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Neurobehavioral functioning in Parkinson's disease: The role of basal ganglia-thalamocortical circuit loops in predicting performance

Bondi, Mark William, Ph.D.

The University of Arizona, 1991

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NEUROBEHAVIORAL FUNCTIONING IN PARKINSON'S DISEASE: THE ROLE OF BASAL GANGLIA-THALAMOCORTICAL CIRCUIT LOOPS IN PREDICTING PERFORMANCE

by

Mark William Bondi

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF PSYCHOLOGY

In Partial Fulfillment of the Requirements
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DOCTOR OF PHILOSOPHY

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1991

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GRADUATE COLLEGE

As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Mark William Bondi

entitled NEUROBEHAVIORAL FUNCTIONING IN PARKINSON'S DISEASE: THE ROLE OF BASAL GANGLIA-THALAMOCORTICAL CIRCUIT LOOPS IN PREDICTING PERFORMANCE

and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

Alfred W. Kaszniak	12/21/90 Date
Richard R. Bootzin	12/21/90 Date
Lynn Nadel	12/21/90 Date
Steven Z. Rapcsak	12/21/90 Date
Alan B. Rubens	12/21/90 Date

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Dissertation Director Alfred W. Kaszniak	12/21/90 Date

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ABSTRACT

Motivated by current neuroanatomic theories of basal ganglia-thalamocortical circuit loops, this study assessed whether disturbed neuronal outflow from the striatum (occurring in Parkinson's Disease) would lead to circumscribed deficits in cognitive functions thought to be dependent upon the functional integrity of the frontal lobes, the cortical destination of efferent striatal neurons (particularly arising from the caudate nucleus). Nineteen nondemented Parkinson's disease (PD) patients were matched with 19 normal elderly control subjects on the basis of age, gender, education, and estimated premorbid intelligence. Determination of disease onset and course, severity of motor symptoms, and medication regimen were made on all PD patients. Three categories of neuropsychologic tests were given: (1) tests sensitive to prefrontal cortical dysfunction (the California Sorting Test [CST], a modified version of the Wisconsin Card Sorting Test [WCST], temporal ordering, and generative naming), (2) implicit and explicit memory tests (a fragmented pictures test, serial reaction time, continuous recognition memory, and word learning), and (3) ancillary tests measuring psychometric characteristics (including the Block Design and Picture Arrangement subtests of the WAIS-R, Benton Facial Recognition Test, Benton Right-Left Discrimination, and Benton Visual Form Discrimination Test). Consistent with the functional/anatomic hypothesis of subcortical deafferentation of the frontal lobes, the PD patients demonstrated selective deficits in cognitive functions thought to be dependent upon the functional integrity of the prefrontal cortex (e.g., CST, WCST, generative naming, temporal order memory, WAIS-R Picture Arrangement), while other tasks presumed to rely on other cortical regions and processes were not significantly impaired (e.g., learning and memory, visuoperceptual and visuoconstructional skills). Results are discussed in terms of the validity of the outflow model as a construct that has

predictive utility for performances of nondemented PD patients on neuropsychologic measures that are thought to rely upon the functional integrity of the frontal lobes.

CHAPTER 1

INTRODUCTION

Overview

Parkinson's disease (PD) is the most common, and likely best known, disease affecting the basal ganglia. It is a progressive, degenerative neurological disorder that affects 1 in 100 people over the age of 50 in the United States (Duvoisin, 1984). The neurochemistry and neuropathology of PD cause changes in the nigrostriatal system, as well as the mesolimbic and mesocortical pathways (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973; Taylor, Saint-Cyr, & Lang, 1986). The motor symptoms of PD include a resting tremor, generally increased muscle tone (termed rigidity), and difficulty in initiating voluntary movements. Symptoms of this kind have now come to be associated with dysfunction of the basal ganglia, and are termed *extrapyramidal* symptoms; such terminology may be misleading, however, because at least some of the involuntary movements are actually effected through the *pyramidal* tract, particularly the corticospinal tract (Nolte, 1988).

James Parkinson originally described the disease that bears his name as having changes in motor function only, leaving the senses and intellect "uninjured," yet research has demonstrated PD to adversely affect cognitive and other psychologic functions as well (Pollock & Hornabrook, 1966). Motor and cognitive functions are affected by these neuropathologic changes, with the majority of patients developing some intellectual deficits, and a sizeable percentage further developing dementia (Hietanen, & Teravainen, 1986; Lees, 1985; Mayeux & Stern, 1983; Pirozzolo, Hansch, Mortimer, Webster, & Kuskowski, 1982). Complicating matters, PD patients may also have a greater risk, than is true for the general population, for the development of Alzheimer's disease (AD). Conversely, AD patients appear to have an increased risk of developing extrapyramidal

symptoms (Hakim & Mathieson, 1979; Hirano & Zimmerman, 1962; Leverenz & Sumi, 1986; Molsa, Marttila, & Rinne, 1984). Affective disturbances appear common in PD also, with approximately 40 percent of PD patients developing a major depression or dysthymic disorder (Mayeux, Stern, Williams, Côté, Frantz, & Dyrenfurth, 1986). In some cases the affective disorder can precede the onset of motor signs (Celesia & Wanamaker, 1972; Mayeux, Williams, Stern, & Côté, 1984). While far from being conclusive, recent evidence has linked depression to the pathologic changes in PD (Cantello, Gilli, Riccio, & Bergamasco, 1986; Girotti, Carella, Grassi, Soliveri, Marano, & Caroceni, 1986; Mayeux, et al., 1986), including the identification of altered serotonin metabolism (Mayeux, Stern, Côté, & Williams, 1984). This finding suggests the possibility that a subgroup of PD patients may be predisposed to developing depression. The relationship between depression and cognitive functioning, however, is unclear (Girotti, et al, 1986; Mayeux, 1982).

The present review first outlines relevant anatomic structures, biochemical changes, and pathophysiology of PD. This is followed by a review of recent research concerning affective and cognitive changes, including intellectual deterioration and deficits in language, visuospatial skills, learning and memory, and frontal lobe functioning.

The Basal Ganglia

Terminology. The term "basal ganglia" refers to large regions of the telencephalon located beneath the cerebral cortex. Specifically, a number of structures have been included in the basal ganglia, with its original description referring to all the masses of gray matter buried within the cerebrum, including the *caudate nucelus, putamen, globus pallidus* (also termed *pallidum*), *amygdala*, *claustrum*, and the *thalamus* (Cotman & Angevine, 1981; Klawans, 1973; Nolte, 1988). Even today, there remains some ambiguity as to the exact

structures thought to comprise the basal ganglia; but as our understanding of the structures, functions and connections of these nuclei has developed, so too has the definition of the basal ganglia changed. Nolte (1988) decribes the basal ganglia within a functional framework, referring to those structures whose damage causes extrapyramidal syndromes, which includes the caudate nucleus, putamen, globus pallidus, *subthalamic nucleus*, and *substantia nigra* (Latin for "black substance"). Cotman and Angevine (1981), however, include the amygdala because of its continuous neural connections to other basal ganglia structures.

A multitude of names have been ascribed to different combinations of nuclei within the basal ganglia. For example, the caudate nucleus and putamen together comprise the *striatum*. The combination of the putamen and globus pallidus is termed the *lenticular nucleus*, while combination of caudate, putman and globus pallidus is referred to as the *corpus striatum* (Nolte, 1988). In addition, these names have given rise to another set of terms referring to the afferent and efferent fibers of different nuclei within the basal ganglia. *Striopallidal* fibers, for example, arise from the caudate or putamen and go to globus pallidus. *Corticostriate* fibers travel from the cerebral cortex to the caudate or putamen, *pallidothalamic* fibers go from the globus pallidus to thalamus, and *nigrostriatal* fibers arise from the substantia nigra and go to caudate or putamen.

Particular attention has focused on the nigrostriatal fibers because of their primary role in the pathogenesis of PD. Dysfunction of this pathway is the major factor causing many of the signs and symptoms of PD (Denny-Brown, 1962; Marsden, 1982; Nolte, 1988). A deficiency in striatal dopamine occurs as a consequence of dopaminergic cell loss in the subtantia nigra, which supplies the striatum with dopaminergic afferents via the nigrostriatal pathway. The substantia nigra is a structure located bilaterally between the cerebral peduncles and the tegmentum. The substantia nigra is the largest of the

mesencephalic nuclei and contains large amounts of neuromelanin, giving the nuclei their characteristic dark pigmentation. Two distinguishable zones make up the substantia nigra: a ventral pale zone (*pars reticulata*) and a darkly pigmented zone (*pars compacta*). The neurons of the pars compacta are dopamine rich cells (Carpenter, 1976), and the degree of their pigmentation is proportional to the concentration of dopamine they contain (Côté & Crutcher, 1985).

Connections of the Basal Ganglia. Globally, the principal circuit involving the basal ganglia receives input from widespread areas of the cerebral cortex to the striatum, in a topographical fashion. That is, specific areas of neocortex project to different parts of the striatum; overlap, however, does exist, with no single portion of the striatum receiving exclusive influence from specific cortical areas. The striatum, in turn, projects to the globus pallidus,which then projects to the ventrolateral and ventroanterior (VL/VA) complex of the thalamus. The VL/VA complex projects to the supplementary motor cortex, thereby exerting an influence upon the activity of descending motor pathways (Nolte, 1988).

Further specification of the complex connections of the basal ganglia reveals a number of interrelated systems (Côté & Crutcher, 1985), two of which hold particular importance for understanding the neuropathology of PD. "The first loop . . . runs from the neocortex to the basal ganglia and thalamus and then back to the frontal neocortex; [t]he [other] loop runs from the striatum to the substantia nigra and then back to the striatum." (Côté & Crutcher, 1985, p. 526).

Nigrostriatal fibers originate from both regions (i.e., pars reticulata and pars compacta) of the substantia nigra. However, fibers originating from the pars reticulata are small in number, and are thought to be non-dopaminergic. The pars compacta, in contrast,

contains vast dopaminergic projections to the striatum. Although there is some controversy, most evidence indicates that dopamine exerts an inhibitory influence upon the striatum (Beart, 1984; Côté & Crutcher, 1985; Dray, 1980).

Nigrostriatal fibers project to the VL/VA complex of the thalamus in addition to the striatum. The thalamic nuclei then project back to neocortex, thereby closing a loop that began in neocortex. Early evidence (Allen & Tsukahara, 1974) suggested that the basal ganglia functioned primarily as an integrator of separate and diverse inputs from the cerebral cortex, acting to funnel information, via the ventrolateral thalamus, to the motor cortex. "In particular, the basal ganglia were thought to provide a route whereby influences from the cortical association areas might be transmitted to the motor cortex and thereby participate in the initiation and control of movement." (Alexander, DeLong, & Strick, 1986, p. 358). More recently, suggestions of two distinct basal ganglia-thalamocortical loops were delineated. DeLong and Georgopoulos (1981) and DeLong, et al. (1983) first proposed the concept of "motor" and "complex" loops existing between basal ganglia and frontal cortex.

The "motor" loop, as the name implies, controls the parameters of movement. Diverse cortical influences arising from the supplementary motor area, arcuate premotor area, motor and somatosensory cortex send projections to the putamen. The putamen in turn sends topographically organized projections to the ventrolateral two-thirds of both the internal and external segments of the globus pallidus, and to caudolateral portions of the substantia nigra. The pallidum continues by sending its projections to the ventrolateral nucleus of the thalamus, which projects back to supplementary motor cortex--thereby creating the closed loop (see DeLong, et al., 1983, for review).

A separate "complex" loop is thought to transmit information through basal ganglia to granular frontal association areas thought to be involved in more purely mental

operations (see Figure 1). Alexander, et al. (1986) reappraised this proposal, and found at least two distinct basal ganglia-thalamocortical circuits that selectively influence separate prefrontal areas. The first circuit they termed the dorsolateral prefrontal circuit. Corticostriate projections arising from dorsolateral frontal cortex, the posterior parietal cortex and the arcuate premotor area terminate within the dorsolateral head of the caudate nucleus and throughout a continuous rostrocaudal expanse that extends to the tail of the caudate. Rostral portions of the caudate nucleus in turn project to the dorsomedial globus pallidus and to rostral portions of the substantia nigra. The pallidal segment projects to the ventral anterior nucleus of the thalamus, while the substantia nigra has been shown to project to the dorsomedial nucleus of the thalamus. These in turn project back to dorsolateral prefrontal cortex. While Alexander and colleagues do not attribute any functional characteristics to this circuit, they do state that evidence from lesioning and single-cell recording studies suggest that "this system may participate in processes subserving spatial memory" (Alexander, et al., 1986, p. 371).

The second circuit is termed the lateral orbitofrontal circuit. The ventromedial sector of the caudate nucleus receives projections arising from the lateral orbitofrontal cortex, and the superior and inferior temporal gyri. The caudate then projects to dorsomedial portions of the internal pallidal segment, and to rostromedial substantia nigra. It is the nigral projections that lead to the medial parts of the ventral anterior nuclei and to the dorsomedial nuclei of the thalamus, and in turn project back to the lateral orbitofrontal cortex. Again, no functional characterization of this circuit has been established. Alexander, et al. (1986) mention, however, that bilateral lesions in primates restricted to the lateral orbitofrontal cortex or the portion of caudate projecting to it "result in a perseverative interference with an animal's capacity to make appropriate switches in a behavioral set" (Alexander, et al., 1986, p. 371).

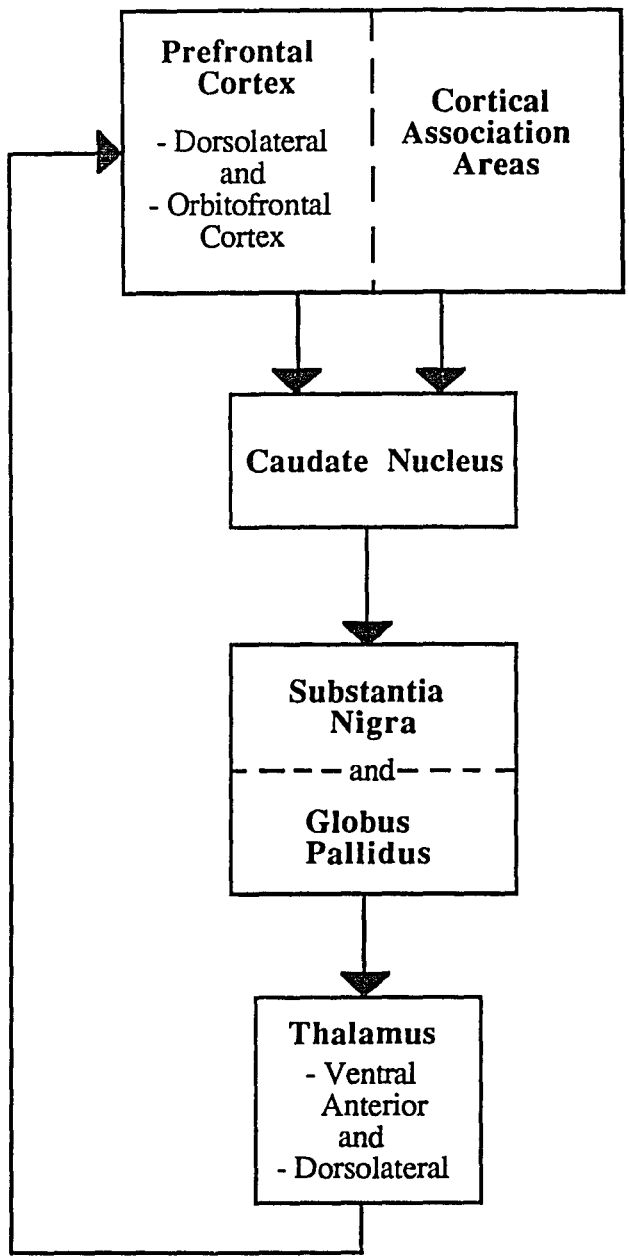


Figure 1. Schematic diagram outlining neuroanatomic sites comprising the "complex" loop circuitry. As noted, widespread regions of cortex project and terminate within the caudate nucleus, which in turn project to both the globus pallidus and substantia nigra. These terminal sites themselves project to thalamic nuclei, which in turn project to prefrontal cortex, thereby closing a loop that began in the cortex.

The Motor Symptoms of Parkinson's Disease

Despite the recent findings of affective, cognitive, and intellectual changes occurring in PD, it was orignially conceptualized as, and remains today, primarily a disorder of movement. James Parkinson (1817) provided the first descriptions, based upon the observations of several patients, sharing similar features in their clinical presentation: an "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace, the senses and intellect being uninjured" (1817/1974, p. 10).

PD patients often present with a tetrad of classic motor signs, including tremor, akinesia (or bradykinesia), rigidity, and changes in postural reflexes (Bradley, 1984; Klawans, 1973). Most visible among these signs appears to be the tremor, seen at rest; characteristically, the hands may demonstrate a "pill-rolling" movement. The resting tremor dissipates once the involved muscle groups are activated, but can quickly reappear--even within the same movement. Rapid oscillations between agonist and antagonist muscles within a given group account for the tremor; movements occur on the average of 3-5 oscillations per second, and most often appear in the distal portions or extremities of the body (Klawans, 1973).

Akinesia literally refers to inability in movements, while bradykinesia refers to a generalized slowing of movement. Akinesia exhibited in PD patients generally presents itself as a continuum of slowed physical movement (Marsden, 1982), with an attending decrease in spontaneous actions (Klawans, 1973), often evident when the PD patient attempts to stand up from a sitting position. Marsden (1983) has attributed bradykinesia to a slowing of motor planning, while Denny-Brown and Yanagisawa (1976) emphasized the

apparent problems in movement initiation; problems in the execution of motor activities have been described as well (Anderson & Horak, 1984).

Two varieties of rigidity have been reported in PD (Klawans, 1973), so termed cogwheel and lead-pipe, because of their characteristics during examination of the large joints of the body. Cogwheel rigidity refers to the sensation of alternating rigidity and relaxation of muscular tension when the patient is tested by the examiner's movement of the limb. That is, it presents as a discontinuous rigidity with sudden reinstatement of opposition within a given movement. Lead-pipe rigidity presents as a consistent resistence of agonist and antagonist muscles throughout a given movement.

Abnormalities in postural reflexes were among the first symptoms described (Parkinson, 1817), and are readily observable in PD patients; in addition, there is an easily disturbed postural equilibrium. PD patients often manifest a stooped posture, while maintaining an adequate ability for locomotion. An interesting feature of PD patients' altered equilibrial abilities is observed when they encounter a retropulsive or propulsive force, causing great difficulty in maintaining balance. Marsden (1982) has explained this difficulty as centering upon a loss of anticipatory postural reflex(es). The patient apparently cannot anticipate a corrective postural action following a retro- or propulsive force before it is required, thereby resulting in an inability to initiate the corrective reflex at the needed moment.

The motor difficulties associated with PD are presumed to arise because of abnormalities within the basal ganglia, resulting from a loss of dopamine produced by the pars compacta of the substantia nigra (Anderson & Horak, 1984; Jellinger, 1986; Klawans, 1973; Marsden, 1982). The loss of dopamine-producing cells within the SN decreases the amount of dopamine available for use by the basal ganglia, causing deprivation of a vast amount of circuitry entering and exiting basal ganglia structures.

The manifestation of tremor and rigidity in PD patients has been attributed to a loss of an inhibitory influence within the basal ganglia, leading to an abnormal outflow of neuronal activity from the globus pallidus to the ventral anterior and ventral lateral nuclei of the thalamus, and finally to the cortex (Côté & Crutcher, 1985). This presumed action is what first prompted surgical intervention back in the 1950's for the alleviation of motor symptoms in PD. Surgical interruption of the basal ganglia outflow, with target sites being either the globus pallidus or the ventral lateral nucleus of the thalamus, decreased the abnormal neuronal activity, thus alleviating tremor and rigidity. Unfortunately, these palliative effects were often short-lived, with tremor and rigidity recurring within 1-3 years following surgery. In addition, surgery often failed to provide any measureable benefit upon patients' disabling bradykinesia or changes in postural reflexes, thus rendering no significant improvements in their daily activities (Côté & Crutcher, 1985).

The Pathology of Parkinson's Disease and Parkinsonism

Variants of Parkinsonism. Parkinsonism refers to a broad group of disorders commonly recognized condition marked by a characteristic set of motor symptoms (Duvoisin, 1984), and is differentiated from the most prevalent subset of parkinsonism known as *idiopathic* Parkinson's disease (i.e., parkinsonism of unknown etiology). A numbers of syndromes exhibit parkinsonian symptoms, have varying degrees of similarity based on neuropathological comparisons, and possess their own classificatory schemes. A partial list of such movement disorders that have symptom overlap with idiopathic PD might include juvenile onset parkinsonism, Shy-Drager Syndrome, Progressive Supranuclear Palsy, Parkinson-dementia complex of Guam, Steele-Richardson-Olszewski Syndrome, Hallervodren-Spatz disease, Corticobasal degeneration, drug-induced parkinsonism, and postencephalitic parkinsonism. Although discussion of each of these

conditions is beyond the scope of this review, discussion of these last two conditions, drug-induced parkinsonism and postencephalitic parkinsonism, will be briefly described.

Postencephalitic Parkinsonism. Individuals who develop Parkinson's disease secondary to an encephalitis are classified as postencephalitic parkinsonian patients under current nomenclature. In 1917, a world-wide epidemic of "sleeping sickness," or *encephalitis lethargica*, broke out, and many of these individuals further developed parkinsonian symptomatology (Duvoisin, 1984). The acute inflammatory process of *encephalitis lethargica* was presumed to be caused by a virus, which Von Economo (1931) stated had a predilection for the mesencephalon and diencephalon (Gibb, 1989). Interestingly, Lewy bodies (discussed below) are not part of the pathological findings (Gibb, 1989) in postencephalitic parkinsonism. As the mortality rate of those individuals exposed to the *encephalitis lethargica* epidemic of 1917 continues to increase, the incidence of postencephalitic parkinsonism is thought to be decreasing (Klawans & Cohen, 1970). With respect to medications, although anticholinergic drugs provide an average of 20 to 25% reduction of symptoms in idopathic Parkinson's disease, their efficacy in postencephalitic Parkinsonism is much greater (Duvoisin, 1984).

Drug-induced Parkinsonism. Administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to humans and other primates induces persistent parkinsonian symptoms; these symptoms also show palliative responses to classical antiparkinsonian drug therapy (see Jenner & Marsden, 1989, for discussion). Approximately one hour following administration of the toxin to primates, animals become increasingly akinetic and exhibit rigidity of the limbs, freezing episodes, postural instabilities, and loss of vocalization and blink reflex. There is, however, a low incidence of tremor and evidence of partial recovery following MPTP administration, unlike idopathic PD, probably reflecting the limited pathological foci of MPTP-induced parkinsonism

(Jenner & Marsden, 1989). The single postmortem study of MPTP in man demonstrated that the toxin destroyed the cells of the pars compacta of the substantia nigra, but not cells of the locus ceruleus (Davis, Williams, Markey, Ebert, Calne, Reichert, & Kopin, 1979). As in postencephalitic parkinsonism, anticholinergic drugs provide a significant reduction of symptoms, and can often completely abolish drug-induced parkinsonism (Duvoisin, 1984).

