timed and subjects are only provided minimal feedback from the examiner with a response of "correct" or "incorrect". If an incorrect choice is made on any trial, the subject will be asked to make another choice. A score of ten is obtained for each trial for a maximum total score of 40 points.

As mentioned earlier, the DLPFC is also thought to mediate aspects of working memory (e.g., MacDonald et al., 2000; Nagahama et al., 1998). Previous work has demonstrated that spatial working memory task performance, for instance, generally activates the right DLPFC (e.g., Jonides et al., 1993), while verbal/auditory working memory task performance activates the left DLPFC (e.g., Paulesu, Frith, & Frackowiak,

1993). The *Spatial Span Test* (WMS; Wechsler, 1997) is a test of spatial working memory. Subjects are asked to observe the experimenter tapping an increasing number of fixed blocks in a random fashion. After the experimenter finishes the sequence on each trial, the subject is asked to reproduce it from memory. Subjects are asked to recall random sequences in the same order (e.g., forwards) for one trial and in the reverse order (e.g., backwards) on another. Scores from the forward and backward components of this test (i.e., the total number of correct numeric sequence repetitions) can be evaluated separately to study attention span (forward condition) apart from working memory (backward condition). Hence, only scores for the backwards condition will be considered here yielding a maximum score of 15 points.

The *Digit Span Test* (WMS; Wechsler, 1997) is a test of verbal working memory. Scores from the forward and backward components of this test (i.e., the total number of correct numeric sequence repetitions) can be evaluated separately to study attention span (forward condition) apart from working memory (backward condition). During administration of both components, subjects are read an increasing length of digit strings (starting with two digits). For the forward component, the subject is asked to repeat the digits in the same order back to the examiner. For the backward component, the subject must alternatively repeat the digits in the reverse sequence back to the examiner. A combined raw score can be obtained for the forwards and backwards conditions yielding a maximum score of 30, however, as with the Spatial Span test, only the backward condition will be considered which also yields a maximum score of 15 points.

The *Verbal Fluency Test* (Delis, Kaplan, & Kramer, 2001) evaluates word-list generation abilities with phonemic and semantic cueing. Subjects were asked to provide

as many words they can think of beginning with a particular letter of the alphabet (e.g., F/A/S) or belonging to a particular semantic category (e.g., animal names) for 60 seconds. Test instructions do not permit responses that are proper names of people or places, numbers, or alterations of the word (i.e., suffixes and/or prefixes). In addition, this particular version incorporates a *set-shifting component* (i.e., alternating fluency) during semantic fluency. In other words, subjects will be asked to generate as many words as they can while alternating between two semantic categories (e.g., fruits and furniture). Set shifting performance and maintaining word-list generation over time (i.e., holding task information online) has been associated with DLPFC function (Dias et al., 1996; MacDonald et al., 2000; Nagahama et al., 1998; Stuss et al., 1998; Wise et al., 1991). Principal dependent variables will include: (a) letter fluency [total correct], (b) category fluency [total correct], (c) category switching [total correct], and (d) switching accuracy (i.e., number of correct consecutive shifts between categories).

The *Petrides Conditional Associate Learning (CAL) Test [modified]* (Petrides, 1985) requires a subject to learn arbitrary associations between pairs of spatial locations using a trial-and-error strategy. Conditional associate learning tests were originally designed for animal experiments, where they were shown to be sensitive to damage to the prefrontal cortex (Petrides, 1985). Petrides (1985) adapted the test for humans and confirmed the sensitivity of the tests to damage to the DLPFC. PD patients have been reported to perform poorly on this measure (e.g., Gotham et al., 1988; Lichter, 2000; Postle et al., 1997). Levine et al. (1997) was able to demonstrate that CAL performance was related to specific activation of the DLPFC in frontal brain-damaged patients and elderly normal control subjects. Here, impaired performance was attributed to strategic

rather than basic associative processes due to its trial-and-error format. Performance errors were explained in terms of the patients exhibiting difficulties in using past information to guide more current task behavior.

For CAL administration, four identical blocks are placed in specified locations in front of the subject. In addition, four identical blank white index cards are also positioned next to each other in a row in front of the blocks. The blocks are labeled with numbers 1 through 4 and can only be viewed by the examiner for scoring purposes. The subjects are given very minimal instruction and are told that each index card is associated with one of the four blocks. When the examiner points to a block, the subject is instructed to point to the card they believe is associated with that particular block. The only feedback the examiner provides is to indicate whether the association made is "correct" or "incorrect". Subjects are forced to use trial-and-error in order to learn the associations. Principal dependent variables include (a) the total number of trials to criterion (i.e., 12 consecutive correct responses), and (b) total number of errors.

The *Frontal Systems Behavior Scale* (FrSBe; Grace & Malloy, 2001) is a self-report rating scale consisting of 46 items designed to measure behaviors associated with damage to the specified frontal regions of the cortex. The scale has been shown to assess behavioral problems in PD patients related to frontal lobe dysfunction and incorporates three subscales: (A) Apathy Scale; (D) Disinhibition Scale; & (E) Executive Dysfunction Scale. The design of the scale was based upon evidence of frontostriatal circuit disruption. Each item is rated on a Likert scale ranging from 1-5 (1= Almost never, 2 = seldom, 3= sometimes, 4= frequently, and 5 = almost always). The subject is asked to rate their current behavior and personality. The scale was standardized so that individual

scores can be obtained for each of the three aforementioned scales. Elevated scores on the *Executive Dysfunction (E) scale* may represent behavioral problems indicative of DLPFC disruption such as sustained attention, working memory, organization, planning, sequencing, and problem solving. An example of a statement for this scale is as follows "Cannot do two things at once". There are 17 items on this particular scale.

ACC Tasks

The ACC-related tasks selected reflect abilities associated with cognitive/behavioral functions such as response monitoring, inhibition, initiation, and apathy.

The *Stroop Color-Word Test* (SCWT; Golden, 1978; Stroop, 1935) measures one's cognitive flexibility and ability to conform to changing demands and suppress a habitual response in favor of an unusual one. There are three parts to the test. In Part 1, the subject reads randomized color names (blue, green, and red) printed in black ink. In Part 2 (i.e., congruent color naming), the subject has to name the color of 4 X's (e.g., XXXX) in blue, green, or, red ink. In Part 3 (i.e., incongruent color naming), the subject reads color names (blue, green, and red) printed in colored ink (blue, green, and red), but he/she must name the color in which the color names are printed and disregard their verbal content. The test consists of 5 columns with 20 items in each. The subject is permitted 45 seconds for each of the three parts. In addition, an interference index score (an index of cognitive flexibility) can be obtained by subtracting a predicted Color-Word incongruent score from the raw Color and Word naming scores. The interference score is obtained using the following formula:

$$Interference = wc - ((c \times w) / (c + w))$$

$$c = color\ score;\ w = word\ score$$

Increased reaction time and errors on *Part 3*, as well as a low Stroop Interference Index score have been shown to correlate with increased activation (in normal controls), as well as damage, to the ACC (e.g., MacDonald et al., 2000; Pardo et al., 1990; Stuss et al., 2001). Thus, the dependent variable selected to potentially mediate ACC function will be incongruent color naming performance (Part 3) and the interference index score.

Verbal fluency performance during the first 15 seconds of a trial was selected as a measure of response initiation for the current study since this ability has been associated with ACC function in normals (e.g., Raichle et al., 1994) and brain-damaged patients (e.g., Stuss et al., 1998). For the *Verbal Fluency Test* (Delis, Kaplan, & Kramer, 2001), a raw score will be derived for the total number of responses made within the first 15 seconds of the task. This variable is calculated by taking the sum of the number of words generated during the first time interval (0-15 seconds) for the phonemic, category, and category/switching conditions respectively.

Since lesions to the ACC may result in symptoms of apathy in brain-damaged patients (Cohen et al., 1999), the *Apathy (A)* scale of the *Frontal Systems Behavioral Scale* (Grace & Malloy, 2001) was administered to all subjects. In light of findings indicating a moderate prevalence of apathy in PD (e.g., Pluck & Brown, 2002) it is essential to assess these levels since previous findings indicate relationships between apathy and ACC dysfunction. Elevated scores on this scale may indicate behavioral and personality characteristics associated with ACC disruption, such as initiation, spontaneity, drive, persistence, lack of concern for self-care, and blunted affective

expression. Because of some of the behavioral similarities (e.g., decrease motivation) between apathy and depression, it is important to differentiate these disorders, especially since evidence suggests that apathy is related to ACC dysfunction, whereas depression is related to OFC dysfunction. An example of an item for this scale is as follows: "I sit around doing nothing". This scale has 14 items.

OFC Tasks

OFC-related tasks selected reflect abilities associated with functions such as disinhibition, decision-making, impulsivity, and perseveration.

The *Beck Depression Inventory* (BDI; Beck, 1987) will also be used as an investigational measure for the OFC circuit in PD patients. Depressive symptoms have been attributed to disruption to the OFC in brain-damaged and patients with PD (Mayberg, 2000). Please see above for BDI description and scoring parameters.

The *Twenty Questions Test* (Delis, Kaplan, & Kramer, 2001) requires subjects to guess a previously designated item from a display of 30 living and non-living pictures. As mentioned above, the OFC mediates reward-punishment contingencies in regards to decision-making and hypothesis-testing. Previous reports have demonstrated that patients with a lesion to the OFC tend to exhibit poor decision-making and reasoning abilities, indicating impulsive and/or careless response generation (Bechara et al., 1994; Damasio, 1994; Upton & Thompson, 1996, 1999). In our study a reward-punishment contingency schedule was not established, however this particular test is still useful as a measure of impulsivity.