The discovery of MPTP as a highly selective neurotoxin that targets the substantia nigra for cell death has helped not only to provide an animal model to study PD, but has also contibuted to the evolution of hypotheses regarding the etiology of PD. The identification of a chemical agent producing PD lends support to the claim (Barbeau, 1984) that PD may be an environmentally-based disease, acquired through exposure to unknown neurotoxins that--over a lifetime--destroy neural tissue with great precision and selectivity. This hypothesis is concordant with recent genetic studies which have failed to demonstrate an increased occurrence of PD in monozygotic twins; Ward, Duvoisin, Ince, Nutt, Eldridge, and Calne (1983), for example, found only one of 43 twin pairs studied concordant for PD. However, investigations have also demonstrated that a genetic susceptibility may exist when considering subtypes such as early-onset parkinsonism (Alonso, Otero, D'Regules, & Figueroa, 1986; Barbeau & Poucher, 1982). Given the concordance of tremor-dominant PD in monozygotic twins, it has been suggested that genetic susceptibility is important in this variety of Parkinson's disease (Jankovic & Reches, 1986).

Morphological Changes. Morphological changes in parkinsonism vary according to its etiology. Idiopathic Parkinson's disease comprises the most common form, with other forms, such as parkinsonism arising from cerebrovascular disease, trauma, toxic

substances, tumors, and postencephalitic parkinsonism, causing less than 20 percent of the cases (see Jellinger, 1986, for review). Idiopathic Parkinson's disease (PD) causes damage to brainstem regions, which produces dysfunction of the basal ganglia because of the dopaminergic projections received from the brainstem. Tretiakoff (1919) first discovered the loss of pigmented cells of the substantia nigra, upon postmortem examination of a small sample of PD patients. The lesions he observed resulted from a loss of the melanin-containing, dopamergic cells. Threshold for the development of the mild motor symptoms associated with PD requires a disproportionately high level of destruction, approximately 80% cell loss, within the substantia nigra (Bernheimer, Birkmayer, Hornkiewicz, Jellinger, & Seitelberger, 1973).

Not all the symptoms of PD, however, are exclusively attributable to the dopaminergic cell loss of the nigrostriatal pathway. Losses occur in the noradrenergic neurons of the locus ceruleus, the nucleus basalis of Meynert, the serotonergic neurons of the raphé nuclei, and the dorsal motor nucleus of the vagus (Côté & Crutcher, 1985; Jellinger, 1986). Both the locus ceruleus and the raphé nuclei have widespread projections throughout the brain, including the cerebellum and neocortex. Dopaminergic projections to the limbic system and the frontal neocortex also exist. Thus, because of the widespread morphological changes in PD, it remains difficult to be certain of the specific loci and synaptic mechanisms that account for all of the parkinsonian symptoms (Côté & Crutcher, 1985).

Lewy Bodies. Cellular inclusions, termed Lewy bodies, are found in the majority of PD patients, although they are not exclusively pathognomonic of PD (Forno, 1986), just as neurofibrillary tangles are not exclusively found in Alzheimer's disease (AD). Nonetheless, Lewy bodies are highly characteristic of PD, with the greatest concentrations found in the substantia nigra and locus ceruleus (Duffy & Tennyson, 1965; Greenfield &

Bosanquest, 1953) and not in the dorsal motor nucleus of vagus or substantia inominata, as Lewy himself first thought (Lewy, 1912,1923). Speculation regarding the predominance of Lewy bodies in the substantia nigra and locus ceruleus centers around the role of neuromelanin promoting or inducing the formation of these inclusion bodies (Forno, 1986).

Lewy (1912) described these cellular inclusions, with the aid of the Mann stain (a trichrome stain), as red spherical or elongated staining structures within a blue halo of cytoplasm. The electron dense core contains predominantly protein-rich bundles of fragmented neurofilaments. It is a distinctive neuronal inclusion that appears wherever there is an excessive loss of neurons; thus, it is always found in the substantia nigra upon autopsy in PD patients. Lewy bodies are therefore found in every case of clinically diagnosed PD (except in a few cases with the pathology of an alternative disorder such as postencephalitic parkinsonism--see above), thereby enabling the neuropathologist to utilize the presence and distribution of Lewy bodies to diagnose PD. "PD and Lewy body-PD are, therefore, . . . synonymous terms, bearing in mind that a number of patients clinically labeled as PD have alternative clinical and pathological diagnoses." (Gibb, 1989).

Biochemical Changes. PD was the first documented example of a disease of the brain consistently correlated with a deficiency in a specific neurotransmitter (Hornykiewicz, 1966). In PD, dopamine concentrations are markedly reduced in all structures belonging to the nigrostriatal system, including the pars compacta of the substantia nigra, and the corpus striatum (Bernheimer, et al., 1973; Hornykiewicz, 1973). Also, dopamine-synthesizing enzymes such as tyrosine hydroxylase and DOPA decarboxylase, as well as metabolites like homovanillic acid, dihydroxyphenylacetic acid, and 3-methoxytyramine are all reduced in PD (Hornykiewicz & Kish, 1986).

Dopaminergic System. The striatum contains more than 80% of the total brain dopamine (Hornykiewicz, 1966). Dopamine, as mentioned previously, is presumed to have an inhibitory effect within the basal ganglia (Côté & Crutcher, 1985; Dray, 1980), keeping in balance the presumed excitatory effect of striatal acetylcholine. With dopaminergic reduction in PD, and therefore a reduction of inhibitory influence, a greater abundance of excitatory acetylcholine could lead to disinhibition and abnormal discharge of the cells in the struatum and in the globus pallidus--the result being exemplified in increased muscle tonus (i.e., rigidity) (Klawans, 1973).

Noradrenergic System. Concentrations of norepinephrine are reduced in varying degrees in many brain regions in PD, including the striatum, substantia nigra, hypothalamus, cortex, cerebellum, and spinal cord. This widespread decrease in norepinephrine is presumably a result of the characteristic cell loss in the locus ceruleus known to occur in PD, as well as changes in the lateral tegmentum (Hornykiewicz & Kish, 1986). Jellinger (1986), for example, reports a loss of the pigmented neurons of the locus ceruleus ranging from 50 to 80%.

Serotonergic System. Moderate decreases of serotonin have also been found in many brain regions and the spinal cord in PD patients, suggesting that there may exist a moderate loss of the raphé nuclei cells giving rise to ascending and descending serotonergic fiber tracts (Hornykiewicz & Kish, 1986).

Cholinergic System. Hornykiewicz and Kish (1986) state that several cortical regions innervated by the cholinergic cell groups located in the nucleus basalis of Meynert and the medial septal area of the basal forebrain have shown significant reductions in choline acetyltransferase (CAT) activity (a cholinergic neuron marker enzyme). They further state that the CAT reductions in cortical and hippocampal areas are most likely related to cell losses in the nucleus basalis/medial septal region regularly seen in idiopathic

PD. Tagliavini, Pilleri, Bouras, and Constantinidis (1984) conducted a histopathological study of 6 patients with idiopathic PD and demonstrated neuronal loss in the nucleus basalis ranging from 30 to 68% (mean 46%), with numerous surviving cells containing Lewy inclusion bodies. They concluded that the damage to the nucleus basalis of Meynert in PD is less severe than that generally observed in AD. Further, despite the apparent similarity with known nucleus basalis cell loss in AD, Nakano and Hirano (1984) demonstrated that in the majority of cases the cell loss exhibited in PD was not associated with other common pathologic changes in AD (such as senile plaques or neurofibrillary tangles). Whitehouse (1986), however, suggests that if AD and PD patients are matched on dementia severity, the characteristic neuropathologic patterns found in AD and PD may be more similar than originally claimed (cf. Mayeux, Stern, Rosen, & Benson, 1983). Finally, equivocal results have been obtained in studies of striatal levels of CAT, showing either normal or reduced activity (see Hornykiewicz & Kish, 1986, for discussion).

Peptidergic System. Several peptidergic systems are affected in PD, as indicated by the reduction of substance P, metenkephalin, and cholecystokinin-8 in the striatum, external globus pallidus, and substantia nigra, while somatostatin is affected in cortical areas. However, overall degeneration of peptidergic neurons appears to be limited to a small population in the parkinsonian brain (see Jellinger, 1986, for discussion).

GABAnergic System. In PD patients, Gamma-aminobutyric acid (GABA) concentrations have been found to be elevated in the striatum, whereas the activity of the GABA neuron marker enzyme, glutamic acid decarboxylase (GAD), shows reductions throughout the basal ganglia (Hornykiewicz & Kish, 1986). Kish, et al. (1986) consider that the increased striatal GABA levels in PD patients may be related to the loss of nigrostriatal dopamine neurons which have been proposed to form synapses with GABAnergic neurons in the striatum.

Pharmacologic Treatment of Parkinson's Disease. Treatment of PD dates back to the 1860's, when it was discovered that certain plant derivatives such as scoplamine, hyoscyamine, and atropine had beneficial effects on reducing tremors observed in many patients. Ordenstein in 1867, and Charcot in 1869, first mentioned the use of such extracts, which continued unabated for more than 75 years. Later it was surmised that the effects of these medications were due to their anticholinergic activity. This led to the production of additional synthetic anticholinergic agents used in the pharmacologic treatment of PD (see Duvoisin, 1984; Klawans, 1973, for discussion).

In the 1960's, however, the pathologic changes and subsequent biochemical deficiencies in brain dopamine were discovered (Hornykiewicz, 1966), and targeted for replacement therapy.

> "In fundamental terms, the drugs currently available for the treatment of parkinsonism act either by replenishing brain dopamine, mimicking the action of dopamine, or by modifying the function of the brain in such a way as to compensate in some degree for the deficiency of brain dopamine" (Duvoisin, 1984, p. 60).

Logically, dopamine itself was initially attempted for replacement therapy with no success, because of its inability to cross the blood-brain barrier (Klawans, 1973). Birkmayer and Hornykiewicz (1976) demonstrated, however, that a precursor to dopamine, L-3,4-dihydroxyphenylalanine (L-DOPA), was effective. These investigators injected L-DOPA intravenously and observed a remarkable, but brief, remission in their patients' symptoms (see Côté & Crutcher, 1985, for discussion). Once ingested or injected, L-DOPA is presumably synthesized into dopamine (Dray, 1980) for action within the striatum.

The exact nature of L-DOPA's action remains unclear, however. Côté and Crutcher (1985) emphasize that approximately 90% of the dopamine-producing neurons in the striatum have degenerated in patients with PD. Apparently the few remaining intact

dopaminergic neurons must be able to compensate by carrying out the entire function of the nigrostriatal system once the rate-limiting enzyme for the synthesis of dopamine (tyrosine hydoxylase) is bypassed with the large amounts of L-DOPA. Another possibility is that DOPA decarboxylase, which is not specific to dopaminergic neurons alone and which is abundant throughout the brain, can synthesize dopamine from L-DOPA in nondopaminergic neurons (e.g., serotonergic neurons, and possibly glial cells). This newly formed dopamine might then be released or secreted in sufficient amounts to act on target neurons (see Côté & Crutcher, 1985, for discussion).

Current pharmacologic therapy for PD includes a plethora of drugs, providing alternative means to increasing dopamine action within the striatum, or providing ancillary action to the primary use of L-DOPA. Carbidopa, for example, when used in combination with L-DOPA, inhibits the conversion of L-DOPA at peripheral synapses, thereby increasing the amount of L-DOPA synthesized to dopamine within the central nervous system (Klawans, 1973); this is the chemical composition of the most widely used antiparkinson drug *Sinemet*. Dopamine receptor agonists (e.g., bromocryptine) have also been used, and imitate the action of dopamine. Deprenyl currently enjoys much attention, and its action presumably serves to inhibit the enzyme monoamine oxidase (MAO) only in the brain and does not act in the heart or on the adrenal gland, as do other MAO inhibitors (Duvoisin, 1984). Traditionally, MAO inhibitors are strictly contraindicated when current medication regimens include L-DOPA, because of their potential for accumulating dopamine, epinephrine and norepinephrine rapidly to abnormal levels in many organ systems; MAO inhibitors block the breakdown of dopamine at the synapse, thereby acculumating excessive dopamine levels. Deprenyl's action, however, is presumed to occur within the brain only, enhancing the desired effects of L-DOPA without carrying the risk of provoking hypertension and rapid heart rates (Duvoisin, 1984).

Recently, studies have shown that the effects of MPTP can be fully prevented in experimental animals by inhibiting monoamine oxidase B (Heikkila, Manzino, Duvoisin, & Cabbat, 1984; Langston, Irwin, Langston, & Forno, 1984). Given these findings, Tetrud and Langston (1989) conducted a double-blind, placebo-controlled study in patients with early untreated Parkinson's disease to determine whether deprenyl would delay the need for L-DOPA therapy by slowing the progression of the disease. Results demonstrated that disease progression (as monitored by five different assessment scales) was slowed by 40 to 83% per year in the deprenyl group compared to placebo. They concluded that early deprenyl therapy delays the requirement for antiparkinsonian medication, possibly by slowing the progression of the disease (Tetrud & Langston, 1989).

Medication Effects on Cognitive Functioning. Two basic classes of antiparkinson drugs have been investigated with respect to alterations in cognitive functioning: anticholinergics and dopaminergic agents. Beginning with studies of normal subjects, Drachman and Leavitt (1974) demonstrated that the administration of scopolamine produced significant decreases in free recall of words and supra-span digits, and poorer performance on WAIS subtests; no deleterious effects were observed with digit span performance, however. Drachman (1977) later investigated more specifically the role anticholinergics have in memory functioning. Administration of scopolamine, again, produced poor memory performance. However, administration of physostigmine--which is an anticholinesterase that acts to inhibit the breakdown of acetylcholine (ACh), thereby leaving more ACh available at the synapse--reversed the deficits. From these results, Drachman concluded that the cholinergic system has a specific relationship to memory. Similar effects of anticholinergic medications on memory have been observed in PD patients; impairment in delayed recall of items persists despite unimpaired immediate

memory, such as digit span (Sadeh, Braham, & Modan, 1982; Syndulko, Gilden, Hansch, Potvin, Tourtellotte, & Potvin, 1981).

Palliative effects with regard to cognitive functioning have been noted in studies investigating L-DOPA medications. Beardsley and Puletti (1971), for example, found significant improvement in the intellectual functioning of PD patients following six months of L-DOPA treatment, whereas PD patients treated with anticholinergic drug therapy showed slight decreases in intellectual functioning after the six month period. Subsequent studies found similar improvements initially in L-DOPA treated PD patients, but also noted a return to pre-treatment levels of intellectual functioning following longer-term treatment intervals (Loranger, Goodell, Lee, & McDowell, 1972; Riklin, Wheliham, & Cullinan, 1976).

Autonomic Changes. PD has been shown to cause disturbances in autonomic functioning since it was first described by Parkinson (1817). This finding may not be surprising when considering that pathological changes in PD include disturbed metabolism of catecholamines, and lesions in hypothalamic and locus ceruleus structures, all of which are involved in central autonomic regulation (Ludin, Steiger, & Ludin, 1987). Autonomic dysfunction is not infrequent, and complaints concerning salivation, micturition, gastrointestinal function, cardiovascular reflexes, seborrhea, breathing and sleep have all been reported by PD patients (Korczyn, 1989).

Cardiovascular Reflexes. Studies investigating cardiovascular reflexes in PD have not been entirely consistent with regard to the normality of resting blood pressure (BP) and heart rate (HR), and of the BP and HR responses to various bodily manipulations (Pollak, Mallaret, Gaio, Hommel, & Perret, 1986). Antiparkinsonian drugs may also play a role in autonomic alterations. In a recent study Ludin, et al. (1987) investigated cardiovascular

reflex function only in patients diagnosed with idiopathic PD. Resting BP was reported to be significantly decreased in patients taking dopaminergic agents, whereas it was normal in those patients who received only levodopa and anticholinergics. Resting HR and resting beat-to-beat variation were normal in the patients, as was the BP response to standing and the postural HR response. No pathological response to the Valsalva maneuver was found. Conversely, HR variation evoked by deep breathing as well as the BP and HR response to sustained isometric exercise were found to be significantly diminished in PD patients. Ludin, et al. (1987) concluded that disturbances in cardiovascular control reflected central nervous system dysfunction, whereas the corresponding peripheral pathways appear normal.

Breathing. Respiratory complications, also, are not infrequent symptoms in PD. This finding is underscored when one considers that aspiration pneumonia is among the most common causes of death in PD patients (Hoehn & Yahr, 1967). Tachypnea (or rapid beathing) is a common respiratory abnormality, and may be due to stiffness of the chest wall caused by increased muscular rigidity, or by central factors affecting the respiratory rhythm generator within the brain stem (Gardner, Langdon, & Parkes, 1986).

Sleep Apnea. Discussion of breathing patterns in PD should include mention of sleep disturbances. For example, sleep apnea as well as shorter periods of sleep have been reported in both idiopathic and postencephalitic parkinsonism (Efthimiou, Ellis, Hardie, & Stern, 1986; Goetz, Wilson, Tanner, & Garron, 1986). Further, Efthimiou, et al. found that sleep apneas were usually of an obstructive/mixed type, although central apneas were also recorded in both patients groups, suggesting that the pathological process may affect the integrity of brainstem respiratory centers. Efthimiou, et al. speculate that sleep breathing abnormalities may contribute to the predominance of deaths in PD occurring at night.

Affective Changes in Parkinson's Disease.

Although Parkinson (1817) contended that the "senses and intellect remain uninjured," he did observe that his patients displayed dysphoric moods, and research has demonstrated that clinically significant depression frequently occurs in PD. The prevalence of psychological depression in patients with PD has been estimated to range from 39% (Mayeux, Stern, Côté, & Williams, 1984) to 90% (Mindham, 1970).

The etiology of depression in PD, however, remains poorly understood. Whether depression in PD is an integral part of the disease process itself or is primarily a situational reaction to the increased disability is not established (Bieliauskas, Klawans, & Glantz, 1986). It has been recognized that, in some cases, depressive symptoms can precede the occurrence of parkinsonian motor signs (Celesia & Wanamaker, 1972). Mayeux, Williams, Stern, and Côté (1984) estimate this to occur in 15 to 25% of patients. Fibiger (1984) argues that such observations implicate a neurobiologic substrate to depression in PD, and suggests that the degenerating mesolimbic and mesocortical projections in PD, and resultant dopamine depletion, are related to the affective disturbances. Consistent with such hypotheses are recent findings of medication-related mood changes, such as increases in depression and anxiety during the "off" phase in PD patients who experience "on-off" phenomena in response to their L-DOPA pharmacotherapy (Girotti, et al., 1986), as well as increased depressive affect during the temporary immobility (or "freezing") experienced by PD patients who exhibit typical "end-of-dose-deterioration" (Cantello, Gilli, Riccio, & Bergamasco, 1986). It should be noted, also, that high doses of dopaminergic medications (such as L-DOPA) can cause hallucinatory experiences, and that such symptoms are, in fact, utilized as diagnostic indications of dopamine overdose (Klawans, 1973). In addition, investigators have pointed to altered serotonin metabolism (Mayeux,

Stern, Côté, & Williams, 1984), suggesting a subgroup of patients with PD who are predisposed to depression; another finding showed that CSF 5-hydroxyindoleacetic acid (5-HIAA) levels were lowest in those PD patients with major depression, and related to psychomotor retardation and loss of self-esteem (Mayeux, Stern, Williams Côté, Frantz, & Dyrenfurth, 1986).

Despite these converging findings of potential neurobiologic contributions to depression in PD, there remains a lack of consensus concerning clinical and cognitive correlates. There appears to be little relationship between depression and the severity of PD as formally measured or assessed by stage (Bieuliaskas, et al., 1986), "or any other factor including the patient's sex, treatment, or duration of illness" (Mayeux, Stern, Williams, Sano, & Côté, 1986, p. 451). Bieuliaskas and Glantz (1989) point out that depression, thus, does not appear to increase as the disease progresses, as might be expected if both shared the same substrate. Recently, however, some investigators have reported severity of depression to be greater in younger PD patients with fewer parkinsonian signs (Santamaria, Tolosa, & Valles, 1986), though others find depression to be positively related to motor symptom severity and unrelated to age of onset (Gotham, Brown, & Marsden, 1986; Swanda & Kaszniak, 1984). Yet in other recent studies, depression was not related to severity of neurological disability (Hietanen & Teravainen, 1986), or was related to rigidity but not tremor (Ransmayr, et al., 1986).

Similar discrepancies exist in studies correlating depression with cognitive measures. For example, although it has been reported that depression is unrelated to standard psychometric measures of memory functioning (Hietanen & Teravainen, 1986; Oyebode, Barker, Blessed, Dick, & Britton, 1986; Taylor, Saint-Cyr, & Lang, 1986), some investigators do report a relationship between depression and performance on

experimental memory (Swanda & Kaszniak, 1984) or verbal fluency tasks (Oyebode, et al., 1986).

Much of the contradiction in the results of published studies of depression correlates in PD appears due to marked methological variance between investigations. Sample sizes, measures of the presence and severity of depression, indices of neurologic signs, and choice of cognitive measures all vary considerably. Particularly problematic is the exclusive reliance upon self-report measures of depression in some studies (e.g., Hietanen & Teravainen, 1986; Swanda & Kaszniak, 1984). Given evidence for "executive function" deficits (Taylor, et al., 1986) among nondemented PD patients, interpreted as reflecting damage to connections between the basal ganglia and limbic and frontal lobes (Lees & Smith, 1983), as well as more general memory and intellectual impairment in demented PD patients, the reliability of depressive symptom self-report in PD must be questioned (c.f., Kaszniak, Sadeh, & Stern, 1985). In studies of PD, the application of reliable and valid interview and observation rating scales (cf., Gallagher, 1986) would be preferable, as has been done by Mayeux, et al. (1986).

Indeed, for non-PD patient groups, depression has been found to be related to deficit on a wide variety of cognitive tasks. In reviewing studies concerning cognitive functioning in depression, Weingartner (1986) concludes that depression impairs "effort-demanding" cognitive processes that are "substantially modulated by brain systems that are extrinsic to those directly involved in the storage and maintenance of memories" (p. 224). Weingartner suggests that this extrinsic system is involved in the regulation of arousal and activation, in which the noradrenergic-dopaminergic system probably plays an important role. He further argues that, in contrast, the types of cognitive processes that are involved in some "automatic" operations, particularly those involved the storage and retrieval of knowledge, are dependent upon neocortical structures, and are not impaired by depression.

These latter cognitive processes are impaired in dementia (cf. Heindel, Salmon, Shults, Walicke, & Butters, 1989; Kaszniak, 1986; Salmon, Shimamura, Butters, & Smith, 1988).

Cognitive Changes in Parkinson's Disease.

Intellectual Impairments. Cognitive changes are commonly reported in studies of patients with PD. "The majority of parkinsonians do not become demented, but subtle intellectual deficits can be detected in many well functioning patients if appropriate tests are used" (Stern & Mayeux, 1986, p. 405). However, before focusing upon specific cognitive domains, a brief discussion of dementia in PD is warranted.