During the task, the subject is instructed to ask questions in an attempt to guess the name of the object the examiner has in mind. The examiner can only respond "yes"

or "no" to the subjects' questions. The total number of questions asked is recorded. The "guessing" game is completed after 4 trials. Principal dependent measures include (1) an initial abstraction score, (2) the number of total questions asked, and (3) the total weighted achievement score. The initial abstraction score quantifies the level of abstract thinking represented in the first question asked by the examinee for each item. The most efficient first question will eliminate the greatest amount of objects from the display. For example, asking, "Is the object a living thing?" will eliminate 15 out of 30 items from the display. A poor initial abstraction question would be "Is the object on this page?" since it does not eliminate any items. A low initial abstraction score reflects impaired categorical processing and impulsive responding behavior. The total number of questions asked serves as a global achievement measure. The fewer questions the subject asks before correctly guessing the object indicates that he/she was more efficient in their line of questioning, suggestive of preserved abstract thinking with a lack of impulsivity. During the test, subjects are awarded bonus points for questions that are not concrete and that eliminate the most number of items. Thus, the more concrete a subject is in their responding, the fewer bonus points they will receive, hence a lower total weighted achievement score.

In order to assess perseverative errors, all subjects will be asked to copy drawings of alternating letters and patterns (*Alternating Loops and Letters*; Luria, 1966). Each subject was supplied with a sheet of paper with designs (loops) and letters (m & n). They were then asked to make 10 copies of each design. The number of errors was recorded.

Elevated scores on the *Disinhibition Scale (D)* of the *Frontal Systems Behavioral Scale* (Grace & Malloy, 2001) might be indicative of behavioral problems associated

with disruption to the OFC such as poor disinhibition, impulsivity, hyperactivity, socially inappropriate behavior, lack of conformity to social conventions, and irritability. An example of an item for this scale is as follows: "I do things impulsively". The test was selected since it assesses several behavioral and personality symptoms that have been shown to be present in patients with OFC dysfunction (for review, see Lichter & Cummings, 2000; Litvan, 2000). This scale has 15 items.

STATISTICAL ANALYSES

Select statistical procedures were used to investigate the different objectives of this study. The *first objective* was to assess group differences in order to establish whether group membership influenced task performance based on circuit (i.e., DLPFC, ACC, and OFC). The *second objective* was to investigate whether PD patients alone exhibited variations in task performance across circuit. Here, special analyses were performed in order to permit placement of the dependent variables (for PD group only) into one analysis for comparison. The *third objective* was to determine if patterns of individual frontal/executive performance by circuit could discriminate between groups. The *forth objective* was to explore relationships among the cognitive and behavioral tasks collapsed across groups via a data reduction procedure. All statistical procedures were performed using SPSS 11.0.

Demographic and Screening Variables

Continuous demographic, screening, and comparison variables (age at testing, years of education, occupational level, estimated Full Scale IQ, mental status, basic visual spatial perception, basic sustained attention, index of depression, and motor dexterity) were examined using descriptive statistics. *Student Independent Sample t-tests* were conducted to evaluate potential group differences for these variables. In addition, a *Chi-Square* analysis was performed in order to assess potential gender differences.

Group Comparisons

We were interested in determining the extent to which group differences exist across circuit. The multivariate *Hotelling's T^2 Test* for two independent samples was conducted. Three separate Hotelling's T^2 tests were performed (one for each circuit).

This test is a special case of multivariate analysis of variance (MANOVA) for only 2 independent samples (PD versus NC). Hotelling's T^2 test can differentiate the extent of between-group differences on tests associated with the DLFPC, ACC, and OFC circuits. Estimates of effect sizes (i.e., strength of associations) were generated using a *Partial Eta-square statistic* for each condition. The partial eta-square statistic describes the proportion of total variability attributable to differences on a factor (Cohen, 1988; Tabachnick & Fidell, 1996).

Next, in order to assess whether an interaction exists between group and circuit, a 2 (Group [PD, NC]) X 3 (Circuit [DLPFC, ACC & OFC]) factorial *Analysis of Variance (ANOVA)* was performed. In order to appropriately enter all 20 variables into the same analysis, all data were normalized and entered as standard scores. The procedure is as follows. Z-scores were first generated for all NC subjects. Z-scores for the PD subjects were obtained by utilizing the NC group as a normative sample. For each subject, z-scores were summed across variables and then divided by the number of variables within each condition (i.e., 10 for DLPFC, 4 for ACC, and 6 for OFC). The Kolmogorov-Smirnov test was performed to assess whether the z-score distributions were normal. After all computations were completed, each subject had three composite (mean standard deviations) scores, each signifying circuit performance. The factorial ANOVA procedure allowed us to designate which circuit(s) was significant in demonstrating group differences. As a result, we were able to assess the extent of circuit dysfunction in PD subjects relative to NC subjects.

PD Performance Differences by Circuit

In order to enter the DLPFC, OFC, and ACC related variables into a single analysis; a *binomial sign test* comparison was conducted. This procedure allowed us to analyze performance differences by circuit for the PD group only (adapted from Raskin et al., 1992). First, cut-off scores for each task were obtained using normative data (the 5^{th} percentile was selected as the cutoff for impaired performance). For the PD subjects, a score of '1' was assigned to indicate performance below cut-off (i.e., impaired performance) on a particular task, while a score of '0' was assigned to indicate performance above cut-off (i.e., unimpaired performance). For this analysis, subject's index scores (i.e., 0 and 1) were summed and averaged separately for each of the three task circuit conditions (i.e., 10 for DLPFC, 4 for ACC, and 6 for OFC). A *Binomial Sign Test* was utilized to determine the significance of index score differences across the three circuits for the PD subjects only. The three sign test comparisons were as follows: DLPFC vs. ACC, DLPFC vs. OFC, and ACC vs. OFC.

Group Classification

Since our test battery was developed with three distinct subsets of tasks, it would be worthwhile to investigate whether or not individual subject performance can predict group membership. This would allow us to determine the extent and pattern of frontal/executive impairment in PD and how it may relate to frontostriatal disruption. Furthermore, if classified successfully, the analysis may help validate our test battery and/or inclusion criteria for future use in assessing frontal/executive cognitive and behavioral impairment in PD patients.

Logistic Regression permits one to predict a discrete outcome such as group membership from a set of variables that may be continuous, discrete, dichotomous, or mixed. Logistic regression is more flexible than other related analyses (e.g., discriminant functions analysis) since it carries no assumptions about the distributions of the predictor variables. The predictors do not have to be normally distributed, linearly related, or of equal variance within each group. In addition, logistic regression can also compute predicted probabilities (Tabachnick & Fidell, 1996).

After logistic regression, it is possible that some PD patients may be labeled as "NC" (based upon their patterns of neuropsychological task performance) or vice versa. After obtaining these results, we assessed potential differences across demographic and screening variables for the subgroups of PD and NC subjects separately. For PD subjects, comparisons were conducted to assess differences on measures of PD motor severity (e.g., Hoehn & Yahr scale score), age of PD clinical onset, as well as other demographic and screening variables. In spite of the fact that all PD subjects in this study are nondemented, this procedure would help us designate clinical determinants that may predispose patients to greater frontal/executive impairments (e.g., age or clinical severity).

Relationships between Frontal/Executive Tasks

The literature has shown that frontal/executive tasks may vary in their ability to assess "frontal" functions (e.g., Rezai et al., 1993; Stuss & Alexander, 2000). According to our review of the literature, it appears that each of the three frontostriatal circuits may mediate select sets of functions. Thus, it would be of interest, on an exploratory basis to verify whether neuropsychological task performances for one circuit (e.g., DLPFC)

would correlate with each other as compared to other task performances mediated separately by the two remaining circuits.

A *Principal Component Factor Analysis* was conducted to determine which variables form coherent subsets that are relatively independent of each other. In this procedure, variables that are correlated with one another, but largely independent of other subsets of variables, will combine into factors. Factors are thought to reflect underlying processes that have created the correlations among variables (Tabachnick & Fidell, 1996). Factor analysis is often used in data reduction by identifying a small number of factors which explain most of the variance observed in a much larger number of manifest variables as used in this study.

A principal components factor analysis with varimax rotation was performed to determine how task performances across different circuits related to each other collapsed across groups. The varimax rotation of factors is a process whereby the results are more interpretable without disturbing the underlying mathematical properties of the statistical procedure (Tabachnick & Fidell, 1996). Data from both groups were entered into the analysis simultaneously since task performance was viewed as falling on a continuum in spite of expected group differences. In other words, the observed group differences were considered as being more quantitative than qualitative. For verification of the overall factor solution, factor analyses were conducted for the NC and PD groups separately as well.

Based upon our review of the literature, we hypothesized that task performances categorized by the three circuits would load separately following orthogonal rotation (varimax). Ideally, factor loadings should be $\geq .50$ [absolute value] in order to better

construe meaning for the derived factor. This designated cutoff value signifies that 25% of the variability shared among any given variable and the particular factor is accounted for (Comrey & Lee, 1992). Thus, only those variables loading at .50 (absolute value) or higher were considered significant. The pattern of significant factor loadings, according to circuit, may provide evidence supporting the specificity of frontal/executive based neuropsychological measures. Furthermore, as suggested by the literature (e.g., Sarazin et al., 1998), an analysis of this sort may instead reveal factor loadings separating cognitive from behavioral performance. This can be demonstrated statistically, for instance, with the existence of two independent factor loadings: one for neuropsychological task performance mediated by the DLPFC and ACC circuits and another solely for the OFC circuit.

RESULTS

Demographic and Screening Comparisons

Before conducting experimental analyses, we examined group differences on several demographic/screening variables to determine the necessity, if any, to control for these variables in the experimental analyses. See Table 1 for group means, standard deviations, t values and p values for each variable. Student independent sample t-tests were computed comparing scores across Group (PD and NC) for each of the eleven demographic/screening variables (e.g., age, education, occupational level, MDRS total, estimated Full Scale IQ, basic visual perception (VFDT), depression (BDI), sustained attention (BTA), and motor dexterity (Purdue Pegboard test). Three variables were extracted from the Purdue Pegboard test in order to assess unilateral (dominant/nondominant hand) and bilateral manual dexterity. Among the 11 univariate analyses conducted, the only significant differences revealed were those for the three variables of the Purdue Pegboard test. This was expected given the nature of motor impairments in PD. Furthermore, a Gender X Group Chi-Square analysis revealed that men and women were well distributed across groups, $\underline{X}^2 = .755$, $\underline{p} = .385$. See Table 2 for group means and standard deviations for the 20 experimental variables.