Dementia. Dementia, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R), requires impairment in memory and at least one other cognitive function that is sufficient to interfere with usual social or occupational activities (American Psychiatric Association, 1987). Estimates of the prevalence of dementia in PD vary greatly, from as little as 2% to as high as 93% (Lees, 1985; Lieberman, Dziatolowski, Kupersmith, Serby, Goodgold, Korein, & Goldstein, 1983; Loranger, Goodell, McDowell, Lee, & Sweet, 1972; Martin, Loewenson, Resch, & Baker, 1973; Martilla, & Rinne, 1976; Mindham, Ahmed, & Clough, 1982; ; Mortimer, Christiensen, & Webster, 1985; Pirozzolo, Hansch, Mortimer, Webster, & Kuskowski, 1982). Various investigators (Growdon & Corkin, 1986; Pirozzolo, et al., 1989) argue that these estimates have limited value because the definition of dementia, as well as the methods of assessing it, have varied substantially from study to study. They state that the problem is further compounded because most investigators fail to make a distinction between dementia and isolated specific cognitive deficits. The possibility exists that the neuropathology of PD, when restricted to the substantia nigral-basal ganglia system, is associated with deficits in a restricted domain

of cognition, whereas other aspects of cognition are preserved; in PD with multifocal pathology extending beyond the nigrostriatal system to other subcortical and cortical structures, behavioral deficits may involve multiple cognitive domains (see Growdon & Corkin, 1986, for discussion). However, autopsy cases have been reported of PD patients with progressive dementias showing neuropathology limited to the substatnia nigra (Oyanagi, Nakashima, Ikuta, & Homma, 1986). Despite the methodologic problems mentioned above, it has been estimated that 20-30% of PD patients have cognitive impairments severe enough to cause pronounced difficulties in their lives (Dakof & Mendelsohn, 1986; Lees, 1985; Mayeux & Stern, 1983). Dakof and Mendelsohn (1986), however, state that many more, perhaps the majority of patients, report some reduction in their mental capacities (cf. Pirozzolo, et al., 1982).

The neuropathological and neurochemical bases of intellectual impairment in PD are unclear (Pirozzolo,et al., 1989). Some investigators have reported that demented patients with idiopathic PD have cortical lesions indistinguishable from those of AD patients (Boller, et al., 1980; Hakim & Mathieson, 1979). Variations in subcortical and cortical lesions may explain some of the clinical similarities and differences between the dementias of PD and AD; degeneration of the nucleus basalis of Meynert and locus coeruleus, for example, are common to both disorders (see Growdon & Corkin, 1986). However, more recent studies (Ball, 1984; Chui, et al., 1986; Mann & Yates, 1983) have found little evidence for a systematic association between AD and dementia in PD (see Pirozzolo, et al., 1989).

Growdon and Corkin (1986) summarize three patterns of cortical change found in studies of PD patients with dementia: (1) plentiful neuritic plaques and neurofibrillary tangles similar to those commonly seen in AD, (2) an absence of neuritic plaques or neurofibrillary tangles in numbers beyond those expected by age alone, and (3) Lewy

bodies scattered throughout the cortex. All three patterns are associated with dementia but prospective studies are needed to relate neuropathologic analyses to specific cognitive impairments or severity of dementia (see Growdon & Corkin, 1986, for discussion).

Neurochemical changes also demonstrate similarities and differences between AD and PD with dementia. Both diseases show decreased acetylcholine, somatostatin, norepinephrine, and serotonin. Dopamine reductions in AD, however, are smaller and more variable than in PD (see Growdon & Corkin, 1986). Agid, Ruberg, Dubois, and Javoy-Agid (1984) posit that reductions of choline acetyltransferase activity in nondemented PD patients indicate that the degeneration of subcortical cholinergic neurons precedes the intellectual decline commonly associated with decreased cholinergic activity. Denervation hyperactivity of the remaining cholinergic neurons is proposed to maintain normal intellectual functioning at this stage, but will no longer be able to do so once neurons are unable to adequately compensate for neuronal loss (see Pirozzolo, et al., 1989, for discussion).

Rather than a single syndrome, and underlying neuropathology, characterizing the dementia of PD, one or more specific intellectual disorders appears likely, resulting from different lesions (Pirozzolo, et al., 1989). Thus, "one might expect to see correlations between specific neurotransmitter deficiences and particular cognitive disorders. This issue hopefully will be settled by the clinicopathological investigations of well-studied patients currently in progress" (Pirozzolo, et al., 1989, p. 432).

Subtypes of PD Based on Patterns of Intellectual Impairments in PD. Dakof and Mendelsohn (1986) call attention to the possibility of subtyping parkinsonism by the extent or patterning of cognitive deficits, and discuss such typologies based upon research. The first was derived from a study conducted by Lieberman, et al. (1979), who found that the majority of PD patients with clear evidence of dementia were significantly older at the time

of study and at the time of disease onset than nondemented PD patients. Lieberman and colleagues suggested that two types of Parkinson's disease are suggested by these findings, one an exclusively motor disorder occurring predominantly in young patients and the second a motor and cognitive disorder occurring in older patients. Other studies have both supported (Martilla & Rinne, 1976; Mayeux, Stern, Rosen, & Leventhal, 1981; Rondot, de Recondo, Coignet, & Ziegler, 1984) and refuted (Globus, Mildworf, & Melamed, 1985; Loranger, et al., 1972) this conclusion.

A second possibility was delineated by Mortimer, Pirozzolo, Hansch, & Webster (1982). They reported that bradykinesia was inversely correlated with psychomotor speed, visuospatial reasoning, and spatial orientation memory. By contrast, resting tremor was positively correlated with performance on a spatial orientation memory test. Rigidity, however, was independent of any of the cognitive measures. Based upon these findings, two forms of PD were suggested: (1) a bradykinetic form with significant impairment of visuospatial reasoning, and (2) a tremornergic form with intact visuospatial function. More recent findings from the same investigators (Mortimer, Jun, Kuskowski, & Webster, 1988) demonstrated that patients with and without visuospatial and memory impairment have similarly severe motor impairment, in apparent conflict with their previous research. Pirozzolo, et al. (1989) state, however, that a more detailed examination of the Mortimer, et al. (1988) data reveals that the negative association of visuospatial function with bradykinesia and the positive association with tremor are preserved within the individual subgroups, including the patients with no cognitive deficits (p. 432). They add that the apparent dilemma raised by these findings might be explained by a relatively weak association between dopaminergic function and visuospatial reasoning in conjunction with a memory disorder which is independent of the dopaminergic lesion.

Again, further data, including prospective studies, are needed to establish the validity of such proposals. "It is reasonable to believe that the cases presently grouped together under the diagnostic category idiopathic Parkinson's disease may represent not a single disease process but rather a family of related neuropathological conditions" (Dakof & Mendelsohn, 1986, p. 382).

Language Function. Few investigators have published studies specifically related to language or communication deficits in PD. Direnfeld, Albert, Volicer, Langlais, Marquis, and Kaplan (1984), for example, compared language, visuospatial, and memory functions in PD and AD patients, and normal control subjects. Language tasks included the *Boston Naming Test* (Kaplan, Goodglass, & Weintraub, 1983) and a sample of written descriptive discourse, and were used to derive a language score. When compared to scores on memory and visuospatial tasks, results showed no significant differences between the PD patients and controls. Girotti, Caltagirone, Masullo, & Miceli (1980) reported no significant differences between PD patients and normal control subjects on tasks of verbal fluency, phrase construction, and verbal memory. Hines and Volpe (1985) also found no differences between PD patients and normal control subjects in access to semantic memory, but concluded that cognitive effects in PD do fall most heavily on tasks that require effortful attention and processing. This suggests that certain language tasks may be more vulnerable to the effects of PD, similar to the hypotheses of Weingartner (1986) on the effects of effort-demanding tasks in depression.

In a broader investigation of language abilities in PD, Matison, Mayeux, Rosen, and Fahn (1982) administered the *Boston Naming Test* (Kaplan, Goodglass, & Weintraub, 1983), the Vocabulary subtest of the *Wechsler Adult Intelligence Scale* (Wechsler, 1958), verbal fluency tests, and sentence repetition. Results demonstrated that

PD patients' confrontation naming performance, as well as category naming and a sentence repetition task were significantly lower than normal control subjects, despite normal WAIS Vocubulary subtest performance. They concluded that "a type of anomia may occur in Parkinson's disease which shares the clinical characteristics of the 'tip-of-the-tongue' phenomenon and 'word production anomia' seen in some aphasics" (p. 567). In addition, post-mortem case studies have reported on PD patients who exhibited prominent aphasia during the course of the disease, and whose brains showed morphological changes consistent with PD pathology, but not AD pathology (Chui, Mortimer, Slager, Zarow, Bondareff, & Webster, 1986; Oyanagi, Nakashima, Ikuta, & Homma, 1986).

Many investigations of language functioning in PD patients fail to sample a broad range of abilities with comprehensive language evaluations, and are thus limited in their generalizability to other language-mediated tasks. The application of comprehensive evaluations in future studies investigating language function in PD would be preferable, given the apparent specificity of deficits within other cognitive domains.

Visual-Spatial Function. Considerable controversy exists over the question of whether PD causes primary impairment in visuospatial function. Passafiume, Boller, and Keefe (1986) conclude that available data "strongly suggest that visuospatial impairment is universally present in patients with Parkinson's disease" (p. 379), whereas Brown and Marsden (1986) state that neither a review of the literature, nor the results of their own research, give support to the idea of a generalized visuospatial deficit in Parkinson's disease. Most investigators agree, however, that visuospatial function is not a unitary phenomenon, and includes concepts of spatial perception and thought, space exploration, personal space cognition, topographical memory, and constructional ability (DeRenzi, 1980). There also exist alternative classifications of visuospatial function, such as (1) the

appreciation of the relative positions of stimulus-objects in space, (2) the integration of those objects into a coherent spatial framework, and (3) the execution of mental operations involving spatial concepts (Boller, Passafiume, Rogers, Morrow, & Kim, 1982) (see Brown & Marsden, 1986, for review).

Beginning with animal studies, for example, rodents with caudate lesions have demonstrated deficits on maze-solving tasks (Thompson, 1974); these results were interpreted as reflecting the animal's inability to monitor its spatial orientation relative to its starting position. Also, Caan and Stein (1979) demonstrated, after unilateral cooling of the globus pallidus, that monkeys seem to have "spatial" difficulty in locating auditory stimuli and tracking stimuli in the field contralateral to the lesion (see Passafiume, et al., 1986, for discussion). However, to the extent that such tasks (i.e., maze-solving and tracking) involve procedural learning, which may be impaired in patients with striatal damage (Butters, Wolfe, Martone, Granhom, & Cermak, 1985; Saint-Cyr, et al., 1988), the interpretability of these studies as demonstrating visuospatial deficits *per se* becomes clouded.

Brown and Marsden (1986) point out that consistent findings of lowered performance IQ scores in comparison to verbal IQ scores on such tests as the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1958) have been interpreted as evidence for a spatial deficit in PD. Loranger, et al. (1972) found a verbal-performance split of more than 20 points in nearly 60% of PD patients, compared with lowered percentage splits of normal controls (2%) and depressed individuals (20%). Loranger, et al. and others (Meier & Martin, 1970) have concluded that these results are indicative of a primary cognitive deficit linked to visuospatial dysfunction. Brown and Marsden, however, contend that a more parsimonious explanation might be that deficits reflect impairments in motor speed and manual dexterity; they further state that this issue can only be resolved with experiments

designed to separate and analyze individually the different functional components of such tasks.

Early studies designed to specifically examine visuospatial function in PD utilized a rod and frame apparatus (Proctor, Riklan, Cooper, & Teuber, 1964; Teuber & Proctor, 1964). The procedures required subjects to adjust a line to a vertical position when they were (1) in an upright position, and (2) when blindfolded and tilted in a chair; they were also required to adjust themselves to an upright position while blindfolded and tilted. PD patients had no difficulty with the first condition (i.e., adjusting a line to vertical), but were significantly impaired in adjusting the line once tilted, and in uprighting themselves.

Bowen, Hoehn, and Yahr (1972; Bowen, 1976) utilized other visuospatial tasks with PD patients. Bowen et al. (1972) first used a route walking task, in which nine 'spots' were laid out on the floor in a 3x3 grid, and subjects were given a paper map with the same floor pattern represented on it. On the map a path was drawn, passing through a number of the dots. Subjects were instructed to use the map to guide them while walking on the grid, following the same path outlined on the map held in their hands. "The crucial instruction was that the subject was not allowed to turn the map around, so that on some occasions the subject would have to turn his body in the opposite direction to that represented literally on the map." (Brown & Marsden, 1986, p. 989). Results demonstrated PD patients to have greater confusion with right and left turns, especially on those occasions when the subject was required to extrapolate the body image to interpret the map correctly (see Brown & Marsden, 1986, for discussion). Bowen (1976) later showed subjects a dorsal and ventral representation of a human figure and required them to point out on their own bodies the body parts and locations indicated on the representation. Again, PD patients demonstrated impairment, particularly on those items that required a mental rotation.

Brown and Marsden (1986) contend that such results are not indicative of a spatial deficit, but instead reflect an inability in *shifting* mental perspectives from one orientation to another, which has been demonstrated to be impaired in PD patients on tests of both cognitive and motor abilities (Cools, et al., 1984; Lees & Smith, 1983).

> The ability to shift a cognitive or motor strategy or 'set', is not in itself a spatial function. However, an impairment in 'shifting ability' may manifest itself in poor performance on a spatial task where shifting is required. Such poor performance is not a spatial deficit . . . In no study is there unequivocal evidence for a spatial deficit in Parkinson's disease." (Brown & Marsden, 1986, p. 989).

It should be noted such "visuospatial" deficits have also been shown by patients with structural damage to the frontal lobes. For example, Teuber and Mishkin (1954) showed frontal lesion patients to be poor at the rod and frame test when in the tilted, but not in the upright, position. Similarly, Semmes, Weinstein, Glent, and Teuber (1963) showed frontal patients to be poor at a personal spatial orientation task involving a dorsal and ventral human figure representation.

Because of the complexity involved in many of the tasks used to assess visuospatial function in PD, it has been difficult to delineate the specific influence of visuospatial factors from other cognitive, praxic, and memory factors in completing such tasks; DeRenzi, Faglioni, & Scotti (1971) suggests that a more definite answer might be obtained by employing elementary tasks, which tap the basic mechanisms underlying spatial abilities (see Brown & Marsden, 1986, for discussion). Della Sala, DiLorenzo, Giordana, and Spinnler (1986), for example, found no significant differences between PD patients and normal controls on tests requiring prediction of line trajectories from line segments. In a study conducted by Mortimer, Christensen, Kuskowski, Eisenberg, and Webster (1982), the authors concluded that "visuo-spatial impairment in Parkinson's disease may be a function of deficiencies in spatial memory or the manipulation of spatial information, rather than defects in simple visual discrimination" (p. 4). Brown and Marsden (1986) tested

right-left discrimination and the manipulation of those concepts in different spatial perspectives, and found that Parkinson's disease patients did not differ from normal subjects in the spatial components of the task. Similar findings were also reported by Taylor, Saint-Cyr, and Lang (1986). It should be noted that Brown and Marsden paid careful attention to matching subjects on variables such as age, sex, education, affect/arousal state, and intelligence, in addition to describing their particular sample of PD patients with regard to duration of illness, severity of motor symptoms, and medications. Such preliminary matching is vital for future studies in order to limit potential confounding factors in the interpretation of data.

Memory Function. Nearly 100 years ago William James discussed memory as being the "knowledge of a former state of mind after it has already once dropped from consciousness . . ." (James, 1890). Little has changed in the basic formulation of learning and memory: "Learning is the process of acquiring new information, while memory refers to the persistence of learning in a state that can be revealed at a later point in time." (Squire, 1987, p. 3). However, current conceptualizations of memory suggest diverse abilities which serve unique psychologic functions. The various types of memory appear to have different rules of operation, and depend upon different neuroanatomical structures and circuits that can be differentially impaired by disease.

No longer is memory thought of as mediated by a singly located, neuroanatomic center; nor is it thought of as a unitary process. This is illustrated by the results of research on normal subjects and on patients with memory disorders. A number of theoretical accounts of memory function now exist, each having explanatory power with a proportion of the data derived from current research (see Richardson-Klavehn & Bjork, 1988; Schacter, 1987, for review). The predominant theme of the vast majority of theories

now pertaining to long-term memory function encorporate a dichotomous distinction. That is, long-term memory is viewed as being composed of two or more hypothetical forms, or put another way, exhibited by two different types of testing procedures (see Squire, 1987, for a summary). On the one hand are tests that require the subject to remember a particular learning episode in order to extract the appropriate information to complete the task, such as tests of free-recall, cued-recall, and recognition. On the other hand are tests that reveal learning through improved performance--without requiring explicit reference to the episode(s) in which the information was encoded.

> Instead of being asked to try to remember recently presented information, subjects are simply required to perform a task, such as completing a graphemic fragment of a word, indicating a preference for one of several stimuli, or reading mirror-inverted script; memory is revealed by a facilitation or change in task performance that is attributable to information acquired during a previous study episode. (Schacter, 1987, p. 501)

While there has been a great deal of evidence concerning the existence of these different forms of memory and testing, there has been much debate about how to classify and explain them in a theoretically sound framework. Examples of such classificatory schemes include Graf & Schacter's (1985) *explicit* versus *implicit* memory distinction, memory with and without awareness (Jacoby & Witherspoon, 1982), memories versus habits (Mishkin, Malamut, and Bachevalier, 1984), and *declarative* versus *procedural* memory (Cohen & Squire, 1980) to mention but a few. The explicit/implicit and declarative/procedural memory distinctions are most germane to the current research.

Definitions. Because of the multiplicity of memory-related phenomena, a brief overview of some of the different conceptualizations will be presented.

Sensory Memory is a system required before any long-term or secondary memory processes can operate. It is described as a modality specific persistence of neural activity, primarily at the peripheral receptor organ (see Squire, 1987, for discussion). It is

preattentive and highly unstable. Information within it decays rapidly. Breakdowns in this system result in sensory and perceptual problems.

Working Memory. Baddeley (1986) proposed a model similar to that of the modal model of short-term memory (Atkinson & Shriffrin, 1968). Working memory functions as a control system for processing, storing and retrieving information. It is a multi-component system composed of a central executive that coordinates a group of slave systems. Working memory has access to the products of recent sensory and perceptual analyses, facts from long-term or secondary memory, and motor plans that are being developed. The capacity of working memory is limited and has been documented to be approximately seven units of information plus or minus two units (Miller, 1956). Information within working memory quickly fades if attention is not directed to it.

Although the neuroanatomical substrates of working memory are not fully understood, the frontal lobes are considered essential for operations of the central executive component (Baddeley, 1986). Patients with frontal lesions have difficulty placing remembered events within their proper contexts, and difficulty with judgments of recency, but do not have difficulty with secondary or long-term memory (Milner, 1971, 1974). Clearly, working memory is not a medial temporal lobe function because it is spared when medial temporal lobe damage has occurred. It appears that frontal cortex allows information to be recalled in the correct temporal order while medial temporal regions operate upon this information for encoding, storage and retrieval processes.

Baddeley (1986) suggested that working memory comprises a central executive component and modality-specific slave systems, two of which have been termed an articulatory loop and visual-spatial sketch pad. The slave systems function to maintain information for brief periods of time, while the central executive determines, directs and executes the information processing goals. The central executive has the capacity to process

and integrate multi-modal sources of information, including sensory and perceptual information, as well as knowledge structures from secondary memory.

Primary and Secondary Memory. William James (1890) originally proposed two distinctions of memory processes. The first, or primary memory, refers to information in the focus of current attention and occupying the stream of consciousness: "it was never lost; its date was never cut off in consciousness from that of the immediately present moment" (James, 1890, p. 646). Thus, it is characterized by a reliance upon the encoding of information according to sensory modalities, has a limited capacity, and rapid decay. Secondary memory, however, refers to "the knowledge of a former state of mind after it has already once dropped from consciousness" (James, 1890, p. 648), and is characterized by encoding along semantic and conceptual parameters, has a theoretically unlimited capacity, and decays more slowly.

Explicit and Implicit Memory. Although not mutually exclusive of the above distinctions, other theorists have contrasted implicit with explicit memory. Schacter (1987) describes implicit memory as being revealed by a facilitation or change in task performance that is attributable to information acquired during a previous study episode, and is outside of the subject's phenomenal awareness. Instead of being asked to specifically remember information, subjects are simply required to perform a task. Explicit memory refers to the conscious recollection of recently presented information or experiences. That is, a subject has an awareness of remembering a learning episode. In addition, explicit memory can be either *involuntary* or *intentional*: an intentional explicit memory refers to a conscious and effortful attempt to reconstruct or re-experience the contents of a learning episode, while an involuntary explicit memory is a spontaneous reconstruction or re-experience of that episode.

Declarative and Procedural Memory. Still another distinction has been drawn between declarative and procedural memory. Cohen and Squire (1980) have described declarative memory as refering to the recall and recognition of facts, dates, ideas or other material acquired through learning. It is directly accessible to conscious recollection, and appears adapted for one-trial learning. In contrast, procedural memory is contained within skills or other modifiable cognitive operations. It is expressed as the ability to gradually acquire a specific motor, perceptual-motor, perceptual pattern-analysing, or cognitive skill through repeated practice in that specific activity. This type of memory process is considered more automatic, not accessible to conscious awareness, and appears adapted for incremental learning.

Declarative memory is hypothesized to be dependent upon intact neuronal circuitry in cortico-limbic-diencephalic structures. This hypothesis has been supported by the results of studies with both human and non-human primates where damage to the hippocampus and amygdala, or to the dorsomedial nucleus of the thalamus, interferes with the learning and retention of declarative types of knowledge. Procedural memory, on the other hand, does not appear to depend upon the brain structures damaged in amnesia. Further, because of the diversity of preserved learning abilities contained under the rubric of "procedural memory," it would not appear to depend upon any one structure or location. "One therefore should not expect that a single lesion would affect all of procedural memory, in the way that a lesion of, for example, the hippocampus can affect declarative memory" (Squire, 1987, p. 164). Nonetheless, recent proposals have been forwarded to suggest possible anatomical substrate(s) invloved in procedural learning. Mishkin, Malamut, and Bachevalier (1984) suggested that the cortico-striatal neuronal circuitry may play a role in what they termed *habits* (similar to the procedural memory system). An example of the type of study motivated by this hypothesis is that of Martone, Butters,

Payne, Becker, and Sax (1984). They compared patients with Huntington's disease (HD), in which there is relatively circumscribed damage to the striatum, to those with Korsakoff's syndrome (KS), who suffer damage to the dorsomedial thalamus and mamillary bodies. The HD patients were significantly worse at acquiring the procedural skills necesary to improve at a mirror reading task, while maintaining near-normal performance on the declarative task of word recognition memory. The KS patients exhibited the opposite results: impaired word recognition, but intact acquisition of the procedural task of mirror reading. Thus they demonstrated a double dissociation between these two hypothetic forms of memory.

Similarly, Salmon, Shimamura, Butters, & Smith (1988) demonstrated, with a number of different patient populations including Alzheimer's disease (AD), Korsakoff's syndrome, and Huntington's disease, a selective deficit in AD patients on lexical and semantic priming tasks. They concluded that the memory capacities of AD patients are characterized by a breakdown in the structure of semantic memory. AD was thus hypothesized to result in a deficiency in activating preexisting representations (i.e., word associates) stored in semantic memory. Not only was this impairment evident with the explicit tests of memory, but also with the implicit tests (e.g., lexical and semantic priming). However, it should be noted that a previous study conducted by Nebes, Martin, and Horn (1984) obtained different results: AD patients demonstrated impairment only on more "effortful" memory tasks, such as tests of recall or recognition. On tasks that require more "automatic" processing (i.e., priming), they found evidence leading them to conclude that AD patients' semantic memory is normal.

In sum, amnesic and demented populations have demonstrated a variety of preserved learning abilities in the domains of perceptual, perceptual-motor, and cognitive skills, as well as in priming phenomena. Thus, a logical extention from these results

would be to explore additional clinical populations with relatively circumscribed neuroanatomic damage, such as patients with Parkinson's disease; such populations provide an additional means to examine potential dissociations both between and within implicit and explicit forms of learning and memory.