Group Comparisons

Multivariate Hotelling's T^2 test comparisons between groups were conducted separately for the DLPFC, ACC, and OFC circuit conditions. Raw scores were used as dependent variables in this analysis. Each comparison was found to be statistically significant [DLPFC, $\underline{F}$ (10, 50) = 3.61, $\underline{p} = .001$; ACC, $\underline{F}$ (4, 56) = 4.53, $\underline{p} = .003$; OFC, $\underline{F}$ (6, 54) = 3.09, $\underline{p} = .011$] indicating that NC subjects were performing significantly better

Table 2

Group Means and Standard Deviations for Experimental Variables by Circuit

	PD N= 32 Mean/SD	NC N=29 Mean/SD
ACC		
Apathy Scale	29.5/9.5	23.4/5.2
Initial Fluency	34.9/8.0	41.9/8.4
Stroop Color/Word	43.1/8.2	49.2/7.5
Stroop Interference	2.6/6.1	5.8/6.2
DLPFC		
Category Fluency	33.8/10.2	41.8/12.6
Digit Span	5.7/1.8	7.0/2.4
Executive Scale	34.7/10.4	29.2/7.5
Letter Fluency	37.0/13.1	45.9/15.7
OMOT	30.6/6.4	37.2/5.3
PCAL – Criterion	60.0/14.9	45.2/17.7
PCAL – Errors	43.4/24.9	27.2/19.1
Spatial Span	5.1/1.9	7.1/1.5
Switching Fluency	12.4/4.2	14.6/2.9
Switching Fluency Accuracy	11/1/4.2	14.0/3.3
OFC		
BDI	7.7/6.0	5.5/4.5
Disinhibition Scale	23.5/5.4	23.4/6.2
Alternating Loops	.78/2.7	.00/.00
Twenty Questions Test – Abstraction Score	23.2/11.7	33.5/13.9
Twenty Questions Test – Total Questions	33.8/11.6	26.2/5.9
Twenty Questions Test – Weighted Score	13.7/4.1	15.7/3.0

* See Appendix B for range and scoring for each experimental variable

than the PD subjects across circuit condition. See Table 3. The multivariate procedure also generated univariate comparisons for each measure. Univariate task performance differences between groups were as follows: for DLPFC, all 10 variables revealed significant findings; for ACC, all 4 variables revealed significant findings; for OFC, only the 3 variables from the Twenty Questions Test revealed significant group performance differences. Indices of depression (p = .112), disinhibition (p = .954), and motor perseveration (p = .119) did not achieve statistical significance.

Effect sizes, using the partial eta-squared statistic, were also computed for each multivariate comparison by circuit condition. The partial eta-squared statistic describes the proportion of the total variance explained by the differences between groups. In spite of the overall significant findings across circuit condition, this statistic established the magnitude of the differences found. The following values were obtained: DLPFC = .419; ACC = .244; OFC = .256. The observed differences across the effect sizes generated were sizeable with the DLPFC exerting a larger effect size, whereas both the OFC and ACC exerted medium effect sizes (Cohen, 1988). These differences were not significant for a two-tailed test. See Table 3.

Group Differences and Interaction Effect

A 2 (Group) X 3 (Circuit) factorial ANOVA was conducted in order to assess group differences across circuit. Dependent variables used were circuit composite scores (procedure described above). The Main effect of circuit was significant, F (2, 118) = 4.63, p = .012. Post-hoc tests revealed that DLPFC composite scores (M = -.443, SD = .78) were significantly lower (Least Significant Difference [LSD]; p = .012) than OFC

Table 3

Multivariate Hotelling's T^2 test Comparisons and Estimated Effect Sizes by Circuit

Circuit	F value	df	p value (exact)	Partial eta-square*
DLPFC	3.611	50	.001	.419 (large)
ACC	4.531	56	.003	.244 (medium)
OFC	3.091	54	.011	.256 (medium)

DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; OFC = orbitofrontal cortex; * = Cohen's d statistic for effect sizes (Cohen, 1988)

composite scores (M = -.232, SD = .61). Furthermore, ACC composite scores (M = -.448, SD =.86) were significantly lower than OFC scores (LSD; p = .012). There was no significant difference between mean DLPFC and ACC composite scores (LSD; p = .949). The Main effect of Group was also significant, F (1, 59) = 26.4, p < .001, with the PD group (M = -.725, SD = .10) performing significantly lower than the NC group (M = .012, SD = .104). The Group X Circuit interaction was not significant, F (1, 118) = 2.50, p = .086, but it did reveal a trend. Here, the extent of the difference between the PD and NC groups appears to be less for the OFC condition in comparison to the DLPFC and ACC conditions. See Figure 2. This suggests that PD subjects tend to perform worse compared to NC subjects on tasks mediated by the DLPFC and ACC circuits compared to the OFC circuit. However, these results should be interpreted with caution since statistical significance was not obtained at the .05 level.

PD Within-Group Comparison by Circuit

In order to assess individual subject differences for the PD group, three separate binomial sign tests were conducted (procedures described above). No significant differences were revealed for indices of impairment when comparing performances for the DLPFC versus the ACC condition, observed probability = .54, p = .845, and for the ACC versus the OFC condition, observed probability = .68, p = .134. For the DLPFC versus the OFC circuit comparison, a significant difference was revealed, suggesting that individual PD subjects demonstrated a greater incidence of impairment for tasks within the DLPFC circuit condition compared to those within the OFC circuit condition, observed probability = .74, p = .021. See Table 4.

Figure 2

Group (PD, NC) by Circuit (DLPFC, ACC, & OFC) Analysis of Variance

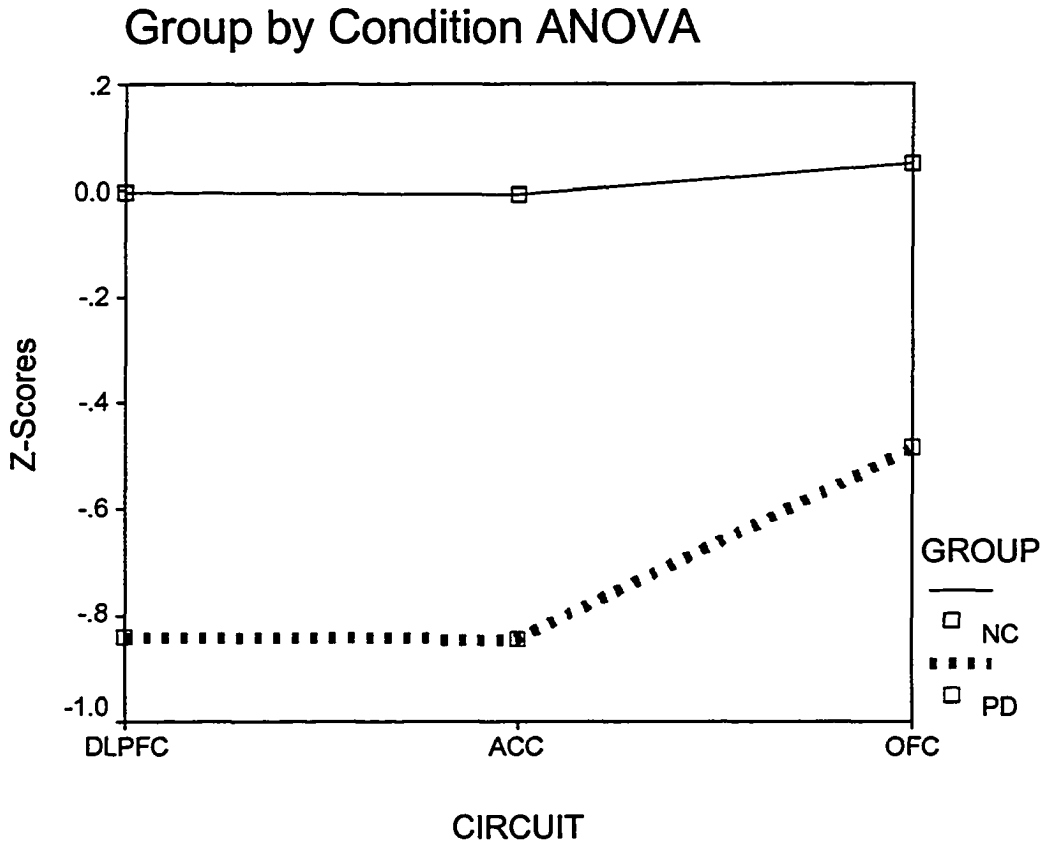


Table 4

Binomial Sign Test Circuit Comparisons for Indices of Task Impairment

Circuit Comparison	Observed Probability	p value (exact)
DLPFC vs. ACC	.54	.845
ACC vs. OFC	.68	.134
DLPFC vs. OFC	.74	.021

Group Membership Prediction

A direct logistic regression analysis was performed using circuit composite scores (DLPFC, ACC, and OFC). The standardization score transformation procedures are the same as those described above. These circuit composite scores were used to predict group membership since they quantify the level of circuit function in our sample. The beginning block classification table (i.e., relative frequency) indicated that 52.5% of the sample would be classified as PD. After the composite scores were entered, an overall test of the model indicated that it was statistically significant; suggesting that the three variables entered into the equation impacted the dependent variable ($\underline{X}^2 = 26.02$; $\underline{p} <$ .001). The Nagelkerke pseudo R-squared statistic revealed that 46.3% of the variance was accounted for by the three variables entered. The Hosmer and Lemeshow Test was not significant ($\underline{X}^2 = 5.274$, $\underline{p} = .728$), indicating that there were no significant differences between the observed and expected frequencies. Classification results from the analysis indicated that of the 32 PD subjects in the study, 8 had performance profiles more similar to NC subjects as a whole. On the contrary, only 5 of the NC subjects had performance profiles similar to PD subjects as a whole.

The analysis revealed that the DLPFC composite score significantly contributed to prediction of group membership (WALD = 3.744 (1), $\underline{p} = .05$). The expected probability generated indicated that subjects who obtained high DLPFC composite scores were approximately four times as likely to be in the NC group as the PD group. The ACC (WALD = .997 (1), $\underline{p} = .318$) and OFC (WALD = 2.803 (1), $\underline{p} = .094$) composite score probabilities did not reach significance.

On an exploratory basis, using the findings from the logistic regression analysis, we wanted to identify any differences between the eight "NC-like" PD patients from the 24 correctly identified PD patients. We performed student independent sample t-tests comparing these two subgroups on the eight demographic and screening variables. Our findings revealed that for demographic variables, the 24 correctly identified PD subjects were significantly older [t (30) = -2.304, p = .028], older at age of initial PD diagnosis [t (30) = -2.367, p = .025], and had lower levels of education [t (30) = 2.04, p = .05]. For screening and comparison variables, these same 24 patients reported greater symptoms related to depression [t (30) = -2.320, p = .027], lower scores on a measure of sustained attention [t (30) = 2.51, p = .018], and slower reaction time for dominant hand motor dexterity [t (30) = 2.128, p = .042] and for bilateral motor dexterity [t (30) = 2.275, p = .03]. See Table 5.

Separate independent sample t-tests were conducted on demographic and screening data to assess differences between the 5 "PD-like" NC subjects and the 24 correctly identified NC subjects. It was revealed that the 5 "PD-like" NC subjects had significantly lower levels of education (t (27) = 4.55, p < .001 [M = 13; SD = 1.73]) and estimated IQ (t (27) = 5.787, p < .001 [M = 107.4; SD = .89]) relative to the 24 correctly identified NC subjects (education M = 16.83; SD = 1.71 and estimated IQ M = 117.04; SD = 3.65). No other significant differences were found. See Table 5. In comparing the two separate sets of analyses conducted, it appears that differences between "NC-like" PD patients and those correctly identified were mostly related to factors underlying disease progression (e.g., attentional capacity), whereas differences within the NC group were solely related to demographic characteristics (e.g., education).

Table 5

Univariate Comparisons for PD and NC Subgroups Determined by Logistic Regression Analysis

Variable	NC (N = 24) Mean/SD	NC/PD (N = 5) Mean/SD	t value
Education	16.83/1.71	13.0/1.73	4.55**
Estimated IQ	117.04/3.65	107.4/.89	5.79**
	PD (N = 24) Mean/SD	PD/NC (N = 8) Mean/SD	t value
Age	68.67/6.7	61.5/10.1	-2,304*
Age at PD Dx	63.83/8.1	55.75/9.27	-2.367*
Education	14.83/2.66	17.0/2.39	2.04*
BDI	9.04/6.0	3.75/4.2	-2.32*
BTA	16.63/1.7	18.38/1.8	2.51*
Purdue (right)	8.67/2.51	11.13/3.68	2.13*
Purdue (bilateral)	6.38/1.69	8.13/2.42	2.28*
Hoehn & Yahr	2.38/.557	2.0/.534	-1.66

* = $p < .05$

** = $p < .001$

NC/PD = NC subjects classified as PD by logistic regression analysis

PD/NC = PD subjects classified as NC by logistic regression analysis

Frontal/Executive Task Associations

A principal components factor analysis with varimax rotation was performed using 20 experimental variables derived from the neuropsychological test battery. NC and PD subjects (N = 61) were included in the analysis together. Principal components extraction was generated prior to principal factors extraction in order to estimate presence of outliers, absence of multicollinearity, and factorability of the correlation matrices (Tabachnick & Fidell, 1996). With a cut-off level of $p = .001$, none of the 61 subjects produced scores that identified them as outliers. The number of factors was forced to three in order to support initial hypotheses signifying individual circuit (DLPFC, ACC, and OFC) involvement.

An initial component factor solution (unrotated) revealed that Factors 1 and 2 were well defined, whereas Factor 3 was not. Communality values tended to be high. With a cut-off of .50 for inclusion of a variable in interpretation of a factor, 17 of the 20 variables loaded significantly. The three variables that did not load on any particular factor for the initial solution were the (a) abstraction score and (b) weighted score of the Twenty Questions Test, and (c) alternating loops and letters. Factor 1 incorporated 12 of the 16 frontal/executive cognitive variables and 2 of the 4 behavioral variables. For factor 2, only the four behavioral measures loaded significantly. Factor 3 included only two variables (alternating fluency and Stroop interference), loading at .555 and -.548 respectively. See Table 6a.

After varimax rotation, initial eigenvalues for the three factors were all greater than 1. Factor 1 explained 35.19% of the total variance, Factor 2 explained 11.47% of the total variance, and Factor 3 explained 9.34% of the total variance. Total cumulative

Table 6a

Combined (PD and NC) Initial Component (Unrotated) Factor Solution

Experimental Test Variables	Factor 1	Factor 2	Factor 3
Letter Fluency (total score)	.738		
Category Fluency (total score)	.758		
Switching Fluency	.684		
Switching Fluency Accuracy	.754		.556
Verbal Fluency Initiation	.823		
Conditioned Associate Learning – criterion	-.585		
Conditioned Associate Learning – total errors	-.685		
Stroop Color/Word	.679		
Stroop Interference			-.548
Digit Span Backwards	.549		
Spatial Span Backwards	.533		
Odd Man Out Test (total score)	.582		
Twenty Questions Test (abstraction score)	------	------	------
Twenty Questions Test (total questions)	-.609		
Twenty Questions Test (weighted score)	------	------	------
Alternating Loops and Letters	------	------	------
Beck Depression Inventory		.623	
Apathy	-.620	.573	
Disinhibition		.736	
Executive Functions	-.660	.649	

percent variance explained by the entire factor solution was 56%. Once again, a cutoff of .50 was chosen for inclusion of a variable in the interpretation of a factor. Of the twenty variables entered, only 2 (Twenty Questions Test; [a] weighted achievement score, and [b] abstraction score) did not significantly load on any of the three factors after varimax rotation. See Table 6b.

For Factor 1, only variables related to verbal fluency performance loaded together. The factor was well defined since all 5 verbal fluency variables loaded at .742 or above. This factor was not related to any particular circuit but its constitution suggests that it might represent a verbal fluency or "processing speed" factor since test performance required subjects to internally generate words (i.e., word retrieval) in a given period of time. In order to test the validity of this factor label, we re-ran the entire factor analysis, on an exploratory basis, with the Stroop word reading and color naming variables. These two variables involve speeded word reading and color naming that is externally guided. The two variables did load significantly on Factor 1 (.796 and .839 respectively) but not on Factor 2 or 3, suggesting that Factor 1 may not underlie intrinsic verbal fluency alone per se, but may instead be described as a *lexical/verbal generation factor,* indicative of both intrinsic and extrinsic speeded word-list generation.

For Factor 2, only executive tasks unrelated to verbal fluency loaded together. As with Factor 1, this factor is also unrelated to any particular circuit since it is comprised of tasks mediated by all three frontostriatal circuits. Factor 2 was well defined since all 9 variables loaded at .509 or above. Interestingly, no behavioral measures loaded onto this factor suggesting that it may be a pure *executive cognitive factor.* The variables that loaded significantly involve cognitive abilities, such as working memory (verbal and

Table 6b

Combined (PD and NC) Varimax (Rotated) Factor Solution

	Factor 1	Factor 2	Factor 3
Eigenvalues	7.04	2.29	1.87
Percent Variance (%)	35.19	11.47	9.34
Experimental Test Variables			
Letter Fluency (total score)	.742		
Category Fluency (total score)	.820		
Switching Fluency	.874		
Switching Fluency Accuracy	.845		
Verbal Fluency Initiation	.811		
Conditioned Associate Learning – criterion		-.657	
Conditioned Associate Learning – total errors		-.592	
Stroop Color/Word		.600	
Stroop Interference		.738	
Digit Span Backwards		.511	
Spatial Span Backwards		.509	
Odd Man Out Test (total score)		.626	
Twenty Questions Test (abstraction score)	-------	-------	-------
Twenty Questions Test (total questions)		-.524	
Twenty Questions Test (weighted score)	-------	-------	--------
Alternating Loops and Letters		-.517	
Beck Depression Inventory			.764
Apathy			.770
Disinhibition			.746
Executive Functions			.853

Factor 1 = Verbal/lexical generation factor

Factor 2 = Executive factor

Factor 3 = Behavioral/psychiatric factor

nonverbal), conditioned associate learning (nonverbal), set-shifting (nonverbal), response inhibition (verbal), impulsivity/decision making (verbal), and perseveration (nonverbal). Factor loadings for the following measures, although significant, were negative due to the nature of the task design: conditioned associate learning (trials to criterion and number of errors), twenty questions test (total questions), and alternating loops and letters (number of errors). In other words, the higher an individuals' score the worse their performance. See Table 6b.