Memory Function in PD. Saint-Cyr, Taylor, and Lang (1988), for example, have utilized PD patients in their investigations of declarative and procedural memory. They argue that cognitive procedural learning depends on the establishment of heuristic strategies through the action of a circuit which involves the neostriatum and the prefrontal cortex (see "complex" loop discussion in aforementioned Basal Ganglia section). Because the pathophysiology of PD involves both disturbed caudate nucleus outflow and reduced availablity of dopamine in the lateral convexity of the prefrontal regions (Scatton, Rouquier, Javoy-Agid, & Agid, 1982), Saint-Cyr, et al. suggested that the prefrontal component of the "complex" loop is placed in double jeopardy. Saint-Cyr, Taylor, and Lang (1988) compared early stage PD patients, amnestic patients with no prerolandic damage, and early HD patients. Results showed PD patients and HD patients to be selectively impaired in an implicit learning task (the Tower of Toronto puzzle), whereas the amnesic patients were not. In contrast, the PD patients and some of the HD patients exhibited intact recall and recognition, whereas the amnesics did not, illustrating a double dissociation between implicit and explicit learning in the patient groups. Unfortunately, they did not administer additional measures of implicit memory to examine more completely the role of the "complex" loop in various implicit tasks.

Heindel, Salmon, Shults, Walicke, and Butters (1989) compared AD, HD, demented PD, and nondemented PD patients on two implicit memory tests (pursuit-rotor learning and lexical priming). The HD patients were impaired on the pursuit-rotor learning

task, but intact on the priming task. In contrast, the AD patients were intact in pursuit-rotor learning, but impaired in lexical priming. The demented PD patients were impaired on both tasks, while the nondemented PD patients were intact on both. The authors conclude that different forms of implicit memory, all of which are intact in amnesic patients, are dependent upon different neuroanatomic circuitry.

Bondi and Kaszniak (in press) examined the possibility of selective deficits in nondemented PD patients on additional implicit learning tasks, including pursuit-rotor tracking, lexical priming, mirror reading, and a fragmented pictures test. The results demonstrated selective deficits in different implicit memory domains for AD versus PD. The AD patients uniquely exhibited word stem-completion priming deficits, consistent with previous reports of lexical and semantic priming deficits in AD (Heindel, et al., 1989; Salmon, et al., 1988; Shimamura et al., 1987). PD patients, however, were impaired in the skill learning component of a fragmented pictures test, supporting the hypothesis that the neostriatum, vis a vis the "complex" loop (Alexander, et al., 1986), is essential to certain types of skill acquisition, particularly those operations necessarily involved in more purely mental operations. This conclusion was bolstered by comparison with the AD patients' normal acquistion of the cognitive procedures necessary to profit from continued practice with the task (i.e., skill learning), thus demonstrating a double dissociation in performance between AD and nondemented PD patients in skill learning and perceptual memory measures. The results are consistent with previous reports of priming and motor skill learning in AD and PD patients (c.f., Eslinger & Damasio, 1986; Heindel, et al., 1989), and support the conclusion that different forms of implicit memory may be dependent upon distinct neuroanatomic systems.

Consistent with the functional/anatomic hypothesis adopted by Taylor, et al. (1986) and Saint-Cyr, et al. (1988), the PD patients studied by Bondi and Kaszniak demonstrated

selective deficits in cognitive functions that may be primarily dependent upon the integrity of the prefrontal cortex and its connections. Other implicit learning tasks, such as mirror reading and pursuit-rotor tracking, are not thought to be primarily dependent upon the "complex" prefrontal loop, and are thought to utilize other oculomotor and visuomotor loops in order to perform these operations successfully. Thus, the PD patients were not expected to be significantly impaired on these latter tasks, and indeed were not. They demonstrated comparable accuracy and improvement with mirror reading and pursuit-rotor tracking tasks. Recently, Nissen, Willingham, and Hartman (1989) have stated that one of the crucial differences in determining whether amnesic patients can improve on implicit learning tasks is the extent to which the stimulus information constrains response selection. Mirror reading, for example, involves identification of a highly constrained set (e.g., letters), whereas the fragmented pictures test is theoretically an open set of stimuli with few constraints upon response selection. Further research, employing other implicit learning tasks, in which degree of stimulus information constraint can be manipulated, will be necessary to determine whether this dimension accounts for the apparently unique deficit observed in PD patients.

It should be noted, however, that conflicting results have been obtained on motor skill learning tasks such as pursuit-rotor tracking. Harrington, Haaland, Yeo and Marder (1989) showed that PD patients, while not impaired on a mirror reading task or a paired associate (explicit memory) task, were impaired on pursuit-rotor tracking when learning trials were spread over two days of testing. Performance levels on day one were similar to control subjects, consistent with results obtained by other investigators (Bondi & Kaszniak, in press; Heindel, et al., 1989). However, the PD group showed less improvement across days than controls. It was noted that only patients with more advanced symptoms of PD showed impaired rotary pursuit learning, although this could

not be attributed directly to deficits in primary motor or general cognitive function because the motor learning deficits were still observed when initial performance levels were equated. Harrington, et al. (1989) their results are consistent with experimental findings suggesting that along with primary motoric dysfunction, PD involves a disorder in the programming of movements (Bloxham, Mindel, & Firth, 1984; Flowers, 1976, 1978; Harrington, Haaland, Yeo, & Marder, 1989).

Finally, Bondi and Kaszniak (in press) examined explicit memory via free recall, cued-recall, and recognition tests. The AD patients were impaired on the tests of free-, and cued-recall, in addition to the perceptual memory component of the fragmented pictures test, while the PD patients demonstrated impairment only with the more effort-demanding free recall test. These results are consistent with previous research showing "automatic" versus "effortful" processing differences in PD (Lees & Smith, 1983; Weingartner, Burns, Diebel, & LeWitt, 1984).

Frontal Lobe Function. As noted by Delis, Birhle, Janowsky, Squire, and Shimamura (1989), the frontal lobes have historically presented major challenges to neuropsychological investigations. Initially regarded as the "seat of intelligence" (Jackson, 1932), the frontal lobes were later thought to be unimportant for performance on intelligence tests (Teuber, 1964). Recently, however, a number of "higher-level" functions have attributed to the frontal lobes. These functions include concept formation, abstract thinking, planning, organization, initiation, feedback utilization, inhibition of irrelevant responses, and cognitive flexibility. Deficits in these abilities are thought to have their greatest impact on tasks of novel problem-solving (see Delis, et al., 1989, for discussion).

Previous research utilizing PD patients has demonstrated circumscribed deficits on those tasks thought to be sensitive to the integrity of the frontal lobes (Cools, Van Den

Bercken, Horstink, Van Spaeldonck, & Berger, 1984; Lees & Smith, 1983; Taylor, Saint-Cyr, & Lang, 1986). Lees and Smith (1983) were among the first investigators to observe impaired performance on the Wisconsin Card Sorting Test and on verbal fluency tasks in PD patients, including those patients restricted to the earliest, untreated stages of the disease. These deifficts were observed within the context of preserved intellectual and recognition memory functions. These authors, therefore, concluded that the results implied selective dysfunction of the frontal lobes. Also, Cools et al. (1984) demonstrated a "diminished shifting aptitude" in PD patients with intact intellectual functions. PD patients were impaired on tasks involving the ability to reorganize behavior according to the requirements of a task; diminished shifting aptitude was observed on motor and sorting tasks guided by self-generated information.

In efforts to explain such "frontal-like" deficits in PD, Taylor and colleagues adopted a functional/anatomic hypothesis concerning semi-closed neuronal circuitry loops between striatal and frontal cortical areas. DeLong and Georgopoulos (1981; DeLong, Georgopoulos, & Crutcher, 1983) first proposed the concept of "motor" and "complex" loops existing between basal ganglia and frontal cortex. The "complex" loop is thought to transmit information through striatum to granular frontal association areas thought to be involved in more purely cognitive operations. Taylor, et al. (1986) hypothesized that cognitive deficits in PD would occur as a consequence of the disturbed outflow of neuronal activity from the striatum (particularly the caudate nucleus); abilities thought to be dependent upon the integrity of the frontal lobes would, therefore, be affected because of the subcortical deafferentation of the prefrontal cortex. Through extensive testing of memory, visuospatial and executive functions, the presence and degree of circumscribed deficits attributable to the integrity of the frontal lobes were ascertained. Results indicated no evidence of generalized disruption of cognitive processes. Rather, only 5 tests

distinguished PD from the normal control subjects, including the Wisconsin Card Sorting Test, free recall of items from the Rey Auditory Verbal Learning Test, Bead-Tapper (a motor task in which the subject simultaneously sorts beads and depresses a finger tapper), the Delayed Recognition Test spatial list (Albert & Moss, 1984), and immediate recall of the logical passages on the Wechsler Memory Scale.

These deficits were taken to reflect an impairment in the ability to spontaneously generate efficient strategies when relying on self-directed task-specific planning. Since the prefrontal cortex is presumed to play an important role in self-directed behavioral planning, these investigators concluded that the neostriatal outflow model, in predicting the consequences of caudate nucleus dysfunction, was supported. This interpretation is strengthened by the lack of deficits on tests presumably related to other cortical areas, such as recognition memory and most visuospatial tasks (cf. Brown & Marsden, 1986; Flowers, Pearce, & Pearce, 1984).

Taylor, et al. further argue that the disturbed neostriatal outflow model would have to explain not only the lack of deficits associated with all but the frontal region, but also intact performance on tasks which are also associated with the frontal region. Their investigation demonstrated intact performance on tests of verbal fluency (cf. Lees & Smith, 1983) and design fluency, and the ability to maintain an alternating cognitive set on Trails A-B. "The outflow model, in placing emphasis on activity in the frontal lobes, takes account of the massive corticocortical support this region receives in the processing of familiar, structured and rule-bound behaviour" (Taylor, et al., 1986, p. 877). Thus, Taylor, et al. emphasize a loss of internally guided behavior, expressed differentially in the diminished planning of motor, cognitive and emotional behaviors, secondary to disturbed neostriatal outflow to the prefrontal cortical regions which are thought to subserve these abilities.

Recent studies have further implicated frontal lobe dysfunction in the performances of PD patients on tasks of temporal ordering and sequencing (McFie & Thompson, 1972; Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988; Sullivan, Sagar, Gabrieli, Corkin, & Growdon, 1989). Research has demonstrated that the ability to make judgments of temporal order is dissociable from the capacity to recognize previous events (see Schacter, 1987; Squire, 1987, for discussion), "suggesting that recognition memory and recency discrimination are served by independent cognitive processes." (Sagar, et al., 1988, p. 526). Korsakoff's syndrome patients, for example, exhibit a severe deficit in remembering the temporal order of learned material, which is described as being too large to be explained by impaired memory for the material itself (Squire, 1982). Patients with surgical lesions involving the frontal lobes (Milner, 1971, 1974) have demonstrated impaired temporal order memory, but relatively intact recognition memory, suggesting that the frontal lobes play an important role in temporal order judgments.

Recently, temporal ordering and recognition memory in PD patients has been assessed with verbal material. Sagar, et al. (1988) administered a continuous recognition memory and recency discrimination paradigm (cf. Hirst & Volpe, 1982). Test questions appeared at various intervals after presentation of target stimuli. The results demonstrated that PD patients were disproportionately impaired in recency discrimination relative to content recognition, and showed deficits in content recognition only at the short stimulus-test intervals. They suggested that recency discrimination deficits and imparied short-term memory processing are specific cognitive deficits in PD and may be linked to subcortical deafferentation of the frontal lobes.

Finally, standard psychometric tests have been associated with frontal lobe functioning, including the Picture Arrangement subtest of the Wechsler Adult Intelligence Scale (McFie & Thompson, 1972; Sullivan, et al., 1989), and have been administered to

PD patients. Sullivan, et al. (1989) gave PD patients this test to provide an assessment of set formation (creation of a story line) and cognitive sequencing (manipulation of the order of multiple items to produce the logic of a story-line). These authors measured cognitive sequencing by the standard scaled score, and set formation by the tendency of subjects to leave Picture Arrangement story cards in the order presented by the examiner (cf. McFie & Thompson, 1972). Results demonstrated that the PD patients had deficient Picture Arrangement but normal Vocabulary test scores, irrespective of mental status. Sullivan, et al. point out that PD patients showed cognitive deficits qualitatively similar to those manifest by patients with frontal lobe pathology, and that these behavioral patterns may be specific deficits in PD and relfect dysfunction of the frontal lobes or their connections.

Despite the converging evidence of frontal lobe dysfunction with behavioral measures, a shortcoming of neuropsychological tests commonly used to assess problem-solving abilities is that they fail to fractionate overall performance into cognitive components (cf. Delis, et al., 1989). Consequently, when frontal-damaged patients perform poorly on these tests, the mechanisms underlying their impairment is unclear. For example, Delis, et al. discuss that patients may show impaired performance on the Category test (of the Halstead-Reitan battery) for a number of reasons, including failure to identify abstract principles, inability to use feedback to establish or switch cognitive sets, failure to inhibit irrelevant responses (e.g., pointing to a perceptually salient but incorrect stimulus property), or cognitive inflexibility (resulting in perseverative responses). The global achievement scores provided by most of these tests mask each patient's specific deficits. The WCST is unique in that it measures two classes of responses: correct sorts and perseverations. Perseverative errors, however, may reflect different cognitive deficits (e.g., failure to identify new sorting principles; inability to inhibit previous responses), and

these different deficits are not delineated by the WCST (see Delis, et al., 1989, for discussion).

The lack of specifically defining cognitive components of performance in tests sensitive to frontal lobe dysfunction has led to a number of methodological and conceptual problems in this area of research (Delis, et al., 1989). Stuss and Benson (1986) note that researchers often infer deficits in particular "higher-level" functions without operationally defining and specifically measuring these functions. In addition, considerable disagreement exists as to which "higher-level" functions are impaired in frontal patients. Studies have also reported in a dissociation frontal lesion patients between knowing and doing (Luria, 1973; Milner, 1964; Teuber, 1964). In these studies, frontal-damaged patients knew their errors, but were unable to use that knowledge to modify behavior, such that verbalization no longer controled active behavior (see Stuss & Benson, 1986, for discussion). Taylor, et al. (1986) discuss this qualitative occurrence with regard to their study: "PD patients in the present study often stated that 'it must be colour', or, 'is it shape?' while continuing to follow a random response pattern" (p. 869).

Recently, Delis, et al. (1989) constructed a new sorting task designed to isolate and measure specific components of novel problem-solving. Based on past descriptions of frontal lobe dysfunction, it was predicted that frontal lesion patients would display specific deficits in several problem-solving components, including (1) initiation of spontaneous sorts; (2) generation of accurate sorts; (3) verbalizing abstract sorting principles; (4) using abstract and explicit information about sorting principles to direct behavioral responses; and (5) cognitive flexibility (as measured by perseveration rates). Results suggested that frontal damage disrupts several problem-solving functions. Their patients were impaired in generating accurate sorts relative to the number of attempted sorts (which was comparable to normal control subjects' number of attempted sorts), and in verbalizing the rules of both

spontaneous sorts and sorts done by the examiner. Also, patients perseverated more sorts and rule names than normal subjects. These findings suggest that specific functional deficits exist in several "higher-level" functions, and converge to disrupt the problem-solving ability of frontal patients. Studies defining and fractionating specific components of problem-solving with PD patients are needed to determine similarities and differences between PD and frontal lesion patients, ascertaining whether the differing neuropathology in PD (i.e., subcortical deafferentation of the frontal lobes versus frontal lobe structural damage) contributes to different profiles of problem-solving performance. Such work would help explicate more precisely the function of the frontal lobes, and their differential impairment in various neurologic disorders where the frontal lobes are implicated.

Introduction to Experiments and Hypotheses

The present investigation was designed to address the general hypothesis that, in nondemented PD patients, a cluster of deficits would emerge on tasks selected because of their presumed reliance upon the integrity of the prefrontal cortical areas. A primary emphasis in this investigation was the multimethod approach that was utilized to address this hypothesis, as well as an effort to better delineate which cognitive functions show impairment in PD patients. Also, tasks utilized in a wide variety of studies were given to a single homogeneous sample of idiopathic PD patients in the relatively early stages of their disease. This sampling strategy was used hypothetically limit the distribution of regional neuropathology in this sample of PD patients, as well as to address some of the inconsistent findings in the literature with respect to performance of nondemented PD patients across studies. Thus, the focus of the current research is upon converging evidence from a variety of clinical and experimental neuropsychological tests implicating the prefrontal cortex. Also, a new neuropsychological test was administered (*California*

Sorting Test), which was designed to isolate and measure specific components of novel problem-solving. This task was constructed to fractionate specific deficits in several problem-solving components, including (1) initiation of spontaneous sorts; (2) generation of accurate sorts; (3) verbalizing abstract sorting principles; (4) using abstract and explicit information about sorting principles to direct behavioral responses; and (5) cognitive inflexibility (as measured by perseveration rates).

The present investigation assessed the functional integrity of the frontal lobes in PD patients with a variety of tasks thought to be sensitive to frontal lobe dysfunction. In addition, the possiblity of a selective, frontally-related deficit in PD on implicit and explicit learning tasks was examined. The performances of demographically-matched samples of PD patients and healthly elderly subjects were compared on different implicit and explicit memory tasks. PD patients were predicted to show impaired acquisition of certain domains of implicit knowledge, resulting from their striatal damage. Further, because the damage in PD disrupts the "complex" loop circuitry, impairment would be most observed on implicit tasks relying more on cognitive operations thought to be dependent upon frontal cortical integrity (e.g., fragmented pictures test), than those requiring visuomotor or oculomotor operations alone (e.g., serial reaction time). Also, PD patients were predicted to perform more poorly on implicit learning tasks in which the stimulus information does not highly constrain response selection (cf. Nissen, et al., 1989). Both cognitive and motor implicit learning tasks were administered to examine possible dissociations in performance between tasks. Thus, three categories of tests were administered: (1) tests sensitive to prefrontal cortical dysfunction (the California Sorting Test, a modified version of the Wisconsin Sorting Test, verbal and spatial temporal ordering, and generative naming), (2) implicit and explicit memory tests (a fragmented pictures test, serial reaction time, verbal and spatial continuous recognition memory, and word learning), and (3) tests of visuoperceptual and

visuoconstructional skills (including the Block Design and Picture Arrangement subtests of the WAIS-R, Benton Facial Recognition Test, and Benton Visual Form Discrimination Test). All tests contained within category (1), in addition to the fragmented pictures test, short stimulus-test intervals of the verbal and spatial continuous recognition memory, free recall of word learning, and age-corrected performance on Block Design and Picture Arrangement were all predicted to show impairment in the nondemented PD patient group, compared to normal control subjects.

CHAPTER 2

METHOD

Subjects

All subjects selected for inclusion in this study were recruited from an ongoing longitudinal study of communication and neuropsychiatric status being conducted at the University of Arizona, under the direction of Alfred W. Kaszniak, Ph.D. and Kathryn A. Bayles, Ph.D. All subjects in this longitudinal study met the following selection criteria: (1) native speakers of English (with the exception of one subject whose native language was French, but nevertheless has been naturalized in the United States for more than 30 years, and obtained a doctorate from an American university), (2) see well enough to read, (3) hear well enough to pass a speech discrimination test with 80% accuracy, (4) of normal or above average estimated premorbid intelligence as determined by a regression equation, in which demographic information is used to estimate intelligence (Barona, Reynolds, & Chastain, 1984), and (5) nonalcoholic. Further, all subjects had a medical history screening, physical and neurologic examination, and had the following conditions ruled out: (1) myocardial infarction or chronic cardiovascular disease, (2) cerebrovascular accident, (3) alcohol or substance abuse, (4) chronic psychiatric illness or long-term neuroleptic prescriptions, predating the onset of PD, (5) syphilis, (6) brain damage sustained earlier from a known cause (e.g., hypoxia), (7) chronic renal, hepatic, pulmonary, or endocrine disease, (8) hypotensive or hypertensive cardiovascular disease, and (9) metabolic toxicity, or drug interaction. Subjects had physical and neurologic examinations approximately one month prior to participation in the proposed study.

Criteria for Selection of PD Patients. Nineteen nondemented PD patients were selected for study. The following steps were specified for the selection of PD patients: (1) candidates must have met the criteria for all subjects specified above, (2) during the

neurologic examination, determination was made of (a) onset and course of the disease (using information from both patient and family-member informant) (b) past medical history (c) clinical stage (d) drug regimen and response, and (e) severity of motor symptoms. Patients must have had a diagnosis of idopathic PD in order to participate in the study. In addition, patients must not have had a history of stroke, not have met the modified Hachinski criteria (Rosen, Terry, Fuld, Katzman, & Peck, 1980) for multi-infarct dementia, and had no history of stereotaxic surgery. PD patients included for participation were required to be in stage's I, II, or III of the disease according to the Hoehn and Yahr Clinical Disability Scale (Hoehn & Yahr, 1967), must not have had any changes in their anti-Parkinsonian medication in the last three months, and must not have demonstrated severe tremor or bradykinesia (as defined by the Unified Parkinson Rating Scale, see below). PD patients selected for inclusion were examined to determine the absence of dementia, and must have demonstrated a score of 3 or less on the Global Deterioration Scale (GDS) (Reisberg, Ferris, & Crook, 1982), and a score of 26 or more on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). Also, because ON/OFF phenomena (Girotti, Carella, Grassi, Soliveri, Marano, & Caroceni, 1986), and the problem of drug efficacy wearing off during testing (Cantello, Gilli, Riccio, & Bergamasco, 1986) may potentially affect performance on cognitive tasks, patients were tested during periods of maximum drug effect. The following formula helped guide selection of appropriate windows for testing: 0.5 x (drug dose interval) + one-half hour. Testing took place during the interval one-half hour preceding, and one-half hour following, the peak period of drug efficacy. For example, if a patient took medication at 8am and 12 noon, the drug interval was 4 hours. Half that interval was 2 hours, plus the addition of one-half hour, which made the peak period of drug efficacy approximately 10:30am. Thus, testing commenced at 10am and end at 11am for this example.

Neurologic Examination of Patients. The Unified Scale for Parkinsonism was administered by the project neurologist to assess motor signs and symptoms and screen patients. The scale quantitatively assessed bradykinesia, gait, posture, resting tremor, rigidity, and instrumental activities of daily living (dressing, hygiene, eating and feeding, and speech).

Criteria for Selection of Normal Control Subjects. Nineteen control subjects were selected for inclusion and matched on a group basis to the PD patients according to age, sex, years of education, race, and estimated intelligence (Barona, et al., 1984). Normal control subjects were selected from friends and relatives of PD patients, hospital volunteers, and non-patient members of the Parkinson's Disease Support Group of Tucson. Control subjects were also required to meet the criteria for all subjects specified above.

Procedures

Tests Assessing Functional Integrity of the Frontal Lobes

Controlled Oral Word Association (Generative Naming). Because impaired generative naming has been demonstrated with frontal lobe damage, particularly left frontal lobe anterior to Broca's area (Area 44) (Milner, 1974; Ramier & Hécaen, 1970; Tow, 1955), this test was administered to assess the "complex" loop hypothesis of subcortical deafferentation of the frontal lobes in PD. Previous research has produced discrepant results with PD patients on tests of verbal fluency. Lees and Smith (1983), for example, demonstrated impaired performance in PD patients, including those patients in the earliest and untreated stages of their disease. Taylor, et al. (1986), however, demonstrated both intact verbal fluency as well as design fluency in their PD patients. They interpreted this

intact performance to be compatible with the outflow model by emphasizing the massive corticocortical support the frontal region receives in the processing of familiar, structured and rule-bound behavior (p. 877).