Unlike Factor 1, variables loading significantly onto Factor 2 do not require speeded intrinsic verbal/lexical generation. On an exploratory basis, we re-ran the factor analysis with three variables from the Purdue Pegboard test. This was done in order to assess the characteristics of the variables comprising the solution for Factor 1. In other words, should Factor 1 loadings be attributed to speeded verbal/lexical generation or solely to task processing speed? As mentioned earlier, the Purdue Pegboard test is a measure of motor dexterity and speed. The exploratory analysis revealed that all three variables of the Purdue Pegboard test (dominant hand, non-dominant hand, and bilateral involvement) loaded significantly onto Factor 2 (.658, .717, and .803 respectively) but not Factors 1 or 3. In spite of prior notions attributing the solution for Factor 1 to speeded verbal/lexical generation, it appears to be so only for the verbal/non-motor domain, since performance on a task of motor dexterity and speed did not significantly enter that solution. Factor 2 loadings for the three variables of the Purdue Pegboard test suggest that speeded motor dexterity and coordination performance may be better related to executive cognitive task performance. Furthermore, it was also recognized that two fluency variables from Factor 1 that maintained a set-shifting component (more

consistent with the class of Factor 2 loadings) had non-significant loadings on Factor 2 of .124 and below, once again demonstrating the lack of correspondence between Factors 1 and 2. In other words, performance on verbal fluency measures of any sort, at least for this study, does not appear to be related to executive task performance (i.e., set shifting). Hence, verbal fluency performance is speculated to be mediated more by language-based processes than executive-based ones.

For Factor 3, all variables related to self-report behavioral measures significantly loaded together. The factor is well defined as all 4 behavioral measures loaded at .746 or above. This factor was also unrelated to any particular circuit but its constitution suggests that it may be identified as a pure *behavioral/psychiatric factor* since no other "cognitive" measures (from Factors 1 & 2) loaded significantly with this factor. See Table 6b.

For verification of the structure of the rotated matrix solution, on an exploratory basis, we conducted two separate factor analyses one for the NC group and one for the PD group. Although not exact, these factor loadings maintained similar characteristics (i.e., structure) to the previously calculated combined (NC and PD) analysis. When NC subjects were entered alone, 15 of the 20 variables loaded significantly. See Table 6c. Here, Factor 1 remained somewhat consistent with Factor 1 of the original combined rotated analysis, as all five fluency measures maintained similar significant factor loadings of .793 or above. The only difference here was that two additional variables loaded significantly onto this factor (errors on conditional associate learning and Stroop incongruent color and word trial). Factor 2 of the current analysis appeared to be similar to Factor 3 of the original combined rotated analysis, as its loadings included all the

Table 6c

Varimax (Rotated) Factor Solution for NC Group Only

	Factor 1	Factor 2	Factor 3
Eigenvalues	4.9	3.0	2.23
Percent Variance (%)	25.81	15.73	11.74
Experimental Test Variables			
Letter Fluency (total score)	.802		
Category Fluency (total score)	.841		
Switching Fluency	.799		
Switching Fluency Accuracy	.802		
Verbal Fluency Initiation	.793		
Conditioned Associate Learning – criterion	--------	--------	--------
Conditioned Associate Learning – total errors	-.554		
Stroop Color/Word	.620		
Stroop Interference		.617	
Digit Span Backwards	-------	--------	--------
Spatial Span Backwards			.702
Odd Man Out Test (total score)	---------	--------	--------
Twenty Questions Test (abstraction score)	-------	-------	-------
Twenty Questions Test (total questions)			.775
Twenty Questions Test (weighted score)			-.786
Alternating Loops and Letters		-.517	
Beck Depression Inventory		.681	
Apathy		.741	
Disinhibition		.537	
Executive Functions		.801	

Note: Alternating loops and letters (motor perseveration variable) not entered.

behavioral/psychiatric variables. One exception was the significant loading of the Stroop interference variable. Factor 3 did not resemble any of the previous factor solutions. Here, spatial span backwards and the total questions and weighted achievement score variables of the Twenty Questions test loaded significantly. We suspect that the factor solution for the NC subjects alone did not completely resemble the original combined factor solution because we had to omit one variable (alternating loops) from the analysis since it had no variance which violated statistical test assumptions, as all NC subjects performed without error on this particular task.

When PD subjects were entered alone, eighteen of the twenty variables loaded significantly. This solution more closely resembled the original combined rotated factor solution. Here, Factor 1 maintained significant loadings for all verbal fluency measures in the solution with the addition of significant loadings for the (a) total questions and (b) weighted achievement score from the Twenty Questions Test. The solution for Factor 2 was also very similar to the frontal/executive factor from the original combined solution. However, two variables were missing from the current (PD only) solution (spatial span backwards and conditional associate learning [total errors]). Factor 3 was identical to the behavioral/psychiatric factor of the original combined solution. See Table 6d.

Table 6d

Varimax (Rotated) Factor Solution for PD Group Only

	Factor 1	Factor 2	Factor 3
Eigenvalues	6.93	2.64	2.25
Percent Variance (%)	34.67	13.19	11.26
Experimental Test Variables			
Letter Fluency (total score)	.627		
Category Fluency (total score)	.747		
Switching Fluency	.889		
Switching Fluency Accuracy	.864		
Verbal Fluency Initiation	.749		
Conditioned Associate Learning – criterion		-.548	
Conditioned Associate Learning – total errors	-------	--------	--------
Stroop Color/Word		.608	
Stroop Interference		.677	
Digit Span Backwards		.605	
Spatial Span Backwards	--------	--------	---------
Odd Man Out Test (total score)		.529	
Twenty Questions Test (abstraction score)		.670	
Twenty Questions Test (total questions)	-.563	-.512	
Twenty Questions Test (weighted score)	.731		
Alternating Loops and Letters		-.551	
Beck Depression Inventory			.797
Apathy			.819
Disinhibition			.773
Executive Functions			.876

DISCUSSION

In the current study, we examined frontostriatal circuit dysfunction, using standardized frontal/executive neuropsychological tasks in a group of nondemented patients with PD and a group of demographically-matched healthy adults. This study is unique in that it incorporated tasks reportedly mediated by each of three separate frontostriatal complex circuits. The test battery was developed based on findings from the PD, frontal brain-damaged, animal, and neuroradiologic literatures linking frontostriatal circuitry to neuropsychological task function.

Overall group differences on frontal/executive tasks, across the three circuit conditions, suggested that patients with PD performed significantly worse than the NC group. Calculated effect sizes revealed that the greatest magnitude of difference, although non-significant, occurred for tasks mediated by the DLPFC circuit. Second, although a significant Group X Circuit interaction was not achieved, a trend suggested that tasks mediated by the DLPFC and ACC circuits appeared to elicit greater impairments in patients with PD compared to NC. Third, for the PD group alone, our findings indicated that indices of impairment were greatest for tasks mediated by the DLPFC circuit. Fourth, an index of DLPFC circuit performance was discovered to be the only significant composite score in discriminating among subject groups. Finally, overall frontal/executive task performances across groups did not load according to circuit as initially hypothesized, possibly suggesting limited specificity of frontal/executive measures. Instead, the factor loadings may be explained by methodological differences across tasks. Our findings provide neuropsychological-based evidence suggesting

widespread circuit disruption in PD with the DLPFC and its connections to the striatum being predominantly disrupted in nondemented patients with PD.

Between-Group Comparisons

As was expected, given evidence from the literature (e.g., Barbosa et al., 1997; Dubois & Pillon, 1997; Green et al. 2002; Levin et al., 1992; Raskin, Borod, & Tweedy, 1990; Ridenour & Dean, 1999), our sample of patients with PD were impaired relative to normal control subjects on most tasks of frontal/executive function. Overall, group comparisons across measures revealed that the range of impairments exhibited by our PD group was extensive, and at first glance, were not necessarily attributable to any one specific frontostriatal circuit. Upon closer inspection of univariate comparisons, PD and NC subjects did not differ significantly on scales assessing subjective reports of depression (Beck Depression Inventory), disinhibition (FrBSe Disinhibition Scale), and motor perseveration (alternating letters and loops). The syndromes that typically elicit sub-optimal performance on these three particular measures mentioned above have been previously associated with OFC function (e.g., Mayberg, 1990, 2000; Passingham, 1972; Stuss et al., 1982, 1983).

The lack of a significant finding between groups on a scale of depression was unexpected given that the literature indicates that approximately 40% of individuals with PD manifest depression (for reviews, see Aarsland & Karlsen, 1999; Barbosa et al., 1997; Cummings et al., 1996; Lichter, 2000; Starkstein & Kremer, 2000). Our null findings may be attributed to one or both of the following explanations. First, our sample of patients may have exhibited more stable mood fluctuations than those reported in the literature. For instance, our PD sample was receiving dopamine therapy, which has been

demonstrated to temporarily ameliorate depression (e.g., Growdon et al., 1998; Maricle, Valentine, Carter, & Nutt, 1998; Quinn, 1998). Second, due to the nature of recruitment, our sample of normal control subjects was mostly comprised of the spouses/caregivers of our patients with PD, who as caregivers may present with their own psychological stressors. Caregiver distress has been reported in the AD literature (e.g., Thomas, Clement, Hazif-Thomas, & Leger, 2001). Thus, it is quite possible that our NC sample may have, in fact, been more depressed than individuals in the general population.

The lack of significant group differences for subjective ratings of disinhibition was somewhat expected since it is relatively infrequent (roughly 12%) in PD (Cummings et al., 1996). Finally, the absence of group differences on a task of motor perseveration was also expected based upon reports indicating that patients with PD typically create few perseverative errors relative to those patients with cortical dysexecutive syndromes, such as AD and LBD (for review, see Lichter, 2000). In the current study, only 5 out of 32 patients with PD created errors of motor perseveration.

The lack of a significant Group X Circuit interaction (statistical trend) appears to mirror the findings from the univariate t-tests described above. The majority of group differences were significant for each circuit condition, as indicated by computed univariate comparisons. The statistical trend appears to be influenced by the decrease in the superiority of the NC group, relative to the PD group, on measures related to the OFC circuit.