Verbal fluency is designed to measure speeded access to semantic information. A variation on the traditional letter fluency task, where subjects are asked to generate as many words as possible beginning with certain letters in one minute's time, was administered. Letters were used to provide comparison with previous studies, but two additional categories were designated: (1) the first names of people beginning with specified letters, and (2) semantic categories such as fruit and animals.

Procedure

Subjects were asked to provide as many different words as they can think of in one minute that began with a given letter, that are people's first names that began with a given letter, and that within a given semantic category. A practice trial was administered before the two scored trials were attempted. Finally, where appropriate, instructions were given to exclude proper nouns, numbers, and the same word given in different suffixes.

Hypotheses. Clinically, patients with frontal lobe lesions have demonstrated generative naming deficits (see Stuss & Benson, 1986, for review). Thus, PD patients were predicted to be impaired in this task in comparison to the control subjects, because of prefrontal cortical dysfunction as a consequence of the pathophysiology in PD.

Modified Wisconsin Card Sorting Test. Tests of executive function are:

> cognitively demanding task[s] in terms of planning skills as they depend on transforming previously neutral stimuli into task-specific associations to solve novel problems. Such test are not uniquely linked to any sensory modality and do not utilize information stored within the familiar knowledge base. The planning necessary to succeed in such non-routine activities must be spontaneously developed by the subject, via the constant generation and switching of heuristic strategies. (Taylor, Saint-Cyr, & Lang, 1988, p. 109)

Perhaps the single best-known neuropsychologic test of executive function is the Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1948; Heaton, 1981). It has been shown to be very sensitive to frontal lobe damage, particularly dorsolateral prefrontal lesions (Drewe, 1974; Milner, 1963). Thus, the WCST is a particularly good instrument with which to assess the "complex" loop hypothesis of subcortical deafferentation of the frontal lobes in PD. With this test, PD patients have consistently demonstrated impairment (Bowen, 1976; Lees & Smith, 1983; Taylor, et al., 1986). This test is thought to depend on the ability to discover a correct sorting concept and then to shift this without warning so that the subject must formulate a new successful strategy for sorting.

A modification of the WCST was first attempted by Nelson (1976). The modification consisted of removing all response cards sharing two or more attributes with a stimulus card (e.g., the same color and the same form could be matched to one of the four stimulus cards). This left a set of 24 cards in each deck sharing one and only one attribute with each of stimulus cards, totaling a pack of 48 cards to be presented to the subject for sorting. Second, the examiner shifted category criteria after only six consecutive correct responses *and* informed the subjects of such shifts. Thus, Nelson's modification effectively shortened the administration time and reduced the ambiguity in scoring and classifying a subject's response, allowing the examiner to convey unambiguous information to the patient as to the correctness of the category concept being applied. Nelson reasoned that these changes made the test simpler and less stressful to the patient, which she emphasized was particularly important for elderly patients.

Hart, Kwentus, Wade, and Taylor (1988) discuss that older subjects may be more likely to fail to grasp what is required in the test situation and may become distressed as responses are negatively reinforced in a manner that appears arbitrary to the subject. They further argue, however, that Nelson's changes to the WCST decrease its sensitivity to

subtle forms of brain dysfunction. Jenkins and Parsons (1978), for example, found that Nelson's modified WCST was not sensitive to cognitive deficits typically observed in chronic alcoholics as compared with the standard WCST. Jenkins and Parsons were able to clearly differentiate alcoholics from nonalcoholic control subjects by developing a 72 card version of the WCST, using those cards that shared one and only one attribute with the stimulus cards (similar to Nelson), but retaining the original instructions which give no cue regarding category shifts.

Hart, et al. (1988) administered this modified version to normal elderly, depressed elderly presenting with cognitive complaints, and mildly and moderately demented AD patients. AD patients demonstrated impairment relative to normal control subjects, but were not significantly different from depressed elderly subjects on post-hoc tests. They argue that this finding was perhaps not surprising given the type of depressed patients in their sample. Those who were selected complained of cognitive impairment such as diminished ability to think, concentrate or remember information, and all but four were initially referred for a clinical evaluation to rule out early dementia. Finally, Hart, et al. emphasized that this modified version did not cause significant distress in their patient sample; only one depressed patient and one AD patient out of 71 subjects were unwilling or unable to complete the task, and these patients were generally uncooperative with test procedures.

Materials and Procedure

The modified WCST (Hart, et al., 1988; Jenkins & Parson, 1978) used the four stimulus ("key") cards, as in the standard WCST, and the 24 response cards selected by Nelson that share one and only one attribute with the stimulus cards. Three sets of these 24 cards were utilized to comprise a full set of 72 cards. Subject responses and data tabulation

were completed on the Apple Macintosh computer, programmed for use with the modified WCST. The subject was then given these instructions, based on Heaton's (1981) administration:

> "This test is a little unusual, because I am not allowed to tell you very much about how to do it. You will be asked to match each of the cards in this deck to one of the four key cards. You must always take the top card from the deck, and place it below the key card you think it matches. I can't tell you how to match the cards, but I will tell you each time whether you are right or wrong. If you are wrong, leave the card where you've placed it, and try to get the next card correct. There is no time limit on this test."

Following six consecutive correct responses to the initial sorting principle (color), the sorting principle was changed without a cue or warning, to form, then number, and repeated for color, form and number (totaling a possible 6 categories to be completed). The test was discontinued if all six categories (C, F, N, C, F, N) were completed, or when the deck had been exhausted. Total number of categories, total errors, and perseverative responses were scored. Scoring of a perseverative error response required that the subject persist with an incorrect category for at least two consecutive responses after feedback. Perseverative errors were scored beginning with the second consecutive incorrect response to a given category.

Hypotheses. PD patients were predicted to be impaired on the modified version of the WCST, in comparison to demographically-matched control subjects. Comparison of PD patients to the normal control subjects on each of the three test variables (number of categories completed, total errors, and total perseverative responses) was predicted to show significant impairment for the PD patients.

Fractionation of Problem-Solving Abilities (California Sorting Test). To isolate specific components of problem solving, this task was developed using a set of cards that can be sorted accoring to various rules (e.g., shape of objects, color, semantic category of

words on cards, letter shape and size, compound words, etc.), asking subjects to (1) generate as many sorts as possible and name the sorting rules (free sorting condition); (2) name the rules of sorts done by the examiner (structured sorting condition); and (3) sort the cards according to abstract and concrete rules provided by the examiner (cued sorting condition). Delis, Bihrle, Janowsky, Squire, and Shimamura (1989) presented this task to frontal-lobe patients and normal control subjects. Results demonstrated that the problem-solving impairment of frontal lobe damaged patients could be fractionated into specific deficits in initiation of sorts, sorting accuracy, rule naming, switching rules, and abstract rule comprehension. Thus, the California Sorting Test was presently administered to PD patients to support and extend the findings of impaired performance with the WCST (Lees & Smith, 1983; Taylor, et al., 1986) in PD patients with an alternative novel problem solving task.

Materials and Procedure

Briefly, 3 sets of six cards were used in each of three sorting conditions (free sorting, structured sorting, and cued sorting). For example, with the six cards in set 1, the examiner presented the following instructions to the subject for the free sorting condition:

> I'm going to show you six cards that can be sorted in different ways. I'd like to see how many different ways you can sort these cards. Each time you must make only <u>two</u> piles with <u>three</u> cards in each pile. The three cards in each pile should be the <u>same</u> in some way. Each time you sort the card into two piles, tell me how you did it . . . Work as quickly as you can until I say STOP.

Placed in front of the subject at all times was a reminder sheet with large, bold-faced print outlining the major points of the instructions: 2 piles, 3 cards in each pile, cards in each pile sorted same. Similar instructions were used for the structured and cued sorting conditions, with modifications appropriate to the task. In the structured sorting condition, for example, the examiner sorted the six cards and instructed the subject to specify the

sorting rule used. In the cued sorting condition, the examiner instructed the subject to sort the six cards with a clue or rule for how to sort the cards.

Subjects completed all three sorting conditions with the first set of 6 cards before use of the second and third sets of cards. Thus, each set of cards were sorted in the three conditions, totaling 3 free sorts, 3 structured sorts, and 3 cued sorts.

Hypotheses. PD patients were predicted to exhibit impaired performance in comparison to demographically-matched control subjects with the free sorting condition because of hypothesized deficits in self-directed task-specific planning, secondary to pathophysiological processes in PD. No differences, however, were expected in the structured sorting condition because of increased guidance and constraints upon response selection (cf. Nissen, et al., 1989). Small differences were expected in the cued sorting condition because of the administration and scoring procedures of the test: two cues were presented to the subject, first a general cue, followed by a specific cue. If performance was correct following the general cue, 2 points were awarded. If, however, performance was incorrect following a general cue, a specific cue was given and, if correct, the subject received one point. Thus, PD patients were predicted to benefit maximally from specific cues, but less often from general or abstract cues, in comparison to control subjects.

Verbal and Spatial Continuous Recognition Memory and Temporal Ordering. Previous research has demonstrated that the ability to make judgments of temporal order is dissociable from the capacity to recognize previous events, "suggesting that recognition memory and recency discrimination are served by independent cognitive processes." (Sagar, Sullivan, Gabrieli, Corkin, & Growdon, 1988, p. 526). Korsakoff's syndrome patients, for example, exhibit a severe deficit in remembering the temporal order of learned material, which is described as being too large to be explained by impaired memory for the

material itself (Squire, 1982). Patients with surgical lesions involving the frontal lobe (Milner, 1971, 1974) have demonstrated this dissociation as well, suggesting that the frontal lobes play an important role in this type of cognitive operation.

Recently, temporal ordering and recognition memory in PD patients has been assessed with verbal material. Sagar, et al. (1988) administered a continuous recognition memory paradigm (cf. Hirst & Volpe, 1982) with the modification of including both recognition memory prompts and recency discrimination prompts. Test questions appeared at various intervals after presentation of the target stimulus. The results demonstrated that PD patients were disproportionately impaired in recency discrimination relative to content recognition, and showed deficits in content recognition only at the short stimulus-test intervals. They suggested that recency discrimination deficits and impaired short-term memory processing are specific cognitive deficits in PD and may be linked to subcortical deafferentation of the frontal lobes.

The present investigation was designed to replicate the findings of Sagar, et al. (1988), demonstrating verbal recency deficits with PD patients, in addition to extending this methodology to include performance with spatial, non-verbalizable stimuli (i.e., random shapes), in a shortened format. Recently, Sagar and Sullivan (1989) extended their work with non-verbal recognition and recency discrimination measures, obtaining similar results to their previous findings.

Materials and Procedure

The tests were administered on an Apple Macintosh microcomputer; stimulus presentation and test questions were shown on the screen, and responses recorded by the computer. The verbal word list was identical for both the verbal continuous recognition memory (VCRM) and verbal temporal ordering (VTMP) tasks. Similarly, the spatial stimuli were identical for both the spatial continuous recognition memory (SCRM) and

spatial temporal ordering (STMP) tests. The VCRM and VTMP were administered as a pair, and the SCRM and STMP tests were paired together. For example, VCRM was first administered, followed by approximately 15 - 20 minutes of other cognitive testing. VTMP was then administered following this delay.

Sixty nouns were selected as target items for the verbal word list (see Paivio, Yuille, & Madigan, 1968), and were displayed on the computer screen, one at a time, at a rate of one per 3 seconds. All words selected were 4 to 7 letters in length, and had a frequency rating in the English language of 25 per million or more (Kuçera & Francis, 1967). Each word had been scaled on abstractness-concreteness (C), imagery (I), and meaningfulness (M) dimensions by Paivio, et al. (1968). Concreteness was defined in terms of directness of reference to sense experience, and Imagery, in terms of a word's capacity to arouse nonverbal images; Concreteness and Imagery were rated on 7-point scales. Meaningfulness was defined in terms of the mean number of written associations in 30 seconds (see Paivio, et al., 1968, for discussion). For the presently employed stimulus words, concreteness and imagery values were held at a constant high level for the 60 target words [C = 6.0 or above, and I = 5.90 or above]. Meaningfulness was arbitrarily divided into three categories: high, medium and low [High = 7.35 or more; Medium = 6.41 - 7.34; Low = 6.40 or less]. Thus, 20 words had low meaningfulness values, 20 words had medium meaningfulness values, and 20 words high meaningfulness values. Finally, 60 additional words were selected to serve as foil items on the recognition prompts, and adhered to all of the aforementioned specifications. Foils were paired within meaningfulness categories only (i.e., high meaningfulness targets were paired with high meaningfulness foils).

The spatial stimuli were selected from the set of random shapes developed by Vanderplas and Garvin (1959). The random shapes had been quantified along association

value, and complexity dimensions, and were thus suitable in attempting to equate the spatial stimuli with the verbal stimuli. Association value referred to the number of familiar objects or situations of which the shape reminded the subject. Complexity referred to the number of points or angles in the given shape. Shape complexity has been positively correlated with recognition performance (Clark, 1965); the greater the complexity of a shape, the greater its recognizability--comparable to concreteness values for verbal stimuli. Association value, on the other hand, is comparable to meaningfulness for verbal stimuli. Thus, 60 shapes were selected as target items, with complexity held at constant high levels (i.e., selection of shapes were from the four highest configurations: eight-point, twelve-point, sixteen-point, and twenty-four-point shapes), and association values varied. An additional 60 shapes were selected to serve as foil items on the recognition prompts, and adhered to all of the aforementioned specifications.

The VCRM--VTMP, and SCRM--STMP paradigms were constructed similar to the paradigm described by Sagar, et al. (1988). Forty-eight content recognition questions for the VCRM and SCRM tasks were placed within the 60 word list at various intervals after stimulus presentation. Content recognition questions contained a previously presented word and a foil. The test question appeared at the top of the computer screen and read "Which of these words did you see on this test?" for the verbal material, and read "Which of these shapes did you see on this test?" for the spatial material. The two alternative answers appeared side-by-side underneath the question on the screen. The duration of each stimulus-test interval was defined as the number of intervals between events where an event was either another stimulus word or a test question. For example, where a question immediately followed stimulus presentation, the stimulus-test interval was defined as 1 and there were no intervening events; where a question was the third item after stimulus presentation, the stimulus-test interval was 3 and there were 2 intervening items that could

be stimulus words or test questions relating to earlier stimulus words. The position of a content recognition question was defined by such interval specifications. The stimulus-test intervals were 1, 3, 6, and 10; there were 12 exemplars at each position.

The recency discrimination test questions utilized the same 60 target items presented during the VCRM and SCRM tests, also in the same order of presentation. Recency discrimination questions contained 2 previously presented words [or shapes] upon the screen. The test question read "Which of these words did you see more recently?" for the verbal material, and "Which of these shapes did you see more recently?" for the spatial material. Twenty-four recency discrimination questions were placed within the 60 item list at various intervals after stimulus presentation. The duration of each stimulus-test interval was defined the same as mentioned above, with the exception that recency discrimination questions examined 2 previously presented words; the position of a recency discrimination question was therefore defined by two intervals, one corresponding to each item examined in the test. All possible pairings of the 1, 3, 6, and 10 stimulus-test intervals were used (1 - 3, 1 - 6, 1 - 10, 3 - 6, 3 - 10, 6 - 10); there were 4 exemplars for each pairing. In both the VCRM--VTMP, and SCRM--STMP, test questions contained 50% of the correct responses appearing on the left half of the screen and 50% on the right half of the screen in random order.

During administration of the tests, subjects were seated beside the examiner and in front of the screen. For the VCRM test, they were instructed to read and remember each word. For the VTMP, they were instructed to read each word and remember the order in which they were presented. For the SCRM test, they were instructed to read remember each shape. For the STMP, they were instructed to view each shape and remember the order in which they were presented. Subjects were asked to give oral responses to the questions, without time limitation. The examiner entered the response into the computer at

the same time the subject was instructed to keep on reading. The registration of the response triggered the appearance of the next stimulus word.

Hypotheses. PD patients were predicted to demonstrate verbal and spatial temporal ordering deficits, but content recognition deficits limited to only short stimulus-test intervals (i.e., 1 and 3).

Tests of Implicit and Explicit Memory.

Neuropsychological studies have demonstrated that while patients with circumscribed damage to the frontal lobes often are not globally amnesic (see Stuss & Benson, 1986, for review), and cannot be characterized as having a declarative or explicit memory impairment, they nevertheless are impaired on memory tests that require organization, memory access, metamemory, and spatial/temporal context or source memory (see Shimamura, 1989, for discussion). Thus, for the present investigation it was important to administer additional tests of implicit and explicit memory in order to assess more broadly the contributions of the "complex" loop, linking basal ganglia to frontal cortex (Alexander, et al., 1986), to various cognitive and behavioral performance deficits in PD patients.

Fragmented Pictures Test. Assessment of implicit and explicit memory processes was first examined through the use of a fragmented pictures test (Snodgrass, Smith, Feenan, & Corwin, 1987). It provides an index of both learning of the physical configuration of stimuli (i.e., perceptual memory) and increased fluency on the tasks themselves, reflected as improved performance on novel items with task practice (i.e., skill learning) (Corwin & Snodgrass, 1987). Previous research utilizing the fragmented pictures test with AD and PD patients has demonstrated dissociations in performance

(Bondi & Kaszniak, in press), with PD patients demonstrating intact perceptual memory relative to controls, but impaired skill learning. The AD patients, on the other hand, demonstrated intact skill learning relative to controls, but impaired perceptual memory. A replication of this observation was thus attempted in the present study, employing only nondemented PD patients.

Materials

The fragmented pictures test (Snodgrass et al., 1987) was administered on an Apple Macintosh microcomputer. Pictures of common objects or animals obtained from the set of stimuli constructed by Snodgrass and Vanderwart (1980) were displayed upon the computer screen, with eight levels of fragmentation, beginning with the most fragmented form. Identification thresholds and subject responses were recorded by the microcomputer.

Procedure

The fragmented pictures test contained two phases. In the first or training phase, a set of 15 pictures were presented to the subject, who then attempted to identify the picture at the most degraded level possible. Guessing was allowed. Once the subject identified the correct name of the picture, the computer recorded the identification threshold for that picture. The average level of fragmentation required for correct naming was termed the training threshold (TRAIN); complete pictures (i.e., unfragmented stimuli) unable to be named by a subject were recorded as a level of 9. Bondi and Kaszniak (in press) demonstrated that only the AD group experienced any difficulty in naming, failing to name less than 5 percent of the total 540 pictures presented to them (12 subjects each presented with 45 pictures). PD patients and control subjects failed to correctly name less than one percent.

Following a 5 to 10 minute break, the fragmented pictures procedure was repeated with a re-presentation of the training pictures mixed randomly with an equal number of novel pictures. Thus, the test phase consisted of what are termed 15 OLD pictures and 15 NEW pictures.

The data obtained by this experiment were the identification thresholds for the training stimuli during the first phase, and the identification thresholds for the old and new stimuli during the test phase. Two separate measures were derived, given this data. First, a measure of skill learning was indexed by a decrease in thresholds between the training and new pictures (TRAIN - NEW). Second, a measure of perceptual memory was indexed by a decrease in thresholds between the new and old pictures in the test phase (NEW - OLD). Obtaining the perceptual memory measure by this method excluded improvement in performance due to skill learning. In other words, the measure of perceptual memory was corrected for task practice.

Hypotheses. Because confrontation naming abilities of nondemented PD patients are not impaired, no significant differences between training identification thresholds were predicted. Finally, impairments were predicted with skill learning (SL) but not perceptual memory (PM) scores because of hypothesized deficits in perceptual procedural learning in PD (cf. Bondi & Kaszniak, in press; Saint-Cyr, et al., 1988).

Serial Reaction Time. The second implicit learning task administered was a serial reaction time experiment similar to those administered by Nissen and Bullemer (1987), Knopman and Nissen (1987) and Nissen, Willingham, and Hartman (1989). In this paradigm, a stimulus appeared in one of four locations on a video monitor and subjects were instructed to press the one key, out of the four that were available, that corresponded to the quadrant in which the stimulus appeared. A fixed 10-trial sequence of stimulus

positions was used. These investigators determined whether subjects had learned this sequence over the course of 40 repetitions by transferring them to a random sequence following their training on the repeating sequence. Their response times to the random sequence should have slowed to the extent that they had learned the repeating sequence. When given this task, Korsakoff's patients performed similarly to age-matched control subjects, demonstrating the same pattern of improvement with practice on the repeating sequence and the same pattern of slowing upon transfer to the random sequence (Nissen & Bullemer, 1987). The two groups differed, however, in their verbal reports: control subjects noticed a repeating pattern, whereas none of the amnesic patients did.

Further, Knopman and Nissen (1987) performed this task with probable AD patients. They demonstrated that, although the AD patients responded more slowly than the controls, many showed learning of the repeating sequence. Patients who failed to learn the sequence were similar in age and overall severity of dementia to those who were able to learn the sequence, but scored lower on some tasks of nonverbal reasoning, such as block design of the WAIS-R and Porteus mazes.

Materials

The serial reaction time test was administered on an Apple Macintosh microcomputer. Responses were made by pressing one of four keys arranged in a row on a keyboard placed below and in front of the video monitor. The correct response on each trial was to the key that corresponded to the quadrant on the screen. That is, the far left button corresponded to the far left quadrant on the computer screen, the far right button corresponded to the far right quadrant, and so on. The stimulus remained present until one of the four keys was pressed, correct or not, at which time that stimulus was extinguished and the next one appeared after a delay of approximately 500 msec. If the subject pressed

the wrong key, feedback was given regarding its inaccuracy by the sound of a beep. Subject response selections and latencies were recorded by the microcomputer.

Procedure

Subjects were seated in front of the computer screen and keyboard. They were asked to press the key that corresponded to the quadrant where the stimulus appeared. They were instructed to respond as quickly and as accurately as possible. The presence or absence of a repeating sequence was not disclosed to the subjects.

During the experiment subjects completed six blocks of 80 trials each. Successive blocks were divided into two training clusters. In each cluster a random sequence (RANDOM) of 80 trials were presented, followed by a 1 minute rest period, presentation of a 10-trial repeating sequence (REPEAT) of 80 trials, another rest period of 1 minute, and ending with another presentation of the 10-trial repeating sequence (REPEAT). Approximately 10 mintues of other cognitive testing were given in-between the two training clusters. Thus, the order of blocks were: 1-RANDOM 2-REPEAT 3-REPEAT--(BREAK)--4-RANDOM 5-REPEAT 6-REPEAT. The repeating sequence followed a particular 10-trial sequence; designating the four locations as 1, 2, 3, and 4 from left to right, the sequence was as follows: 4-2-3-1-3-2-4-3-2-1. Each block of trials of the repeating sequence consisted of 8 repetitions of this 10-trial sequence. The end, however, of one 10-trial sequence and the beginning of the next was not marked in any way. Thus, in the absence of knowledge of the sequence itself, each block seemed to be a continuous series of 80 trials. For the random sequence, the location of the stimulus on each trial was determined randomly, with the only constraint being that the same position could not be used on successive trials.