PD Within-Group Circuit Comparisons

The extent of circuit involvement in frontal/executive task performances was further assessed in the PD patient group alone. This set of statistical procedures was

conducted in order to exclude any unusual confounding factors attributed to our sample of NC subjects (e.g., endorsement of depression). Using cut-off scores based on standardized normative test data, we discovered that measures mediated by the DLPFC more frequently elicited impaired performances in the PD group relative to OFC-related tasks. Task performances differences between OFC and ACC indices of impairment did not achieve significance. Interestingly, although unexpected, there was a lack of significance for indices of impairment between the ACC and DLPFC variables. On an exploratory basis, we wanted to dismiss the possibility that significant differences were not attributable to a greater number of variables within the DLPFC circuit condition. We combined the average index of impairment scores for the four ACC and six OFC circuit conditions and compared them to DLPFC index scores using a binomial test. The test revealed that the DLPFC-related impairment was significantly greater than indices of impairment seen on the combined OFC and ACC-related tasks (observed probability = .74, $p = .021$), once again indicating that DLPFC related impairment in the NDPD group was not exaggerated due to a larger number of variables being considered.

From a neuropsychological perspective, the lack of a significant difference found between indices of impairment for the ACC circuit condition relative to the DLPFC or OFC circuit conditions may be attributed to the ACC's role in mediating a combination of cognitive and behavioral functions in humans (Cohen et al., 1999; Cummings, 1993). Thus, our findings here may reflect the strong dichotomy between cognitive (i.e., DLPFC) versus behavioral (i.e., OFC) differences, which may have obscured any potential significant comparisons with the ACC circuit related tasks. From a neuroanatomical and neuropharmocological perspective, it is unlikely that the ACC

circuit would be considerably more disrupted than the DLPFC circuit in PD (Lewis et al., 2003; Lichter, 2000). Thus, we would have expected that the DLPFC-related tasks would have elicited significantly greater indices of impairment relative to the ACC-related tasks in addition to those of the OFC in our sample of patients with PD.

Group Membership Prediction

After classifying our study samples using a logistic regression analysis, it was discovered that the DLPFC composite score was the only significant circuit that discriminated PD from NC non-motor profiles. Factors contributing to this finding are elaborated upon below. Other than motor deficits, which are considered the most striking and easily identifiable symptoms of PD, DLPFC- related frontal/executive cognitive deficits appear to be a strong indicator of PD diagnosis in the current study. Furthermore, the subgroup of PD patients correctly identified by the analysis (n = 24/32) was significantly different on particular demographic and screening variables (e.g., age, attention, and depression levels) relative to PD patients misclassified as NC subjects (n = 8/32). Although younger and more educated adults would be expected to perform better on neuropsychological measures of cognitive functioning, our exploratory findings may suggest that that our PD sample varied in terms of their rates of disease severity and progression, with the correctly identified PD patients potentially demonstrating more significant DLPFC dysfunction. Our findings regarding subgroups of NDPD patients are relatively consistent with prior work (e.g., Palazzini et al., 1995) which indicated that "deteriorated" nondemented PD patients, (1) performed worse on a measure of attention, (2) had greater motor impairment, (3) and were older than a group of stable nondemented patients with PD. Similarly, Owen et al. (1992) administered frontal/executive tasks (i.e.,

planning, spatial working memory, and attentional set-shifting) to a group of nondemented patients with PD. PD patients who were receiving dopamine therapy and had more severe symptomatology (e.g., motor deficits) exhibited poor performance on DLPFC-related tasks. However, unmedicated patients with milder symptomatology were unimpaired on all frontal/executive measures administered.

Neurochemical and Neurophysiological Differences Across Circuits

Neurochemical and neurophysiological research have shown that the expression of metabolic changes in nondemented patients with PD appears to exhibit significantly greater DLPFC circuit disruption relative to that of the ACC and OFC circuitry. In PD, cognitive frontal/executive functions reportedly mediated by the DLPFC are particularly jeopardized relative to those mediated by the OFC and ACC. This can be attributed to (1) a substantial dopamine deficiency within the caudate nucleus resulting from a lesion of the nigrostriatal dopaminergic pathway, creating a partial "disconnection syndrome" of subcortical origin (Taylor et al., 1986), and (2) additional depletion of dopamine from the VTA mesocortical system further complicating neural transmission (Agid, Javoy-Agid, & Ruberg, 1987). For instance, Leenders et al. (1990) reported that performance on select cognitive frontal/executive tests correlated with [18F] fluorodopa-uptake in the medial frontal cortex but not the caudate nucleus. These findings may suggest a greater role for VTA dopaminergic system depletion relative to that of the nigrostriatal dopamine system in cognitive frontal/executive deficits in PD. Additional dopamine depletion is also apparent in the mesolimbic, hypothalamic, noradrenergic, and serotonergic neurons, which may further contribute to greater DLPFC circuit dysfunction (Cooper, Bloom, & Roth, 1996).

Dopamine depletion in the caudate nucleus, which appears to be severely impacting executive functions in PD, is greatest in the anterodorsal head of the caudate. This structure is heavily connected to the DLPFC region (Kish et al., 1986; Rosvold, 1972; Yeterian & Pandya, 1991 [in rhesus monkeys]). Rinne, Rummukainen, Paljarui, and Rinne (1989) reported a significant correlation between dementia severity in PD and neuronal loss in the select regions of the substantia nigra that have specific projections to the caudate nucleus. It appears that disruption to specific regions of the caudate nucleus play a critical role in the cognitive and behavioral PD profile, as demonstrated in the current study with more profound DLPFC-related deficits in our patients with PD.

Ventral regions of the caudate, which are connected with more ventral regions of the frontal lobe (i.e., OFC), are relatively intact in early PD, sparing behavioral functions maximally dependent on this neural circuitry (e.g., depression) (Lewis et al., 2003; Yeterian & Pandya, 1991). The ACC and OFC circuits, thus, would appear to be less compromised relative to the DLPFC circuit in NDPD. Lending further support to greater DLPFC dysfunction in NDPD, is that cognitive frontal/executive deficits are more prevalent than behavioral deficits (e.g., Green et al., 2002; Pahwa et al., 1998). In addition, the extent of neural degeneration within the ACC and OFC and corresponding circuitry in PD is debatable depending on the severity of the mood disturbance, whereas DLPFC degeneration is less questionable given extensive evidence from the literature documenting frontal/executive cognitive complaints in PD. In spite of a relative decline in frontal/executive functioning (across circuit conditions) in our patients with PD, as compared to NC subjects, the pattern of performance seems to mirror the rate and

severity of PD DLPFC circuit dysfunction, even in early stages, as reported in the literature.

Our findings suggest that OFC task-related performance was less severely impacted compared to DLPFC-task related performance in our sample of patients with PD. FDG/PET scanning studies of the OFC have reported significant hypometabolism in the ventrodorsal caudate and OFC region of the frontal lobe in depressed patients with PD relative to both non-depressed patients with PD and NCs (for review, see Mayberg, 2000). However, significant executive cognitive impairments (more consistent with DLPFC circuit dysfunction) are prevalent in PD with or without the presence of a mood disturbance when controlled for overall clinical severity (e.g., Troyer et al., 1995). In addition to the mood disturbance reported in PD, tasks typically associated with OFC function appear to be less compromised especially in the early stages of PD (e.g., Cools et al., 2001, Swainson et al., 2000). Similar findings were discovered in the current study, as three OFC-related measures did not elicit significant group differences.

The ACC and its circuitry, on the other hand, have fewer connections with the subcortical regions primarily impacted in PD (i.e., caudate and putamen) compared to the DLPFC circuit. While there is restricted degeneration of the ACC and nucleus accumbens in PD, the ACC circuit is partially or totally disconnected in other movement disorders such as PSP (progressive supranuclear palsy), as several relay nuclei are considerably damaged (for review, see Litvan, 2000). This may also explain the greater incidence of apathy and ACC-related cognitive impairment in patients with PSP compared to those with PD (for review, see Lichter, 2000). Furthermore, Pluck and Brown (2002) reported on the incidence of apathy in a sample of NDPD patients.

Patients who were categorized as "high apathy" (i.e., greater ACC dysfunction) relative to "low apathy" (i.e., lower ACC dysfunction) were found to have greater impairments on tests of frontal/executive cognitive function associated with response initiation and conflict resolution. Implications for these findings may suggest that highly apathetic PD patients represent a distinct subgroup, which reflects more ACC involvement suggestive of greater disease progression (i.e., increased cognitive dysfunction may indicate higher degrees of behavioral abnormalities). However, this notion should be approached with caution, as replication of their study has yet to be conducted. On an exploratory basis, we compared "high" versus "low" apathy PD patients using a calculated median apathy score of 30. Scores below and including 30 were labeled as "low" apathy (n = 17/32), and those scores above 30 were labeled as "high" apathy (n = 15/32). Computed univariate t-tests did not reveal any significant subgroup differences across the experimental tasks. It appears that the progression of ACC disruption in our sample of PD patients may have been minimal.

Our findings, which appear to coincide with neuropathological research evidence, suggest that the DLPFC lends greater influence to the overall frontal/executive impairment found in NDPD patients. The frontal/executive cognitive deficits observed in NDPD patients is thus likely to be a principal consequence of DLPFC circuit disruption at the level of the caudate nucleus resulting from a lesion of the nigrostriatal dopaminergic pathway; however, this is further burdened by additional degeneration of the mesocortical dopamine system. Therefore it is not surprising that increased progression of neuronal degeneration in these prescribed areas correlates with dementia severity in PD (Leenders et al., 1990; Palazzini et al., 1995; Rinne et al., 1989; Scatton,

Javoy-Agid, Rouquier, Dubois, & Agid, 1983). Syndromes and deficits associated with the ACC and OFC may be attributed to secondary or indirect neurochemical and neuroanatomical changes, as they appear to be less frequent in PD.