Hypotheses. The data of interest for this experiment were log-transformed reaction time (RT) latencies. The primary focus of the data was the difference between PD patients

and control subjects in RT, and differences between groups across trial blocks. The PD patients were predicted to have slower RT's than control subjects as a consequence of their disease. However, the slopes of the learning curve for the first block of trials (RANDOM1--REPEAT1--REPEAT2) were predicted to be comparable; no significant interaction was predicted in the GROUP by BLOCK analysis for the first cluster of blocks. Because both groups initially began with a random sequence of trials, attentional demands were thought to be comparable for both groups. That is, with the initial random sequence of trials there was thought to be comparable cost to the limited capacity attentional mechanisms for both groups. With practice and the introduction of a repeating sequence, however, predictability was introduced also. Because practice, in itself, is thought to decrease the attentional demands a given task places upon the subject, and the addition of predictive information similarly reduces attentional demand, the PD patients were hypothesized to benefit from the initial practice and predictability of the information. This benefit should be seen in the similarities between the slopes in the repeating sequences of the first three blocks of trials. Prior research (Bondi & Kaszniak, in press; Heindel, et al., 1989) has shown that nondemented PD patients are equivalent to control subjects with motor tasks that are high in predictability (e.g., pursuit-rotor tracking), at least in the initial phases of learning (cf. Harrington, Haaland, Yeo, & Marder, 1989).

Beginning with the second block of trials (RANDOM2--REPEAT3--REPEAT4), however, differences between the PD patients and the control subjects were predicted because of the shift from predictive to non-predictive information. The cost of this shift in terms of attentional demands was thought to be greater for the PD patients because of their hypothesized deficits in shifting sets (Cools, et al., 1984; Lees & Smith, 1983), again, as a consequence of hypothesized prefrontal cortical dysfunction. This was predicted to be most evident in the second phase of the repeating-sequence blocks, where the PD patients

were predicted to demonstrate a smaller decrease in reaction times from control subjects. The PD patients were thus predicted to exhibit a failure to shift back from the random block of trials (i.e., block 4).

Word Learning (Free Recall, Cued Recall, and Recognition) Explicit memory for the same items across conditions of free recall, cued recall and recognition tasks is desirable in order to address the finding of previous research showing "automatic" versus "effortful" processing differences in PD (Lees & Smith, 1983; Weingartner, Burns, Diebel, & LeWitt, 1984). PD patients have been observed to demonstrate impairment, in comparison to healthy elderly subjects, with more effort-demanding tasks such as free recall.

Materials and Procedure

Sixteen target items were initially presented for study in the following manner. On a page presented to the subject were four words in large, lowercase print. The examiner gave the subject a prompt, which was the superordinate category of one of the four words on the page. For example, if "emerald" was a target item, the examiner instructed the subject to "point to the precious stone." Immediately following correct matching to the superordinate category, the page was taken away, and the subject was asked again to provide the name of the item from the superordinate category specified by the examiner. For example, without the page, the examiner asked "what was the precious stone?" This procedure was repeated in its entirety if the subject did not remember any one of the four target items studied immediately prior to the prompt. This procedure established a 100 percent criterion before free recall was begun. Following establishment of criterion, a 2 minute (minimum) distractor task was administered in which the subject was asked to count backwards from 20. Immediately following the distractor task, the free recall test was given, in which the subject was given two minutes to remember any of the words presented

just a few minutes ago. Any words not remembered during free recall were given cues to assist recall. The cues were the same superordinate categorizations given during study. Following cued recall, recognition was assessed by a random presentation of the 16 target items along with 32 additional distractor items, half of which were semantically related foils.

Hypotheses. Given the previous research on "automatic" versus "effortful" processing differences in PD (Lees & Smith, 1983; Weingartner, et al., 1984), the PD patients were predicted to recall significantly less items upon free recall, than cued recall or recognition, in comparison to normal control subjects.

Tests of Visuoperceptual and Visuoconstructional Skills

Block Design and Picture Arrangement (from the WAIS-R) Administration of standardized behavioral instruments allows for the comparion of our particular patient sample with that of previous studies, allows for the investigation of the relationship between rated symptom severity and psychomotor function, and provides a psychometric marker of performance in a visuoconstructive (block design) and ordering/sequencing (picture arrangement) task. Most recently, Sullivan, et al. (1989) administered the Picture Arrangement (PA) subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) to provide an assessment of set formation (creation of a story line) and cognitive sequencing (manipulation of the order of multiple items to produce the logic of a story-line). Cognitive sequencing was measured by the standard scaled score, and set formation was measured from the tendency of subjects to leave PA story cards in the order presented by the examiner (McFie & Thompson, 1972). Vocabulary subtest scores were used as comparison measures of current intellectual abilities. Results demonstrated that the PD patients had deficient PA but normal Vocabulary test scores whereas AD patients were

impaired on both measures. Further, the deficit in PD was apparent whether or not time was a factor in scoring; nor could the results be explained upon simple visuospatial capacity or motor performance differences between groups, as all patients could distinguish the pictures and manipulate the test cards, and do the first trial correctly.

Materials and Procedure

Administration and scoring of the Block Design (BD) and Picture Arrangement (PA) subtests were according to the Wechsler Adult Intelligence Scale-Revised (WAIS-R) manual (Wechsler, 1981). Please note that, in addition to the standard score, incorrect responses were scored by the method of McFie and Thompson (1972) (as discussed in Sullivan, et al., 1989): for each incorrect response that achieves no credit, "the number of pairs of pictures left (incorrectly) in the presented order" were counted (p. 549). Incomplete performance, that is, completing fewer than all 10 trials, was allowable because according to Wechsler's (1981) instructions, the test is stopped if a subject makes four consecutive failures after trial one. In order to account for the variation in trials across subjects, a corrected score was calculated for each subject as the number of pairs remaining divided by the number of trials attempted. Block Design scores were recorded in standard fashion.

Hypotheses. Both measures were predicted to be significantly lower in PD patients in comparison to demographically-matched normal control subjects because of known psychomotor slowing in PD. However, qualitative differences were expected between the PA and BD subtests, with PD patients performing more poorly than normal control subjects on the PA, but not the BD, subtest because of its presumed reliance on set formation and sequencing abilities, thought to involve prefrontal cortical areas.

Benton Neuropsychologic Tests. Three tasks were selected from the battery of neuropsychologic tests constructed by Benton, deS. Hamsher, Varney, and Spreen (1983); these were designed to test aspects of spatial thinking, and visuoperceptual abilities. Right-Left Discrimination. A 12-item abbreviated version of the Benton Right-Left Discrimination Test (Benton, et al., 1983) was administered to all subjects. The items were made to instruct the subject to point to (1) single lateral body parts on one's own body (e.g., touch left ear), (2) execute double uncrossed commands (e.g., touch your left ear with your left hand), and (3) execute double crossed commands (e.g., touch your left ear with your right hand). Facial Recognition. This test of facial discrimination was selected to provide an index of nonverbal perceptual processing. The 27-item short version of the Benton Facial Recognition Test was designed to provide a matching-to-sample procedure for assessing the capacity to identify and discriminate photographs of unfamiliar human faces. For the first 6 items, subjects were asked to choose the picture, from among six choices, of the same person depicted in the stimulus picture. For items 7-13, subjects were asked to choose the three pictures, from among the six choices, of the same person depicted in the stimulus picture. Visual Form Discrimination. This test was designed as a brief procedure to assess the capacity for visual form discrimination. A 16-item matching-to-sample procedure was presented, and subjects were asked to choose from among four stimulus designs the one which exactly matched the stimulus design.

Hypotheses. PD patients were not expected to differ from control subjects on any of these tasks. None of the tasks were timed, which negated the potential influence of response slowing on performance for PD patients. Also, the documented brain-behavior correlates of these tasks have not been primarily associated with prerolandic damage, but rather implicate both right hemisphere and posterior parieto-occipital functioning.

Mini-Mental State Examination (MMSE). This brief psychometric instrument of cognitive functioning (Folstein, Folstein, & McHugh, 1975) was administered to all subjects selected for inclusion to document the absence of dementia. To be selected for inclusion the subject must have obtained a score of 26 or more on the MMSE, and the individual must not have met the DSM-III-R criteria (American Psychiatric Association, 1987) for dementia.

Table 1. Hypothesized performances of PD patients in comparison to demographically matched elderly control subjects on neuropsychologic tests administered

Task	Hypothesized Performance
Frontally-Related Tasks	
1. Modified Wisconsin Card Sorting Test	Impaired
2. California Sorting Test	Impaired
3. Generative Naming	Impaired
4. Temporal Ordering	Impaired
Tests of Implicit and Explicits Memory	
1. Word Learning (Total Score)	Unimpaired
a. Free Recall	Impaired
b. Cued Recall	Unimpaired
c. Recognition	Unimpaired
2. Fragmented Pictures Test	
a. Skill Learning	Impaired
b. Perceptual Memory	Unimpaired
3. Continuous Recognition Memory	
a. Short Stimulus-Test Intervals (e.g., 1 and 3)	Impaired
b. Long Stimulus-Test Intervals (e.g., 6 and 10)	Unimpaired
Tests of Visuoperceptual and Visuoconstructional Skills	
1. Block Design of the WAIS-R	Impaired
2. Picture Arrangement of the WAIS-R	Impaired
3. Benton Right-Left Discrimination	Unimpaired
4. Benton Visual Form Discrimination	Unimpaired
5. Benton Facial Recognition	Unimpaired

CHAPTER 3

RESULTS

Sample Characteristics

Demographic Characteristics Nineteen patients with PD (13 male, 6 female), and 19 healthy control subjects (7 male, 12 female) participated in the experiments. The groups were matched on the basis of age, sex, education level, and estimated premorbid intelligence (Barona, et al., 1984) as shown in Table 2.

All PD patients underwent a stringent selection process (as specified in the Methods section above), including neurologic examination and medical history, and were given a diagnosis of idiopathic PD. Also, because PD is not a homogeneous disorder (Marsden, 1982), additional information was obtained in order to characterize this particular sample of PD patients: the Mini-Mental State Examination (MMSE) was administered to document the absence of dementia, and disease severity was rated according to the Hoehn and Yahr Clinical Disability Scale (Hoehn & Yahr, 1967). Finally, an estimation of disease duration was established from history.

Table 2 shows the demographic information for both subject groups. Analyses of variance (ANOVA's) were performed on subjects' ages, education levels, and estimated premorbid intelligences, revealing no significant differences between groups on any of these measures [Age: $F < 1$; Education: $F < 1$; Estimated IQ: $F < 1$].

The PD patients exhibited symptom duration ranging from 1 to 17 years, with a median of 8 years. The severity ratings of parkinsonian features were limited to early and middle stages (I, II, and III, Hoehn and Yahr, 1967). Five patients were in Stage I, 9 patients in Stage II, and 5 patients in Stage III. An ANOVA was performed on subjects' MMSE scores (see Table 7), with group as the between subjects factor, revealing no significant differences between PD patients and control subjects [$F\ (1, 36) = 3.36, p =$

.08], thus documenting the absence of dementing illness. At the time of testing, all PD patients were receiving medications.

Analysis of Gender Differences A chi-square analysis was performed on subjects' gender, with a correction for continuity (see Hays, 1981, p. 213). Because gender is a binomial probability and, for purposes of the chi-square analysis, it is treated as if it were continuous, the correction for continuity was used in order to better approximate the normal distribution. Table 2 shows the results of the chi-square analysis with continuity correction, revealing no significant differences between groups [$X^2 = 2.64, p = .10$].

Multivariate Analyses of Overall Group Differences

Before consideration of multivariate analyses, inspection of the variables was done to determine if any were inappropriate for inclusion into the multivariate analyses. Upon inspection it was decided to drop the spatial continuous recognition memory and spatial temporal ordering tasks from any further analyses. While every effort was made to equate complexity and difficulty levels with its verbal counterpart, spatial temporal ordering, in particular, demonstrated overall mean scores for both subject groups approaching chance levels (Control ≈ 16; PD ≈ 15; Chance = 12/24), thus creating floor effects for both groups with this task. Also, serial reaction time was considered to be sufficiently separate conceptually from other tasks to warrant exclusion from any of the multivariate analyses; it was, therefore, examined separately. Finally, performances of PD patients and control subjects on the right-left discrimination task yielded perfect scores. That is, no subject scored other than a perfect score of 12, thus negating its application in any of the statistical procedures (i.e., no variance was associated with this measure).

Before submitting data for multivariate analyses, data reduction procedures were performed on tasks that were composed of multiple variables in order to produce composite

Table 2. Demographic characteristics of Parkinson's disease (PD) patients, and healthy elderly control subjects (Standard deviations are presented in parentheses)

	PD Patients	Control Subjects	F or X^2	p
Subjects	19	19		
Handedness				
Right	18	19		
Left	1	0		
Gender				
Males	13	7		
Females	6	12	$X^2 = 2.64$	n.s.
Age	67.32 (6.85)	69.26 (5.36)	$F < 1$	n.s.
Education	15.26 (2.85)	15.37 (2.54)	$F < 1$	n.s.
Estimated Premorbid IQ	113.71 (4.92)	114.62 (4.75)	$F < 1$	n.s.

scores. For example, the modified WCST produced three variables of interest: categories obtained, errors and perseverations. Because these variables have different numeric scales, each of the variables were first z-transformed and averaged together to derive a single WCST variable [WCST = (categories)(-1) + (errors) + (perseverations) / 3]. The CST provided three variables of interest: percent sorting accuracy, total score, and total perseverations. Variables were z-transformed and averaged together to derive a single CST variable [CST = (percent sorting accuracy)(-1) + (total score) + (total perseverations) / 3]. The six generative naming variables were simply summed together to obtain a single FLUENCY variable for analysis. Finally, the the word learning task yielded three measures: free recall, cued recall, and recognition. These scores were summed to obtain a single LEARN variable. Verbal continuous recognition memory (VCRM), verbal temporal ordering(VTMP), Benton Facial Recognition (FACEREC) and Visual Form Discrimination (VISFORM), Block Design (BD) and Picture Arrangement (PA) of the WAIS-R, and the skill learning (SL) and perceptual memory (PM) scores of the fragmented pictures test all remained unchanged for the multivariate analyses. In sum, 12 variables were submitted for multivariate analysis: 4 frontally-related variables (i.e., WCST, CST, FLUENCY, and VTMP); 4 visuomotor and perceptual variables (i.e., FACEREC, VISFORM, BD, and PA); and 4 learning and memory variables (i.e., VCRM, LEARN, SL, and PM).

A one-way multivariate analysis of variance (MANOVA) was performed on the four dependent variables from each conceptual grouping (frontally-related tests, learning and memory, and visuoperceptual/visuoconstructional skills). Group membership defined the independent variable (control subjects and PD patients). With the use of Pillai's criterion, the combined frontally-related dependent variables were significantly affected by group membership [Pillai's Trace = 0.521; Approximate F (4, 33) = 8.99, $p < .001$]. Similarly, the combined variables of learning and memory were significantly affected by

group membership [Approximate F (4, 33) = 5.29, p = .002], as were the visuoperceptual and visuoconstructional variables [Approximate F (4, 33) = 3.14, p = .027] (see Table 3).

Two additional follow-up MANCOVA's were performed on the four frontally-related variables (see Table 4). Using the four memory-related variables as co-variates in the first analysis (e.g., VCRM, LEARN, SL, and PM), and the four visuoconstructional and perceptually-related variables as co-variates in the second analysis (i.e., FACEREC, VISFORM, BD, and PA), these analyses were performed to test whether the four frontal measures would remain significantly affected by group membership after adjusting for the effects of memory and visuoperceptual operations. With the use of Pillai's criterion, the combined frontal dependent measures (WCST, CST, FLUENCY, and VTMP) were significantly affected by group membership [Pillai's Trace = 0.317; Approximate F (4, 29) = 3.37, p = .022], after adjusting for the effects of the memory-related variables. Similarly, with the use of Pillai's criterion in the second MANCOVA, the combined frontally-related dependent measures (WCST, CST, FLUENCY, and VTMP) were also significantly affected by group membership [Pillai's Trace = 0.358; Approximate F (4, 29) = 4.05, p = .01], after adjusting for the effects of the visuoconstructional and perceptual variables.

Two separate one-way multivariate analyses of covariance (MANCOVA's) followed up these initial analyses (see Table 5). They were used to test whether, after adjusting for the effects of the frontally-related dependent measures (i.e., WCST, CST, FLUENCY, and VTMP), there were any significant group differences in the remaining dependent measures (i.e., memory and visuoperceptual/visuoconstructional operations). The first MANCOVA was performed on four dependent variables that were conceptually grouped together on the basis of visuoperceptual or visuoconstructional tasks: Block Design and Picture Arrangement from the WAIS-R (BD and PA), visual form

Table 3. Multivariate analyses of variance (MANOVA's) comparing performances of Parkinson's disease (PD) patients and healthy elderly control subjects on tests sensitive to frontal system dysfunction, learning and memory, and visuoperceptual/visuoconstructional skills (Standard deviations are presented in parentheses)

Variables	PD Patients (N = 19)	Control Subjects (N = 19)	*F*	*p*
FRONTAL TASKS	X (SD)	X (SD)		
Modified Wisconsin Card Sorting Test°	-0.45 (0.90)	0.45 (0.75)	11.22	.002
California Sorting Test°	-0.35 (0.66)	0.35 (0.50)	13.70	<.001
Generative Naming	70.84 (17.49)	86.16 (17.26)	7.38	.010
Verbal Temporal Ordering	17.63 (3.76)	21.42 (1.71)	15.99	<.001
OVERALL FRONTAL RELATED FUNCTIONING[1]			**8.99**	**<.001**
LEARNING AND MEMORY TASKS				
Verbal Continuous Recognition Memory	39.26 (5.83)	44.16 (2.36)	11.51	.002
Perceptual Memory	0.85 (.36)	1.12 (.53)	3.22	.081
Skill Learning	0.00 (.24)	0.21 (.36)	4.48	.041
Word Learning	61.37 (2.89)	62.53 (1.22)	2.59	.116
OVERALL LEARNING AND MEMORY FUNCTIONING[1]			**5.29**	**.002**
VISUOPERCEPTUAL AND VISUOCONSTRUCTIONAL TASKS				
Block Design	10.26 (2.05)	11.58 (2.63)	2.96	.094
Picture Arrangement	9.74 (2.75)	12.47 (3.08)	8.36	.007
Visual Form Discrimination	29.63 (2.57)	30.47 (1.50)	1.52	.225
Facial Recognition	43.74 (4.84)	47.32 (3.25)	7.16	.011
OVERALL VISUOPERCEPTUAL/ VISUOCONSTRUCTIONAL FUNCTIONING[1]			**3.14**	**.027**

° Mean z-transformed scores based on variables collapsed into a composite score (see text)

[1] Multivariate Analysis of Variance using the four measures in each conceptual grouping

Table 4. Multivariate analyses of covariance (MANCOVA's) comparing performances of Parkinson's disease (PD) patients and healthy elderly control subjects on tests sensitive to frontal system dysfunction, after adjusting for the effects of learning and memory and visuoperceptual/visuoconstructional skills (Standard deviations are presented in parentheses)

Variables	Holding Learning and Memory as Covariates		Holding Visuoperceptual/ Visuoconstructional Skills as Covariates	
FRONTAL TASKS	*F*	*p*	*F*	*p*
Modified Wisconsin Card Sorting Test	2.97	.094	1.98	.170
California Sorting Test	11.37	.002	4.99	.033
Generative Naming	2.13	.115	2.48	.125
Verbal Temporal Ordering	1.27	.268	5.99	.020
OVERALL FRONTAL RELATED FUNCTIONING	**3.37**	**.022**	**4.05**	**.010**

Table 5. Multivariate analyses of covariance (MANCOVA's) comparing performances of Parkinson's disease (PD) patients and healthy elderly control subjects on tests of learning and memory and visuoperceptual/visuoconstructional skills, after adjusting for the effects of frontally-related tasks (Standard deviations are presented in parentheses)

Variables	Holding Frontally-Related Tasks as Covariates	
LEARNING AND MEMORY TASKS	*F*	*p*
Verbal Continuous Recognition Memory	< 1	.362
Skill Learning	< 1	.738
Perceptual Memory	1.24	.275
Word Learning	2.14	.154
OVERALL LEARNING AND MEMORY FUNCTIONING[1]	**1.09**	**.381**
VISUOPERCEPTUAL AND VISUOCONSTRUCTIONAL TASKS		
Block Design	< 1	.673
Picture Arrangement	< 1	.568
Visual Form Discrimination	< 1	.744
Facial Recognition	< 1	.655
OVERALL VISUOPERCEPTUAL/ VISUOCONSTRUCTIONAL FUNCTIONING[1]	**< 1**	**.927**

[1] Multivariate Analyses of Covariance, holding for the effects of frontally-related tasks

discrimination and facial recognition tests from Benton, et al. (1983) (VISFORM, and FACEREC). With the use of Pillai's criterion, the combined dependent variables were not significantly affected by group membership [Pillai's Trace = 0.029; Approximate F (4, 29) < 1, p = .927], after adjusting for the effects of the frontally-related variables.

The second MANCOVA was performed on four dependent variables that were conceptually grouped together on the basis of learning and memory: VCRM, SL and PM components of the fragmented pictures test, and LEARN (a summed score of free-recall, cued-recall and recognition). With the use of Pillai's criterion, the combined dependent variables were not significantly affected by group membership [Pillai's Trace = 0.130; Approximate F (4, 29) = 1.09, p = .381], after adjusting for the effects of the four frontally-related variables (i.e., WCST, CST, FLUENCY, and VTMP).

Post-hoc Analyses of Group Performances on Frontal Lobe-Related Tests

Since the utility of specific tests and subcomponents of these tests were of interest in determining the pattern of neuropsychologic deficits of PD patients, individual tests were examined for descriptive and exploratory purposes.

Controlled Oral Word Association (Generative Naming) Table 6 shows generative naming performances for both groups on each of the six categories, including fruits, animals, words beginning with the letters' "S" and "A", and people's first names beginning with the letters' "M" and "J." One-way analyses of variance (ANOVA's) were performed, revealing PD patients to be impaired for phonemic categories ["S": F (1, 36) = 16.18, p = .0003; "A": F (1, 36) = 11.52, p = .0017], but not for semantic [fruits: F < 1; animals: F (1, 36) = 2.63, p = .11] or proper noun categories [first names beginning with "M": F (1, 36) = 1.38, p = .25; first names beginning with "J": F < 1], compared to normal controls.

With regard to perseverative responses on each of the six generative naming categories, all ANOVA's failed to reveal any significant group differences (p's = .14 to .69).

Modified Wisconsin Card Sorting Test Performances of each group on the modified version of the Wisconsin Card Sorting Test (WCST) are shown in Table 6. One-way ANOVA's were performed on the WCST measures (including categories obtained, errors and perseverations), revealing significant differences between groups on all three of the WCST measures [Categories: F (1, 36) = 10.40, p = .003; Errors: F (1, 36) = 12.61, p = .001; Perseverations: F (1, 36) = 6.25, p = .017].

Fractionation of Problem-Solving Abilities (California Sorting Test) Results of the overall CST performances for each group are shown in Table 6. Total score and total perseverations revealed significant differences between groups [Total Score: F (1, 36) = 8.76, p = .005; Perseverations: F (1, 36) = 10.04, p = .003]. Results for Condition 1 (spontaneous sorting) are shown in Table 7. One-way ANOVA's revealed no significant differences between subject groups in the numbers of attempted sorts (p = .36) or correct sorts (p = .24). The PD patients, however, were impaired relative to control subjects in the percentage of attempted sorts that were correct [F (1, 36) = 8.76, p = .005]. The PD patients were not deficient relative to controls in correctly naming the sorting rules (p = .07). Error analyses revealed that the PD patients provided more perseverative sorts [F (1, 36) = 10.43, p = .003], and perseverative rule names [F (1, 36) = 9.21, p = .005]. The same pattern of results occurred for both the verbal and spatial sorts.

Condition 2 (structured sorting) results are shown in Table 7. Even when the examiner generated the sorts, the PD patients continued to be impaired in correctly naming the sorting rules [F (1, 36) = 5.05, p = .031]. Contrasted with Condition 1, however, the PD patients did not make significantly more perseverative rule names in Condition 2 (p = .65).

Table 6. Neuropsychological performances of Parkinson's disease (PD) Patients, and healthy elderly control subjects on tests sensitive to frontal system dysfunction (Standard deviations are presented in parentheses)

	PD Patients	Control Subjects	*F* (1,36)	*P*
WCST				
Categories	3.42 (1.98)	5.16 (1.26)	10.40	**.003**
Errors	37.37 (12.55)	23.00 (12.39)	12.61	**.001**
Perseverations	13.00 (7.59)	7.00 (7.20)	6.25	**.017**
CST				
Total Score†	78.42 (13.24)	78.79 (9.76)	4.92	**.033**
Total Perseverations•	8.11 (4.33)	3.95 (3.73)	10.04	**.003**
Generative Naming				
Fruits	14.05 (4.14)	14.74 (2.47)	< 1	.540
Animals	14.95 (5.17)	17.90 (6.01)	2.63	.114
"S"	11.05 (4.84)	18.05 (5.85)	16.18	**.0003**
"A"	10.26 (4.12)	15.37 (5.10)	11.52	**.0017**
Names "M"	9.42 (3.10)	10.74 (3.77)	1.38	.247
Names "J"	10.79 (3.46)	11.05 (3.52)	< 1	.818
Verbal Temporal Ordering*	17.63 (3.76)	21.42 (1.71)	15.99	**.0003**

WCST = Wisconsin Card Sorting Test (modified version)
CST = California Sorting Test
† Total score summed across all three sorting conditions (i.e., spontaneous, structured, and cued sorting)
• Total number of perseverations summed across all three sorting conditions
* Number of correct responses (24 points possible)

In Condition 3 (see Table 7), the PD patients were impaired relative to control subjects in sorting the cards according to abstract cues provided by the examiner [F (1, 36) = 6.32, p = .017], thus requiring more concrete cues for correct performance [F (1, 36) = 7.72, p = .009].

Verbal Temporal Ordering The mean scores and standard errors for each of the stimulus-test intervals (i.e., 1-3, 1-6, 1-10, 3-6, 3-10, and 6-10) are shown in Figure 2. One-way ANOVA's were performed on each of these intervals, revealing significant differences between groups on stimulus-test intervals' 1-3, 1-6, 3-10, and 6-10 [1-3: F (1, 36) = 7.70, p = .009; 1-6: F (1, 36) = 7.64, p = .009; 3-10: F (1, 36) = 9.89, p = .003; 6-10: F (1, 36) = 7.11, p = .01], but not on the longest stimulus-test interval of 1-10 [1-10: F (1, 36) = 1.10, p = .30] and the middle interval of 3-6 [3-6: F (1, 36) = 3.52, p = .07].

Post-hoc Analyses of Group Performances on Implicit and Explicit Memory Tests

Fragmented Pictures Test The mean identification threshold scores for both groups on the TRAIN, NEW, and OLD pictures are shown in Table 8. An analysis of variance (ANOVA) was performed on the TRAIN scores, revealing no significant differences between groups on the training identification thresholds [$F < 1$], indicating that subjects' baseline scores were equivalent between groups.

The mean scores for each subject group on the skill learning (SL) and the perceptual memory (PM) scores are shown in Table 9. An ANOVA was performed on each of these composite measures, with groups as the between-subjects factor, revealing a significant difference across subject groups on SL [F (1, 36) = 4.48, p = .041], but not PM [F (1, 36) = 3.22, p = .081].

Table 7. Performances of Parkinson's disease (PD) patients, and healthy elderly control subjects on the California Sorting Test (Standard deviations are presented in parentheses)

Measure	PD Patients	Control Subjects	*F* (1,36)	*P*
Condition 1 (Spontaneously Generating Sorts and Naming Sorting Rules)				
Attempted Sorts	16.21 (4.95)	14.90 (3.78)	< 1	.364
Correct Sorts	11.16 (2.73)	12.16 (2.39)	1.44	.238
% Accuracy of Sorts	71.14 (14.13)	83.17 (10.69)	8.76	**.005**
Correct Rule Naming	8.90 (3.14)	10.58 (2.43)	3.41	.073
Partial Rule Naming	1.63 (1.30)	1.00 (0.82)	3.22	.081
Perseveration of Sorts	4.21 (3.14)	1.68 (1.34)	10.43	**.003**
Persev. of Rule Names	1.53 (1.43)	0.42 (0.69)	9.21	**.005**
Condition 2 (Naming the Rules of Sorts Done by the Examiner)				
Correct Rule Naming	8.53 (2.99)	10.58 (2.63)	5.05	**.031**
Partial Rule Naming	1.11 (0.94)	0.90 (1.10)	< 1	.529
Persev. of Rule Names	2.00 (2.08)	1.63 (2.75)	< 1	.645
Condition 3 (Sorts Done According to Cues Given by the Examiner)				
Abstract Cue	15.47 (2.22)	16.84 (0.83)	6.32	**.017**
Concrete Cue	1.84 (1.30)	0.95 (0.52)	7.72	**.009**

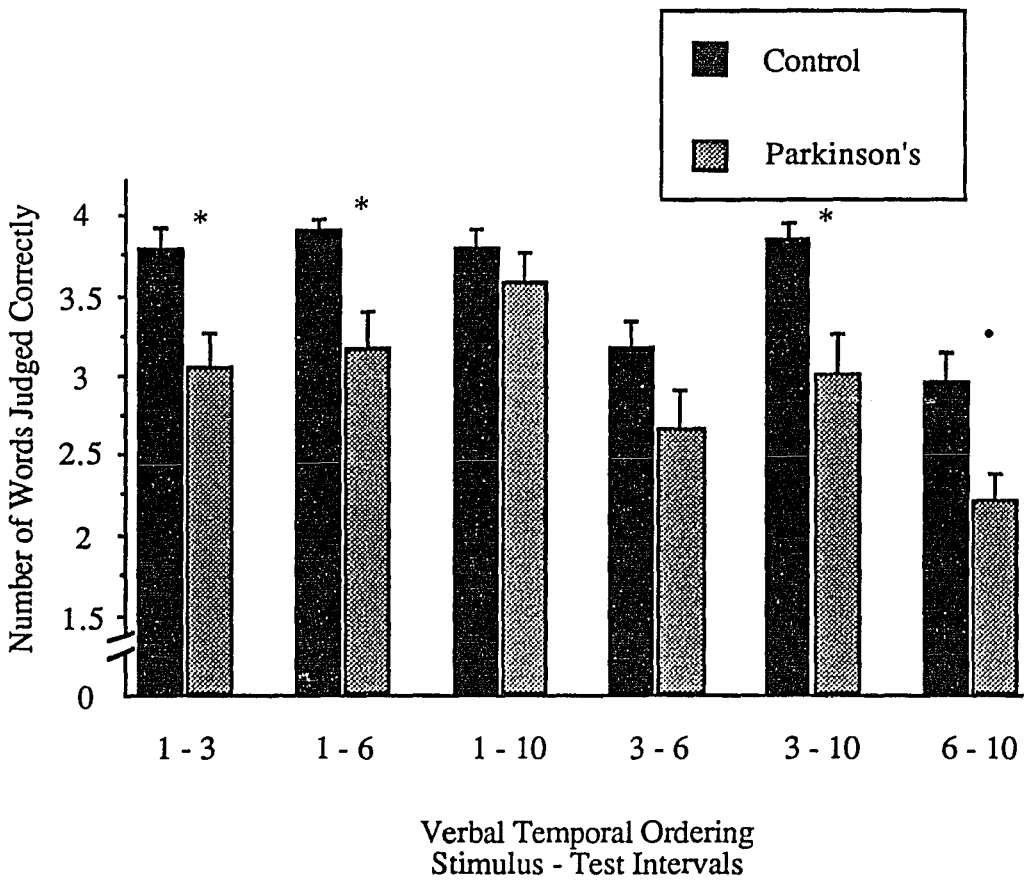


Figure 2. Mean scores of Parkinson's disease (PD) patients and healthy elderly control subjects for each stimulus-test interval (e.g., 1-3, 1-6, 1-10, 3-6, 3-10, and 6-10) on verbal temporal ordering (bars indicate standard error of the mean). Four points were possible with each stimulus-test interval.

Serial Reaction Time Figure 3 shows the performances of both groups on the serial RT task. Mean RT scores were log-transformed to eliminate skewness in the distributions and minimize the magnitude of any outliers in the data. Also, because sphericity violations markedly affect the true Type I error rates and power for the mixed-model tests, and because tests based upon the multivariate analysis of variance (MANOVA) approach are free of sphericity assumptions, a MANOVA was performed on the log-transformed data for repeated measures analysis (see O'Brien & Kaiser, 1985, for discussion). With the use of Pillai's criterion, results of the MANOVA revealed no significant main effect of group (Pillai's Trace = 0.222; Approximate F (6, 31) = 1.47, p = .221), but did reveal a significant group by trial block interaction (F (5, 180) = 2.87, p = .016). Univariate F-tests revealed significant differences between PD patients and control subjects only on trial blocks' 5 and 6 (Block 5: F (1, 36) = 5.30, p = .027; Block 6: F (1, 36) = 4.56, p = .04) (see Table 9 for summary of all post-hoc comparisons, and Table 10 for error rates among the six blocks of trials).

Word Learning (Free Recall, Cued Recall, and Recognition) The mean scores for both subject groups on the free recall, cued recall, and recognition trials of the word learning task are shown in Table 9. ANOVA's were performed on each of these measures, revealing a borderline significant difference between groups on the free recall phase [F (1, 36) = 4.07, p = .051], but no significant differences on either cued recall [F < 1], or recognition [F (1, 36) = 1.69, p = .201].

Because free recall has been observed to be impaired in other clinical studies with nondemented PD patients, there is question as to whether this task may involve frontally-related processes for successful completion (e.g., effortful processing, organizational encoding strategies, active search and retrieval strategies). Thus, inspection of individual subject scores on free recall were compared to the WCST z-scores. It was hypothesized

Table 8. Mean perceptual identification thresholds for the training and test phases of the Fragmented Pictures Test (Standard Deviations are presented in parentheses)

Subject Group	TRAIN	NEW	OLD
Control	5.29 (0.37)	5.08 (0.50)	3.97 (0.54)
PD	5.32 (0.46)	5.32 (0.45)	4.46 (0.59)

Table 9. Performances of Parkinson's disease (PD) patients, and healthy elderly control subjects on Tests of learning and memory (Standard deviations are presented in parentheses)

	PD Patients	Control Subjects	*F* (1, 36)	*p*
Memory for Words				
Free Recall	6.74 (2.49)	8.11 (1.60)	4.07	.051
Cued Recall[%]	87.46 (11.85)	89.24 (12.05)	0.212	.648
Recognition[#]	46.68 (2.16)	47.37 (0.76)	1.69	.201
Verbal Continuous Recognition Memory*	39.26 (5.83)	44.16 (2.36)	11.51	**.002**
Fragmented Pictures°				
Perceptual Memory	0.85 (.36)	1.12 (.53)	3.22	.081
Skill Learning	0.00 (.24)	0.21 (.36)	4.48	**.041**
Serial Reaction Time[†]				
Block 1 (Random)	6.58 (.364)	6.49 (.288)	< 1	.397
Block 2 (Repeat)	6.49 (.435)	6.35 (.275)	1.41	.242
Block 3 (Repeat)	6.44 (.451)	6.25 (.253)	2.53	.120
Block 4 (Random)	6.45 (.361)	6.30 (.243)	2.01	.165
Block 5 (Repeat)	6.37 (.425)	6.12 (.206)	5.30	**.027**
Block 6 (Repeat)	6.37 (.427)	6.12 (.248)	4.56	**.040**

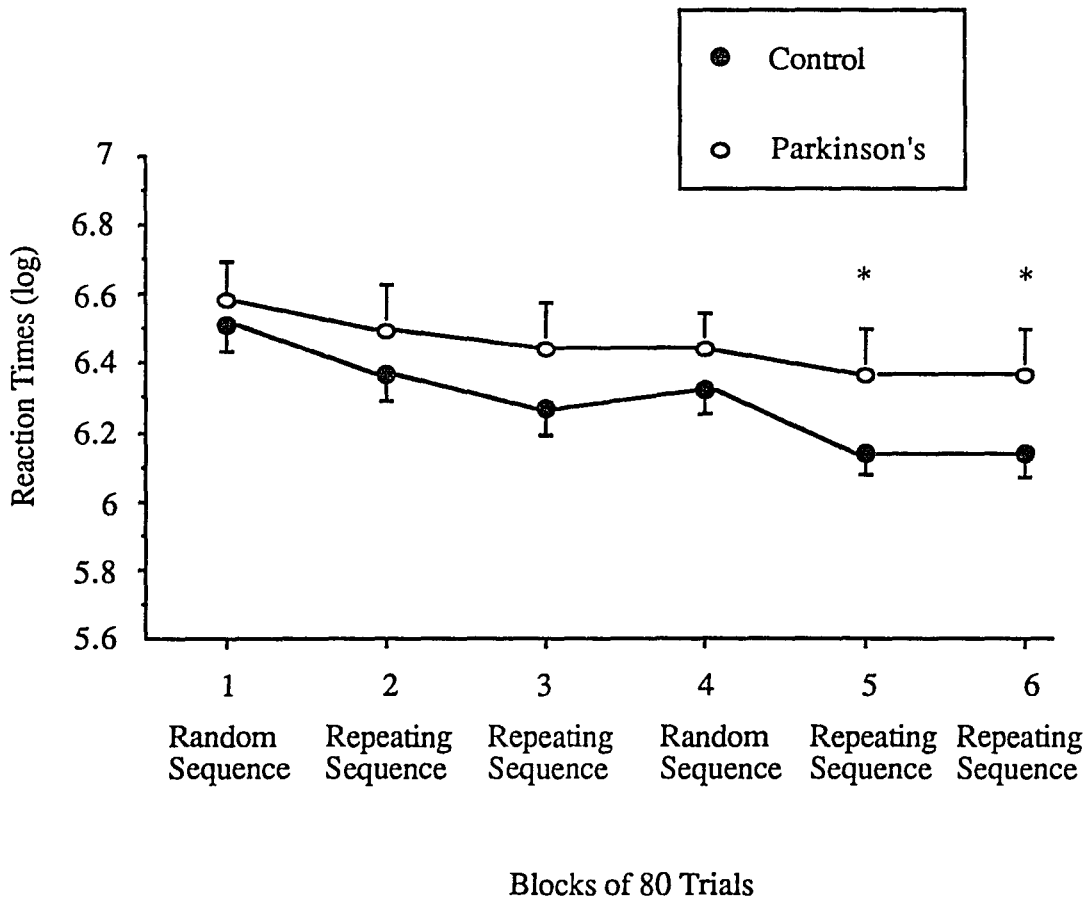
[%] Percentage of correct responses of those items not recalled during free recall

[#] Number of correct responses (48 Points Possible)

* Number of correct responses (48 Points Possible)

° Perceptual Memory = New - Old Perceptual Identification Thresholds
Skill Learning = Train - New Perceptual Identification Thresholds

[†] Log-transformed reaction times (based on 80 trials per block)



* $p < .05$

Figure 3. Log-transformed mean scores of Parkinson's disease (PD) patients and healthy elderly control subjects on each of six blocks of 80 trials on the serial reaction time (RT) task (bars indicate standard error of the mean).

Table 10. Percentage of correct responses on the serial reaction time task for Parkinson's disease patients and healthy elderly control subjects (Standard deviations are presented in parentheses)

	Block					
Group	**1**	**2**	**3**	**4**	**5**	**6**
Parkinson's	94.0 (10.8)	96.8 (3.6)	97.4 (3.2)	97.2 (4.9)	97.6 (3.4)	96.8 (3.6)
Control	99.1 (1.4)	98.9 (2.1)	98.8 (1.8)	98.8 (1.5)	99.3 (1.0)	98.5 (2.0)

that no PD patient who performed poorly on the WCST (i.e., $z \leq -1$) would perform well on free recall, which was defined as one standard deviation above the mean score for control subjects ($X = 8.1$, $SD = 1.6$; cutoff ≥ 9.7). Inspection of the PD patients free recall scores revealed this to be true: no PD patient who performed poorly on WCST performed well on free recall. Similar comparisons were made with the remaining three frontally-related tasks (CST, FLUENCY, and VTMP). Inspection of the PD patients' free recall scores revealed that no PD patient who performed poorly on either FLUENCY (i.e., cutoff ≤ 69) or VTMP (i.e., cutoff ≤ 19) performed well on free recall; only one PD patient who performed poorly on CST (i.e., $z \leq -1$) performed well on free recall, suggesting that consistency between poor free recall and tasks of frontally-related processes may be related to similar dysfunctional systems.

Verbal Continuous Recognition Memory The mean scores and standard deviations for each of the stimulus-test intervals (i.e., 1, 3, 6, and 10) are shown in Figure 4. ANOVA's were performed on each of these intervals, revealing significant differences between groups on stimulus-test intervals' 1, 3, and 6 [1: F (1, 36) = 9.34, p = .004; 3: F (1, 36) = 8.90, p = .005; 6: F (1, 36) = 7.48, p = .01], but not on the longest stimulus-test interval of 10 [10: F (1, 36) = 2.89, p = .10].

Post-hoc Analyses on Tests of Visuoperceptual and Visuoconstructional Skills

Block Design (from the WAIS-R) An ANOVA was performed on subjects' age-corrected scaled scores on the Block Design subtest, revealing no significant differences between groups on this task [F (1, 36) = 2.96, p = .094], as shown in Table 11.

Picture Arrangement (from the WAIS-R) In order to estimate performance on a task assessing cognitive sequencing, an ANOVA was performed on subjects' age-corrected scaled scores on the Picture Arrangement subtest, revealing a significant difference between

groups on this task [F (1, 36) = 8.36, p = .007], as shown in Table 11. Set formation was measured by the tendency of subjects to leave PA story cards in the order presented by the examiner (cf. McFie & Thompson, 1972). ANOVA revealed that PD patients left significantly more cards incorrectly in the presented order than control subjects [F (1, 36) = 6.85, p = .013].

Because PA has been observed to be impaired in other clinical studies with nondemented PD patients (cf. Sullivan, et al., 1989), there is question as to whether this task may involve frontally-related processes for successful completion (e.g., set formation, sequencing). Thus, inspection of individual subject scores on PA were compared to the WCST z-scores. It was hypothesized that no PD patient who performed poorly on the WCST variable (i.e., $z \leq -1$) would perform well on PA, which was defined as one standard deviation above the mean age-corrected scaled score (X = 10, SD = 3; cutoff $\geq$ 13). Inspection of the PD patients age-corrected scaled scores on PA revealed this to be true: no PD patient who performed poorly on WCST performed well on PA. Similar comparisons were made with the remaining three frontally-related tasks (CST, FLUENCY, and VTMP). Inspection of the PD patients' age-corrected scaled scores on PA revealed that no PD patient who performed poorly on either CST (i.e., $z \leq -1$) or VTMP (i.e., cutoff $\leq$ 19) performed well on PA; only two PD patients who performed poorly on FLUENCY (i.e., cutoff $\leq$ 69) performed well on PA. These results suggest that PA may be related to similar dysfunctional processes as the frontally-related tasks.

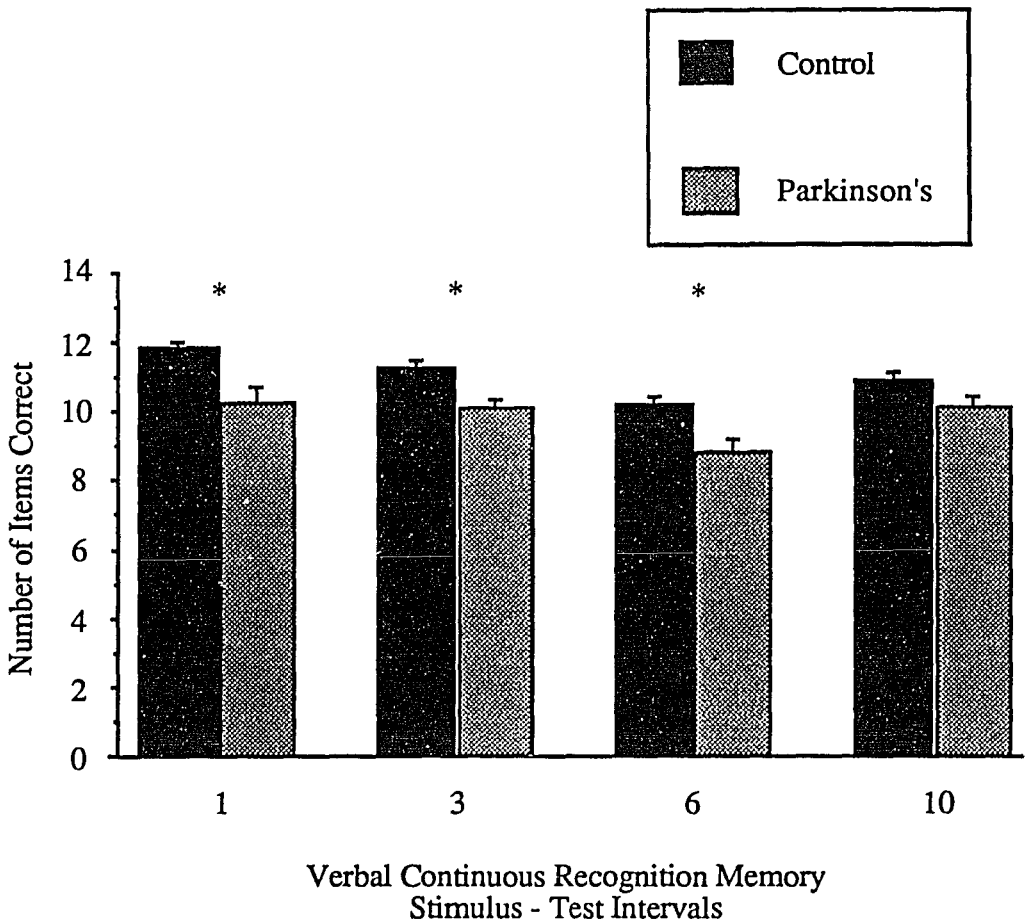
Benton Facial Recognition Test An ANOVA was performed on subjects' age- and education-corrected scores on the Benton Facial Recognition Test, revealing a significant difference between groups on this task [F (1, 36) = 7.16, p = .011], as shown in Table 11. PD patients' mean score (43.74; SD = 4.84), however, falls into the normative range

of scores (i.e., 43-46) (see Benton, deS. Hamsher, Varney, and Spreen, 1983), with only 3 PD patients obtaining defective scores (i.e., < 39) of 36, 38, and 38.

Benton Visual Form Discrimination Test An ANOVA was performed on subjects' scores on the Benton Visual Form Discrimination Test, revealing no significant differences between groups on this task [F (1, 36) = 1.52, p = .225], as shown in Table 11.