Once believed to be a disease solely impacting the dopaminergic system, PD takes it toll on several neurochemical systems. The superficial characterization of PD as a disorder isolated to the dopaminergic system proves to be an unacceptable oversimplification of the pathology of the disease. The mesocortical dopaminergic, noradrenergic, cholinergic, and serotonergic pathways have been shown to be consistently disrupted in PD (Agid et al., 1987; Chinaglia, Alvarez, Probst, & Palacios, 1992; Chinaglia, Landwehrmeyer, Probst, & Palacios, 1993; Forno, 1996; Horykiewicz & Shannak, 1994; Wolters, 2001) and may further contribute to the reported cognitive and behavioral deficits. Similarly, cortical Lewy bodies, which reportedly occur even in the early stages of PD, may also play a contributory role (Byrne, Lennox, Lowe, & Godwin-Austen, 1989; Gibb, Luthert, Janota, & Lantos, 1989).

Neurotransmitter Systems Impacted in PD

Dopamine. As mentioned earlier, it is believed prudent to treat motor deficits in PD with dopamine therapy. However, evidence has shown that frontal/executive deficits are only selectively improved in PD after dopamine therapy is administered (e.g., Gotham et al., 1988). Studies have recently shown that dopamine depletion and medication alleviation differentially affect the frontostriatal circuits that are engaged in motor, cognitive, and/or behavioral functions (e.g., Cools et al., 2001). Typically, patients in the early stages of PD tend to demonstrate motor improvement, whereas cognitive and behavioral improvements are either delayed or non-existent. This might be

explained by the (1) differential rates and patterns of select neurochemical depletion in PD, followed by (2) differential therapeutic doses of dopamine administered to patients. The rate of dopamine depletion in PD appears to be temporally displaced, as motor deficits typically develop first, with subsequent deficits in cognition and behavior. What has been supported in a limited fashion by the findings of the current study is that the DLPFC circuit appears to be initially and possibly more markedly impacted in NDPD relative to OFC and ACC circuits.

Gotham et al. (1988) provided evidence indicating that certain aspects of cognitive performance in PD could actually be worsened by dopamine therapy. They hypothesized that the effects of dopamine therapy were related to the pattern and course of dopamine loss within the striatum in PD. Those regions suffering extensive dopamine depletion, such as the putamen, would have their functions optimally titrated by dopamine therapy (i.e., improved motor functions). Even in patients with mild motor symptoms, a striatal dopamine loss of 70%-80% is observed, while patients with severe motor impairments may have striatal dopamine neurodegeneration in excess of 90% (Cooper, Bloom, & Roth, 1996). By contrast, those regions relatively spared in the early stages, such as the caudate and ventral striatum, would potentially be disrupted by medication, as the level of dopamine function would presumably be set supra-optimally by the drug. This would support an earlier statement indicating that motor impairments are typically first noticed at PD onset and the first to be alleviated after dopamine therapy. This may also explain the variability of findings in the literature regarding the effects of dopamine therapy on cognition and behavior in PD (e.g., Gotham et al., 1988; Growdon et al., 1998). Dopamine depletion within the putamen appears to impact motor

function, caudate depletion appears to impact cognitive abilities, and dopamine depletion of the ventral striatum and the mesocortical regions appears to impact behavioral disturbances (Barbosa et al., 1997; Lichter, 2000; Savage, 1997). Hence, it could be speculated that the greater the severity of behavioral dysfunction (e.g., apathy) in PD, the longer the evolution of the disease process. On an exploratory basis, we had entered scores from the Purdue Pegboard test (motor dexterity and speed task) into the factor analysis. We expected that the variables for this test would load with other speeded tasks on Factor 1 (i.e., verbal fluency tests). Instead, all three variables of the Purdue task loaded with other frontal/executive cognitive tasks on Factor 2. Furthermore, these variables did not significantly load with any of the behavioral measures on Factor 3. These findings appear to suggest that motor performance is more strongly related to frontal/executive (i.e., caudate related functions) than behavioral (i.e., ventral striatum) functioning as reported in the literature.

Swainson et al. (2000) demonstrated that mild PD patients alleviated with dopamine performed poorly on tests of probability reversal learning (described above), which has been shown to be associated with ventral striatum and OFC function (e.g., in animals - Dias et al., 1996; in humans – Rolls, Hornak, Wade, & McGrath, 1994). In contrast, when administered a task of spatial working memory (i.e., DLPFC function), the same patients demonstrated improvements after dopamine therapy. Similarly, Cools et al. (2001) showed that dopamine- alleviated PD patients performed within normal limits on a DLPFC mediated task (i.e., spatial working memory), but poorly on an OFC-mediated task (i.e., reversal learning). The reverse was discovered when the patients were medication-withdrawn. During the dopamine-alleviated condition, neuroradiologic

(PET) findings revealed OFC hypometabolism while PD patients were performing the reversal-learning task. The authors concluded that dopamine therapy could either benefit or impair performance depending on the nature of the task being administered and the basal level of dopamine in the associated frontostriatal circuitry. Thus, what appears to be occurring is that supra-optimal doses of dopamine were improving cognitive executive dysfunction in these patients (i.e., DLPFC-related function) while impairing reinforcement contingency schedules (i.e., OFC-related function). These particular findings demonstrate that in PD, DLPFC circuit disruption is optimally involved even in early stages. Given that an OFC-related task was impaired after dopamine therapy suggests that this circuit may only be impacted minimally or not at all in early stage NDPD patients. If this is the case, then it is conceivable that our sample of PD subjects (whom were all dopamine-alleviated) should have exhibited more profound OFC and ACC task related deficits. However, this event did not occur here as our findings support evidence implicating greater impairment of tasks mediated by the DLPFC.

Acetylcholine. Perry et al. (1985) indicated that nondemented patients with PD have a 17% reduction in cholinergic neurons in the nucleus basalis of Meynert. In addition, Asahina et al. (1998) demonstrated that there is increased muscarinic cholinergic receptor binding in the frontal cortex of patients with PD, which reflects post-synaptic hypersensitivity caused by loss of the ascending cholinergic input from the basal forebrain. In their study, specific regions of interest, such as the DLPFC, were not specified, although, medications either increasing or depleting cortical acetylcholine in patients with PD elicited task performance changes previously associated with DLPFC function (Bedard et al., 1999; Dubois et al., 1987, 1990). Furthermore, using normal

control subjects, Furey, Pietrini, and Haxby (2000) reported that an improvement in the speed of recognizing faces was accompanied by significant metabolic reductions in the DLPFC following administration of physostigmine (prevents uptake of acetylcholine). Their findings indicated that excess acetylcholine decreased the burden on working memory functions, as evidenced by the reduced activity in the DLPFC. Due to the extensive neuronal loss of cholinergic neurons in PD, as well as preliminary reports of cognitive improvement with anticholinesterase therapy (e.g., Hutchinson & Fazzini, 1996), it appears that the cholinergic system has a substantial role in the DLPFC-related cognitive deficits in this patient population, which only adds to the cognitive declines already resulting from dopamine depletion. We can only speculate that additional cholinergic depletion contributed to the frontal/executive deficits in our sample of patients with PD.

Serotonin. The serotonergic system, implicated in behavioral changes and inhibitory control, as opposed to executive cognitive functions, is reportedly impacted in PD (see Mood section). In healthy control subjects, for instance, depletion of tryptophan (serotonin precursor) induced minimal impairment on tests sensitive to executive dysfunction (Park et al., 1994). For example, performances on the Tower of London Test of planning and self-ordered spatial working memory were unaffected. Consequently, the same subjects were impaired on the reversal learning set-shifting task typically associated with OFC function after tryptophan was depleted.

Depressed patients with PD have more severe neuronal loss in the dorsal raphe (serotonin producing neurons) than nondepressed patients with accompanying decreases in serotonin binding sites in the frontal cortex and basal ganglia (Chinaglia et al., 1992;

1993; Paulus & Jellinger, 1991). Thus, it may appear that the extent of OFC circuit dysfunction in PD is directly related to the severity of mood and personality changes. Furthermore, PD patients with higher levels of depression and apathy have exhibited greater impairment on tests of frontal/executive function relative to those patients with either a less severe or nonexistent mood disturbance (e.g., Kuzis et al., 1997; Pluck & Brown, 2002), once again, suggesting that the presence of a mood disturbance coincides with greater overall disease progression. In light of our findings, we can speculate that our sample of PD patients may not have had significant OFC circuit disruption, related to a loss of serotonergic input, given that the majority of our patients with PD were only mildly depressed based on a self-report scale.

Norepinephrine. In humans, noradrenergic projections are thought to influence arousal, selective attention, and anxiety states (Mesulam, 1990). Multidisciplinary studies carried out have provided evidence that denervation of the locus ceruleus (norepinephrine producing region) plays an important role in the pathogenesis of locomotion, dementia, depression, and vegetative states frequently observed in PD (e.g., Briley, 1993; Bertrand et al., 1997). Studies evaluating the distribution of adrenoreceptors within the normal brain have shown that the highest densities are found in the most external laminae of the cortex including the ACC (Jones et al., 1990). This is not surprising given ACC's apparent role in attentional processes (see Attention section).

Decreased concentration and motivation have been shown to correlate with noradrenergic metabolism in PD, suggesting a link between cognitive/behavioral deficits and neuronal depletion in the locus ceruleus (Mayeux, Stern, Sano, Cote, & Williams, 1987). The ACC appears to be secondarily impacted relative to DLPFC degeneration in

PD due to its association with behavioral functions (e.g., apathy) and its neuronal connection to the ventral (limbic) striatum which appears to be more severely impacted in later stages of PD. The data available seem to indicate that reductions of central norepinephrine might significantly influence both the onset and the progression of the damage to the dopaminergic nigrostriatal tract (Soldani & Fornai, 1999). Within this context, substantial noradrenergic depletion might play a dual role in PD: (1) by itself, conditioning non-motor PD symptoms (e.g., attentional processes) via ACC dysfunction, and (2) provoking a worsening of the dopamine nigrostriatal damage (i.e., disease progression). In spite of the fact that patients with PD were impaired on most tasks compared to NCs across circuits in the current study, our overall findings suggest greater emphasis given to DLPFC circuit impairment. Thus, the extent of noradrenergic depletion in our PD sample can only be speculated upon at this time.