Medication-Related Effects On Neuropsychologic Test Performances

At the time of testing, all PD patients were receiving medications. To explore the possibility of medication effects upon the cognitive abilities of this sample of PD patients, a one-way multivariate analysis of variance (MANOVA) was performed comparing performances of PD patients taking dopamine agonists only (n = 9) to PD patients taking a combination of dopamine agonists, anticholinergic and/or psychoactive drugs (n = 10) on all 12 dependent measures used in the multivariate analyses. Results indicated no significant differences between groups [Pillai's Trace = 0.810; Approximate F (12, 6) = 2.13, p = .181]. Follow-up MANOVA's were independently performed on the four variables from each conceptual grouping (i.e., frontally-related tasks, tests of learning and memory, and visuomotor and perceptual skills). Results revealed no significant differences between the two medication groups on the frontally-related tasks [Pillai's Trace = 0.224; Approximate F (4, 14) = 1.01, p = .435], but did reveal significant differences for tests of learning and memory [Pillai's Trace = 0.604; Approximate F (4, 14) = 5.34, p = .008] and visuomotor and perceptual skills [Pillai's Trace = 0.526; Approximate F (4, 14) = 3.88, p = .025] (see Table 11).



$* p < .05$

Figure 4. Mean scores of Parkinson's disease (PD) patients and healthy elderly control subjects for each stimulus-test interval (e.g., 1, 3, 6, and 10) on verbal continuous recognition memory (bars indicate standard error of the mean). Twelve points were possible with each stimulus-test interval.

Table 11. Psychometric characteristics of Parkinson's disease (PD) patients, and healthy elderly control subjects (Standard deviations are presented in parentheses)

	PD Patients	Control Subjects	*F* (1,36)	*p*
MMSE	28.79 (0.98)	29.26 (0.56)	3.36	.075
Block Design• (WAIS-R)	10.26 (2.05)	11.58 (2.63)	2.96	.094
Picture Arrangement• (WAIS-R)	9.74 (2.75)	12.47 (3.08)	8.36	**.007**
Visual Form Discrimination*	29.63 (2.57)	30.47 (1.50)	1.52	.225
Facial Recognition*	43.74 (4.84)	47.32 (3.25)	7.16	**.011**
Right-Left Discrimination*	12.0 (0.0)	12.0 (0.0)	n/a	n/a

MMSE = Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975)
• Age-corrected scaled scores
* Benton, et al., 1983

Table 11. Multivariate analyses of variance (MANOVA's) comparing performances of Parkinson's disease (PD) patients taking dopamine agonists only (Subgroup 1) to PD patients taking a combination of dopamine agonists, anticholinergic and/or psychoactive drugs (Subgroup 2) on tests sensitive to frontal system dysfunction, learning and memory, and visuoperceptual/visuoconstructional skills (Standard deviations are presented in parentheses)

Variables	Subgroup 1 (N = 9)	Subgroup2 (N = 10)	*F*	*p*
FRONTAL TASKS	X (SD)	X (SD)		
Modified Wisconsin Card Sorting Test°	-0.63 (0.98)	-0.29 (0.83)	< 1	.417
California Sorting Test°	-0.22 (0.68)	-0.47 (0.66)	< 1	.438
Generative Naming	63.78 (9.08)	77.20 (21.07)	3.12	.096
Verbal Temporal Ordering	17.67 (4.15)	17.6 (3.60)	< 1	.971
OVERALL MEDICATION EFFECTS ON FRONTAL RELATED FUNCTIONING[1]			**1.01**	**.435**
LEARNING AND MEMORY TASKS				
Verbal Continuous Recognition Memory	38.78 (7.24)	39.70 (4.57)	< 1	.741
Perceptual Memory	1.02 (.326)	0.71 (.327)	4.22	.056
Skill Learning	0.04 (.267)	-0.03 (.231)	< 1	.547
Word Learning	59.78 (3.03)	62.80 (1.93)	6.86	.018
OVERALL MEDICATION EFFECTS ON LEARNING AND MEMORY FUNCTIONING[1]			**5.34**	**.008**
VISUOPERCEPTUAL AND VISUOCONSTRUCTIONAL TASKS				
Block Design	9.89 (1.97)	10.60 (2.17)	< 1	.466
Picture Arrangement	9.89 (2.62)	9.60 (2.99)	< 1	.826
Visual Form Discrimination	28.89 (3.14)	30.30 (1.83)	1.47	.242
Facial Recognition	46.89 (4.73)	40.90 (2.85)	11.47	.004
OVERALL MEDICATION EFFECTS ON VISUOPERCEPTUAL/VISUOCONSTRUCTIONAL SKILLS[1]			**3.88**	**.025**
OVERALL MEDICATION EFFECTS[2]			**2.13**	**.181**

° Mean z-transformed scores based on variables collapsed into a composite variable

[1] Multivariate Analyses of Variance using the 4 measures from each conceptual grouping

[2] Multivariate Analysis of Variance using all 12 measures (4 from each conceptual group)

CHAPTER 4

DISCUSSION

The "Complex" Loop Hypothesis of Subcortical Deafferentation of the Frontal Lobes

The major question examined in this study was whether disturbed striatal functioning in Parkinson's disease would manifest in a cluster of circumscribed deficits on neuropsychologic tasks thought to be sensitive to functioning of the frontal lobes, which are the cortical destination of efferent caudate nucleus circuitry (see Taylor, et al., 1986, for discussion). With respect to the four tasks chosen because of their prior demonstrated sensitivity to frontal lobe damage, impairments were observed in PD patients on each of these tasks.

The impaired performance of PD patients on a modified version of the WCST is strongly suggestive of frontal system dysfunction in this sample, given the consistent and extensive findings of patients with lesions of the frontal lobes of varying etiologies showing impairment with the WCST (Drewe, 1974; Milner, 1963; Robinson, Heaton, Lehman, & Stilson, 1980). The present results are consistent with those of previous studies employing the WCST with PD patients (Bowen, et al., 1976; Lees & Smith, 1983; Taylor, et al., 1986). Similarly, deficits in temporal ordering have been observed in patients with frontal lesions (Milner, 1971, 1974; Squire, 1982) and PD patients (Sagar, et al., 1988), and were demonstrated in this sample of PD patients as well. Impaired generative naming has also been demonstrated with frontal lobe damage, particularly the left frontal lobe anterior to Broca's area (Area 44) (Milner, 1975; Ramier & Hécaen, 1970; Tow, 1955), and in other studies with PD patients (Lees & Smith, 1983). Finally, the present sample of PD patients showed impairments on the CST. Prior research has demonstrated its sensitivity to frontal lobe lesions (Delis, et al., 1990).

The frontal system hypothesis was strengthened when considering additional neuropsychologic tasks which implicated other cortical regions such as the occipital, parietal and temporal lobes. Extensive testing of visuoperceptual, visuoconstructional, memory, and motor skills were completed toward this end, with PD patients showing no generalized deficits in these domains. Through multivariate analyses, mean vectors of visuoconstructive and perceptual variables and memory-related measures, after adjusting for the effects of the frontally-related dependent measures, failed to demonstrate significant differences between groups. The frontally-related measures, however, retained significant differences, demonstrating selective impairments on frontal lobe tests for the PD patients, after adjusting for the effects of either the visuoconstructive and perceptual measures, or the memory-related measures.

In total, these findings suggest relatively circumscribed deficits on neuropsychologic tasks implicating frontal system dysfunction in the absence of generalized or pervasive cognitive deficits in other domains such as learning and memory, visuoperceptual and visuoconstructional skills, or simple motor skills. Further, primary movement disorder or visual impairments cannot properly explain the pattern of impairments found in the present experiments. Timed, speeded tasks such as block design and serial reaction time did not evidence generalized impairments solely attributable to motor dysfunction. Simple visuoperceptual tasks, such as visual form discrimination, were unimpaired, as were perceptual identification thresholds for the training set of the fragmented pictures test. Finally, memory was not impaired across tasks, but was deficient only on those tasks (e.g., free recall, continuous recognition memory for short stimulus-test intervals, skill learning component of the fragmented pictures test) which rely on self-directed planning and efficient organizational strategies for successful completion, presumably operations of the prefrontal cortex.

Comparisons With Other Studies

The present study replicated and extended the findings of previous investigations (cf. Bowen, et al., 1976; Lees & Smith, 1983; Taylor, et al., 1986) using the original version of the WCST, demonstrating similar deficits in nondemented PD patients with a modified version of the WCST. Despite the modifications of the sorting procedures (e.g., using only 72 unambiguous cards), PD patients failed to benefit from this apparent simplification of the test.

With regard to generative naming in PD, previous studies have demonstrated both findings of intact (Gainotti, et al., 1980; Taylor, et al., 1986) and impaired performance (Lees & Smith, 1983). Lees and Smith confined their patient sample to the earliest and untreated stages of PD; thus no generalized cognitive deficits were noted. Taylor and colleagues proposed that the intact generative naming performance of their sample was compatible with the outflow model when considering the massive corticocortical support the frontal region receives in the processing of familiar, structured and rule-bound behavior (p. 877). Interestingly, the deficits observed in the present study were not pervasive across semantic, phonemic or proper name categories, but were exclusive to the two phonemic categories (i.e., words beginning with the letter's "S" and "A"). Recent research has shown a dissociation between semantic and phonemic categories in patients with Alzheimer's disease (AD) (Salmon, Heindel, & Butters, in press). AD patients have demonstrated greater impairments with semantic category naming than with phonemic category naming. Results obtained in the present experiment found the opposite relationship between categories (i.e., poor letter fluency vs. intact semantic category fluency), and suggests that varying neurologic etiologies may contribute to the differential impairments of phonemic and category fluency. Direct comparisons between neurologic

groups will be necessary to examine potential double dissociations in performance on fluency tasks.

Also, the differences between phonemic and semantic categories in the present study suggests that generative naming performance in PD may be dependent upon the degree to which specifications of a task constrain response selection (cf., Nissen, et al., 1989). Semantic and proper-noun category generative naming (e.g., "animals," and first names beginning with the letter "M") appear to provide considerably more constraints with regard to response selection than letter categories (e.g., words beginning with the letter "S"). Given the greater degree of freedom with which to respond to items, PD patients may not be able to generate internally-guided, efficient organizational strategies for generation of exemplars within such phonemic categories.

With regard to temporal ordering, Sagar, et al. (1988) demonstrated that PD patients were disproportionately impaired in recency discrimination relative to content recognition, and showed deficits in content recognition only at the short stimulus-test intervals (e.g., 1 and 3). Results of the present study showed that verbal temporal ordering in PD patients was impaired in four of six stimulus-test intervals, and that verbal continuous recognition memory was impaired in three of four stimulus-test intervals, in comparison to controls. These results suggest more pervasive difficulty with both tasks than would be expected, given the findings of Sagar, et al. However, the pattern of deficits generally adhere to those found by Sagar and colleagues. That is, the longest stimulus-test interval for content recognition (i.e., 10) was unimpaired, while intervals' 1 and 3 were impaired, findings equivalent to Sagar, et al. The only discrepancy was for the interval of 6, in which the PD patients in the present study showed deficits, whereas the PD group of Sagar, et al. did not. It should be noted that 3 of the PD patients in the Sagar, et al. study fulfilled DSM-III criteria for dementia, and thus direct comparisons with the present study

are problematic. However, exclusion of the 3 demented PD patients did not alter the qualitative differences between groups (see Sagar, et al., 1989, p. 530). Finally, modification of the content recognition and recency discrimination paradigms in the present study may also account for some discrepancy between results. The use of 60 nouns in the present study is significantly less than the 493 nouns used in the Sagar, et al. study. Further, the two tasks (i.e., temporal ordering and recognition) were separated in the present study (see Method), and ran as independent tests. Sagar and colleagues combined recency discrimination and content recognition prompts within the same test. Nonetheless, results of the present study generally conform to those of Sagar, et al. (1989), suggesting that recency discrimination deficits and impaired short-term memory processing are specific cognitive deficits in PD and may be linked to subcortical deafferentation of the frontal lobes.

While no direct comparisons with previous studies are possible in PD patients' performance on the CST, the one study conducted by Delis, et al. (1989) highlight its sensitivity to differentiating frontal lesion patients from control subjects. As this test was designed to fractionate specific components of problem-solving abilities, the findings of the present study suggest that frontal damage disrupts several components of problem-solving functions, and closely mirror the results of the Delis, et al. study. Frontal lesion patients in the Delis, et al. study were impaired in generating accurate sorts relative to the number of attempted sorts, and in verbalizing the rules of both spontaneous sorts and sorts done by the examiner. The PD patients in the present experiment were similarly impaired in generating accurate sorts relative to the number of sorts attempted, and were deficient relative to normals in correctly naming the sorting rules of sorts done by the examiner, but not in verbalizing the rules of spontaneous sorts in Condition 1 (free sorting). These findings are consistent with reports of deficient set formation and abstraction abilities

following frontal lesions (Robinson, et al., 1980; Heaton, 1981; Taylor, et al., 1986). In addition, both the frontal lesion patients of Delis, et al. and the PD patients in the present study perseverated more sorts and rule names than normal subjects; these results implicate problems in cognitive flexibility. Both groups were also impaired in generating sorts according to abstract cues provided by the examiner. Delis, et al. regard this as indicative of a deficient use of information to organize and govern their responses.

Delis, et al. further discuss that an unexpected finding was that frontal patients displayed normal performance in the number of attempted sorts, as did the PD patients in the present study. This result suggests that the hypothesis of impaired initiation following frontal pathology was unsupported. Correct verbalizations of sorting principles on the WCST, in the face of continued sorting errors, has been amply demonstrated in frontal lesion patients, and mentioned in reference to PD patients also (Taylor, et al., 1986). This phenomenon suggests preserved set formation coupled with impaired use of the abstract principles to govern behavior, and has been referred to as the dissociation between knowing and doing (see Stuss & Benson, 1984, for discussion). Current findings provide partial support for this hypothesis, as when PD patients were provided instructions by the examiner on how to sort the cards, they nonetheless showed deficient sorting compared to controls. However, Delis et al. found that in addition to this deficit frontal patients were also impaired in identifying and verbalizing the sorting principles, even for sorts done by the examiner, a result consistent with the PD patients. Taken together, findings are consistent with Delis, et al. suggesting that frontal patients and PD patients are impaired in *both* set formation and in using knowledge to regulate their behavior. This conclusion is consistent with the follow-up analysis of the Picture Arrangement subtest of the WAIS-R, implying impaired set formation--as indexed by a greater number of story cards left in the same order initially presented to PD patients.

Delis, et al. offer explanations why frontal patients may be able to identify the sorting principles on the WCST but not on the CST, suggesting that they differ in the number of possible sorts and their degree of difficulty. The WCST involves only three possible sorts that are over-learned, and relatively simple rules (i.e., color, shape, and number). The CST, on the other hand, involves 18 possible correct sorts across the three sets of cards, and the sorting principles vary considerably in their difficulty level. They argue that the multiple stimulus properties on their cards may have been a factor in impeding the frontal patients in selectively attending to and discriminating relevant from irrelevant dimensions.

With regard to learning and memory, this sample of PD patients was very similar in performance to those of previous investigations (i.e., Taylor, et al., 1986; Weingartner, et al., 1984) noting a greater difficulty with the more effort-demanding free recall paradigm than with cued-recall or recognition procedures. Also, similarities exist across other studies in which memory function was assessed with immediate and delayed recall trials. Immediate recall of the Wechsler Memory Scale (WMS), for example, was impaired in the sample of PD patients studied by Taylor, et al. (1986). Delayed recall, however, was unimpaired, and even showed improvement over delay. The impaired memory process for PD patients appeared to be with processing or encoding of information units, as their recall of information improved following a consolidation period. Taylor, et al. postulate that PD patients might have displayed no deficit in the immediate phase of the WMS if the rate of information being conveyed were decreased in its pace. Certainly, the continuous recognition memory paradigm (see above) presented material at a fast pace (one word every 3 seconds), and likely exceeded the PD patients' processing rate for retrieval of this material following short delays. Long delays between stimulus presentation and recognition prompting, however, allowed for periods of consolidation, and aided the PD

patients' performance. Therefore, slowed processing of information-to-be-remembered may account for these findings across different tasks, and would be consistent with the frequently described bradyphrenia of PD.

Bradyphrenia or slowed cognitive processing, however, is controversial in studies of PD. One study, for example, demonstrated slowed mentation in the context of preserved accuracy in older PD patients when scanning verbal material (Wilson, Kaszniak, Klawans, & Garron, 1980). Comparisons were made between young and old PD patients, and demographically-matched control subjects. Scanning time for the older PD patients was significantly greater than for either the younger PD patients or control subjects, as measured by the increased slope of reaction times with increasing set size (employing the Sternberg paradigm; Sternberg, 1966). Neither laterality of parkinsonian symptoms nor severity of parkinsonian disability were investigated in this study, although the latter may have been implicated by subgrouping the PD sample by age. In another study, Rafal, Posner, Walker, and Friedrich (1984) concluded that bradyphrenia is not a feature associated with PD. They investigated PD patients in the "on" and "off" phases of their medication periods, again with the Sternberg paradigm. They found no significant differences in performance between patients in the "on" versus the "off" phase, suggesting that a slowed rate of information processing is not a feature of parkinsonian severity, as would be expected. Taylor, et al. suggest that their own findings with the WMS are consistent with the notion of bradyphrenia in their sample of PD patients. They, however, caution that none of the tasks within their experiments were designed to include an appropriate or direct measure of of bradyphrenia (reaction time), and state that results are merely suggestive of this phenomenon (see Taylor, et al., 1986, p. 867, for discussion). Similarly, none of the tasks in the current study were specifically designed to test bradyphrenia, including the serial reaction time task.

With regard to visuoperceptual functioning, an interesting dissociation in performance was exhibited; PD patients showed intact performance on visual form discrimination but impaired performance on a test of facial recognition. A factor potentially contributing to this dissociation may be that, given evidence of oculomotor abnormalities in PD (White, et al., 1983), greater difficulty in successful visual search strategies is more likely with increasing visual complexity. While both tasks involve a matching-to-sample format, facial recognition appears more visually complex. Subtle differences in facial features, light-shadow distinctions, alterations in facial expressions, and matching side-views with front-views all speak to a greater degree of difficulty than simple visual form discriminations of geometric figures. Such differences imply a greater need to abstract visual information beyond the simple visual form, and infer continuity of facial features despite differences in expressions and the presence of shadows.

Another visually-related task requiring inferential processing of stimuli includes the fragmented pictures test. In particular, the skill learning measure can be thought of as indexing the ability to acquire novel strategies for improving performance across trials with visually-degraded stimuli. Again, inferring patterns in the visual array, focusing upon important details, and abstracting forms beyond what is visably present, all imply processes beyond simple form recognition. PD patients did not appear able to benefit from such practice with novel items, yet appeared to be aided with repetition of the previously presented picture fragments, inferring that memory processes facilitated their performance to essentially equivalent levels of accuracy as controls. The PD patients' impairments in the skill learning component of the fragmented pictures test, thus, supported the hypothesis that the neostriatum, vis-a-vis the "complex" loop (Alexander, et al., 1986), may be essential to certain types of skill acquisition, particularly those operations necessarily involved in more purely cognitive operations. These results are consistent with previous

reports of priming and motor skill learning in AD and nondemented PD patients (cf., Heindel, et al., 1989; Eslinger & Damasio, 1986), and support the conclusion that different forms of implicit memory may be dependent upon distinct neuroanatomic systems.

Finally, PD patients' performance on the Serial Reaction Time task revealed no overall group differences, but impaired performance relative to controls only on trial blocks' 5 and 6. This result is suggestive of deficient skill learning of the repeating sequence of trials. PD patients appeared unable to benefit from repeated practice only during the final phase of the task. They showed equivalent acquisition initially, as noted by their decrease in mean RT's across the first three trial blocks. Also, visual inspection and comparison between the two random blocks of trials (i.e., blocks' 1 and 4) showed that PD patients improved performance. Only following a shift to repeating trial blocks back from the second random trial block did PD patients show deficient performance. Results are suggestive of a failure to shift sets, a result which is consistent across a wide range of tasks in the present experiments (e.g., WCST, CST, PA). However, a competing hypothesis that may account for these results is that a lag in the speed of acquiring the repeating pattern may have existed for the PD patients; a result, again, that suggests the possibility of bradyphrenia. Unfortunately, differentiation as to which of these hypotheses better explains the current results, or the possibility of a combination of the two processes, cannot be ascertained at this time. Further work is needed, and may include systematically varying the inter-block intervals, and increasing the frequency of set-shifting possibilities in this paradigm to better delineate such potential contributions to the PD patients' deficits in serial reaction time.

Limitations and Future Directions

One of the major limitations of this study surrounds the generalizability of these results to the overall study of PD. That is, the current sample of patients is not necessarily representative of PD, *per se*. Patients were selected without general cognitive decline, in efforts to hypothetically control and limit the foci of neuropathology to striatal structures. Other studies demonstrating pervasive and global decline in function may not have utilized stringent selection procedures, thereby creating a more representative sample of PD patients, and thus creating more representative neurobehavioral profiles of PD.

Also, although no formal assessment of depression was undertaken, it is likely that PD patients had higher levels of depressive symptoms, given its increased prevalence in the disease. Depression in non-neurologically impaired individuals has been shown to affect a variety of neuropsychologic measures, including learning and memory. The more effort-demanding free recall task, for example, has been shown to be adversely affected by depression, compared with recognition memory (Weingartner, 1986). Given that the PD patients showed a borderline impairment in free recall in the present study, what contribution might depression have had in their performances? Further, can any of the other results be sufficiently explained by depression? While not directly addressing this question, the most general evidence arguing against its significantly affecting other performances comes from the MMSE. Research has shown MMSE scores to be lowered in depression, compared with normal control subjects (Folstein, Folstein, & McHugh, 1979). This sample of PD patients, however, was not significantly lower than their controls on MMSE scores, suggesting that, if they are significantly more depressed than their normal counterparts, they are not globally affected cognitively. Nonetheless,

additional studies should help to define the relative contributions of depression severity and duration to cognitive processes in PD.

With regard to statistical considerations, these analyses must be considered to be very preliminary evidence suggesting differential impairments on frontally-related neuropsychologic tasks, given the small size of the samples. What the analyses do provide, however, is a consistent neuropsychologic profile and speculation regarding the functional deficits following striatal damage in PD. Also, the presence of outliers affecting the multivariate analyses was investigated. Six individual data points were found to be between 3 and 4 standard deviations from mean values for the 12 dependent measures used in the multivariate analyses. All multivariate analyses performed in these experiments were re-run with those 6 outlier data points excluded, with no differences noted in the trends of the analyses; the outliers did not change any of the pattern of results. Thus, the outliers were not considered to be of consequence, and were left in for the multivariate analyses.

From a functional/anatomic standpoint, specific foci of neuropathology or regional dysfunction can only be inferred from available knowledge of such sequelae in PD. Further work utilizing *in vivo* techniques of regional cerebral blood flow (rCBF) or regional metabolism measures (e.g., Positron Emission Tomography or Single Photon Emission Computed Tomography scans) will help establish functional correlates to the specific cognitive changes in PD noted by these and other experiments. Neuroimaging procedures (e.g. Magnetic Resonance Imaging or Computed Tomography scans) may prove less useful in providing *in vivo* correlative relationships to neuropsychologic data in PD, since the majority of neuropathologic changes are biochemical, and not structural (with the exception of the substantia nigra). Thus, specific structural abnormalities in brain regions such as the caudate nucleus, putamen, globus pallidus, prefrontal cortex, and others, would not be expected.

CHAPTER 5

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