Frontal/Executive Neuropsychological Tests

Frontal lobe regions are clearly not homogeneous anatomically or functionally (Stuss & Alexander, 2000; Stuss et al., 2002). The current study explored the heterogeneity of the frontal/executive measures administered to both PD and NC subjects. We assessed whether frontal/executive neuropsychological tests differed from each other in terms of their ability to assess cognition and behavior mediated by the separate frontal regions and their corresponding circuits (i.e., DLPFC, ACC, and OFC). The neuropsychological tests were categorized according to the three frontostriatal circuits. Overall, findings from a factor analysis did not support the fractionation of neuropsychological tests according to circuit. Instead, our three factor loadings

(combined) appeared to relate to function and test methodology (i.e., verbal generation, frontal/executive, and behavioral).

All variable loadings for Factor 1 included measures of verbal fluency. Hence, we labeled Factor 1 the "lexical/verbal generation" factor. Here, variable loadings involved timed responses for intrinsic and extrinsic word-list generation. For Factor 2, variable loadings spanned across several different frontal/executive cognitive measures (i.e., "executive cognitive factor"). The absence of a verbal timed response measure appeared to be a common denominator throughout Factor 2. For Factor 3 (i.e., "behavioral/psychiatric factor"), only measures assessing self-report behavioral (non-cognitive) traits loaded significantly.

The current study did have certain methodological and statistical limitations. First, our small sample size is not typically ideal for factor analytic procedures (Tabachnick & Fidell, 1996). The NC and PD groups were combined in the factor analytic procedure, as we wanted to view frontal/executive performance on a continuum across subject groups rather than across group differences. Future studies should substantially increase sample size. Second, following the results from the factor analysis, the next step in assessing the heterogeneity of clinical neuropsychological tasks is to test the internal consistency of the tasks categorized by circuit. Third, in spite of the abundance of research associating brain structures with function (via neuroimaging or lesion studies), the current study was restricted to behavioral measures based on neuropsychological tasks. Typically, neuroimaging research studies, which are abundant in the PD literature, utilize modified neuropsychological tasks, usually reformatted for a computer, in order to better suit constraints of time and imaging hardware. The

neuropsychological tests used in the clinic were initially constructed to elicit function and not neuroanatomy. Finally, neuropsychological task performance often requires resources from overlapping cortical regions in order to successfully complete a task (e.g., Goldenberg et al., 1989). In other words, functional neural systems are relative to the task, not absolute. Traditionally, the solution to this obstacle has been to either develop better tasks to isolate specific processes or to look at post-hoc relationships between task measures and standard neuropsychological tests in multiple domains, as attempted in the current study.

Petrides and Pandya (1994) categorized regions of the frontal lobe according to cytoarchitecture. The four surface regions identified were the (a) polar, (b) lateral, (c) superior medial, and (d) inferior medial. The lateral region includes the dorsolateral area; the superior medial includes the cingulate, whereas the inferior medial includes both the orbitofrontal and portions of the cingulate. In spite of this type of neuroanatomical categorization, regional overlap is evident. For instance, the right dorsolateral and right superior medial frontal regions (including the ACC) both were discovered to maintain a role in set-shifting (Stuss et al., 2002). Stuss et al. (1998) attempted to better control frontal brain-damaged patient categorization using a classification regression tree (CART; Breiman, Friedman, Olshen, & Store, 1984). The three frontal groups previously designated in their study (i.e., right frontal, left frontal, and bilateral frontal) were now increased to four (i.e., left and right dorsolateral, superior medial, and inferior medial). By using CART classification, the authors were better equipped in categorizing strategy performance on a verbal fluency task in a group of frontal brain-damaged patients. Regional overlap was still evident, although reduced. Similar classification

studies were conducted using the Wisconsin Card Sorting Test and Stroop task (Stuss et al., 2000; Stuss et al., 2001). In spite of these positive findings, it is very doubtful that a particular standardized neuropsychological test would strictly adhere to a single frontostriatal circuit and/or region of the cortex. More recent work using a partial least squares analysis (PLS: McIntosh et al., 1996) has demonstrated encouraging progress in delineating lesion location and neuropsychological task performance (Stuss et al., 2002). Here, the PLS analysis produces a covariance matrix with sets of mutually orthogonal paired latent variables. In their study, Stuss et al. (2002) were able to extract unique variance from standardized neuropsychological task performance and relate them to different lesion locations. The implications for a similar analysis in a sample of PD patients are promising.

SUMMARY AND CONCLUSIONS

Based on our review of the literature, two explanations are brought forth in describing the overall findings of the current study (i.e., diffuse frontal/executive dysfunction with somewhat greater DLPFC disruption). First to consider is that the DLPFC (with its abundant dopaminergic connections) relative to the OFC and ACC circuitry appears to be predominantly impaired in NDPD at least in earlier stages of PD. In addition, the DLPFC reportedly maintains more abundant connections with other neurotransmitter systems (i.e., cholinergic, serotonergic, and noradrenergic), which may further hinder appropriate DLPFC-related function in PD. This notion is supported by the superiority of DLPFC-related task impairments in our PD sample, as well as corroborating evidence from the PD literature. Second, our findings appear to reflect one particular point in the disease timeline in our sample. In our study, PD patients were only included if they demonstrated mild to moderate clinical impairment. Thus, we did not assess patients at the more severe end of the clinical spectrum. In retrospect, a more quantitative measure of PD disease severity (e.g., the Unified Parkinson's Disease Rating Scale [UPDRS]) would have been helpful in better defining the clinical severity of our patients. We can only speculate that patients in the later stages of PD might have exhibited equivalent levels of motor, cognitive, and behavioral deficits (indicative of equally distributed circuit dysfunction) than our current sample. This was briefly examined in the current study. The 24 correctly identified PD patients, classified after logistic regression, appeared to demonstrate a more profound degree of clinical severity relative to PD patients misclassified as NC. This indicates that our sample of PD patients varied in terms of their degree of overall clinical severity, including DLPFC dysfunction,

as it was the only significant index in discriminating PDs from NCs. In light of the current findings, it is suggested that future studies assessing frontostriatal circuit dysfunction in PD should control for differences in clinical severity. This may be accomplished by using longitudinal or cross-sectional designs (including PD patients in early, middle, and late stages).

From a clinical neuropsychological perspective, the notion that the extent and severity of the neurodegenerative process antemortem within frontal structures in individuals with NDPD is still not entirely clear at this time which makes linking neuroanatomy with specific neuropsychological functions complicated. Thus, newer procedures and techniques to combine neuropsychological task performance and functional neuroanatomy (e.g., PET or fMRI) are warranted.

APPENDIX A

Counterbalanced Test Order

Battery 1	Battery 2	Battery 3
DRS	DRS	DRS
VFDT	BDI	VFDT
BTA	BTA	BDI
BDI	VFDT	PURDUE PEGBOARD
PURDUE PEGBOARD	PURDUE PEGBOARD	BTA
SPATIAL SPAN – WMS	FrSBe SCALE	VERBAL FLUENCY – EFS
VERBAL FLUENCY – EFS	ALT. LOOPS	DIGIT SPAN - WMS
COND. ASSOC. LEARNING	VERBAL FLUENCY – EFS	STROOP TEST
STROOP TEST	COND. ASSOC. LEARNING	SPATIAL SPAN – WMS
DIGIT SPAN – WMS	OMOT	ALT. LOOPS
FrSBe SCALE	STROOP TEST	TWENTY QUES. TEST
TWENTY QUES. TEST	SPATIAL SPAN – WMS	OMOT
ALT. LOOPS	DIGIT SPAN - WMS	COND. ASSOC. LEARNING
OMOT	TWENTY QUES. TEST	FrSBe SCALE

APPENDIX B

Principal Dependent Variables

NP Test	Dependent Variables	Possible Range
DRS	Total raw score	0-144
VFDT	Total raw score	0-32
BTA	Total raw score	0-20
BDI	Total raw score (screening and investigational)	0-30
PURDUE PEGBOARD	Total raw score (right hand) Total raw score (left hand) Total raw score (both hands)	0 - 0 - 0 -
OMOT	Total raw score	0-40
SPATIAL SPAN (WMS-III)	Total raw score	0-30
DIGIT SPAN (WMS-III)	Total raw score	0-30
VERBAL FLUENCY	Total raw score (phonemic) Total raw score (semantic) Total raw score (category switching) Total raw score (switching accuracy) Total raw score (15 sec interval fluency)	0 - 0 - 0 - 0 - 0 -
COND. ASSOC. LEARNING	Total errors Total number of trials to criterion	--------- 0-68
FrSBe	Executive Dysfunction Scale (E – total) Apathy Scale (A- total) Disinhibition Scale (D – total)	0-17 0-14 0-15
STROOP TEST	Color/Word Total Interference Score	0 - 0 -
TWENTY QUES. TEST	Total questions asked Initial abstraction score Total weighted achievement score	0 – 80 0 – 20
ALT. LOOPS	Total errors	0 -

APPENDIX C

Experimental Test Battery Categorized by Circuit

Dorsolateral Prefrontal Cortex

Odd Man Out Test – set shifting

Spatial Span Test – Wechsler Memory Scale 3 – nonverbal working memory

Digit Span Test – Wechsler Memory Scale 3 – verbal working memory

Verbal Fluency Test – response generation and maintenance

- letter fluency
- animal fluency
- alternating fluency (set-shifting)

Petrides Conditional Associate Learning Test – associate learning

Frontal Systems Behavior Scale – executive dysfunction scale

Anterior Cingulate Cortex

Stroop Color/Word Interference Test – response monitoring and conflict resolution

Verbal Fluency Test – response initiation

- Initial fluency (15 seconds)

Frontal Systems Behavior Scale – apathy scale

Orbitofrontal Cortex

Beck Depression Inventory – mood state

Frontal Systems Behavioral Scale – disinhibition scale

Twenty Questions Test – decision making and impulsivity

Alternating Loops and Letters – perseveration

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