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DEMENTIA IN PARKINSON'S DISEASE: A NEUROPSYCHOLOGICAL
ANALYSIS

by

Lorraine McFadden, M.A.

A thesis submitted to
the Faculty of Graduate Studies and Research
in partial fulfilment of
the requirements for the degree of

Doctor of Philosophy

Department of Psychology

Carleton University

Ottawa, Ontario

January 29, 1993

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**The undersigned hereby recommend to
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**"DEMENTIA IN PARKINSON'S DISEASE:
A NEUROPSYCHOLOGICAL ANALYSIS"**

**submitted by
LORRAINE MCFADDEN, B.A., M.A.**

**in partial fulfilment of the requirements
for the degree of Doctor of Philosophy**

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1 Abstract

Separate studies have described dementia of Parkinson's Disease (PD) as including neuropsychological deficits in memory, executive function, and visuospatial skills. However, it is not known to what extent, if at all, the neuropsychological profile in PD dementia represents a more severe form of the mild cognitive deficits seen in nondemented PD patients. If the pattern of demented patients matches that of the nondemented, in all respects except degree of impairment, then it can be argued that dementia represents a progression of the nondemented state. If dementia is not a simple progression of the deficits of the nondemented state, one or more other processes might be at work, likely involving multiple pathogenetic cascades. These issues have implications for research both into the pathogenesis of, as well as treatment for, Parkinsonian dementia. To address these questions, 23 demented Parkinson's disease patients were tested in multiple cognitive domains and compared to 23 nondemented PD patients, and 23 normal controls. Results were analyzed in terms of differences between groups as well as heterogeneity within the dementia group. The PD demented, PD nondemented, and normal controls groups all had unique neuropsychological profiles. The demented PD group was significantly impaired,

compared to both the nondemented group and the normal controls, on all measures, including global intellect, memory, visuospatial, language, attention, and executive functions, with the sole exception of long term memory. Relative deficits, compared to controls, in the nondemented patient group were restricted to episodic memory and visuospatial skills. The memory deficit of the nondemented group, however, was as great as that found in the demented group. A cluster analysis of the demented group identified three neuropsychologically distinct subgroups. Since length of disease, age, and motor status failed to differentiate these clusters it is likely that these are not different disease stages, but rather neuropsychologically distinct subgroups of dementia in Parkinson's disease. Therefore, these findings suggest that dementia in PD is not a simple progression of cognitive deficits, but a separate and distinct process. Current results suggest the presence of three different neuropsychological profiles in this sample.

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This study was done within a context of ongoing projects, as one element in an active and industrious research laboratory. As is usually the case in such situations, individuals end up sharing ideas, time, help, computer expertise, and serendipitous moments. I am indebted to Grace Newman, for never dropping a stitch. In the early, tentative, stages Ilene Rusk was always supportive and encouraging. I shall never forget Scot Purdon's outrageous and heartening non sequiturs. Amanda George knew everybody and everything at the Ottawa Civic Hospital, and always knew who to call. Denise Walker set the precedent of a well crafted and executed graduate thesis. Between motorcycles and pizza, Margaret Sampson kept it all in perspective. Erich Mohr has pulled together a delightful, intelligent, hardworking team, and guided it all with remarkable energy and good humour. I am deeply grateful to Dr. Mohr for his unstinting support and faith.

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3 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder in which approximately 15% of the patients develop such profound intellectual deficits as to be considered demented. Dementia is a general term denoting progressive loss of overall intellectual function, greater than the decline expected with normal aging. The manner in which this loss unfolds in Parkinson's disease, as in Alzheimer's disease, is thought to reflect underlying pathophysiological mechanisms (Chui, 1989). In the literature on Parkinsonian dementia there is ongoing discussion as to what might constitute a typical pattern of relatively impaired and intact cognitive functions, and therefore an appropriate model of cognitive decline. The majority of investigations to date have employed a model wherein Parkinson's disease dementia (PDD) reflects either a coexistent Alzheimer's disease or a subcortical degenerative process resulting in 'subcortical dementia'. Subcortical dementia shares symptomatic and anatomic correlates with Progressive Supranuclear Palsy (PSP) and Huntington's disease. Neither of these models have provided an entirely satisfactory account of all cases of Parkinsonian dementia. An alternative explanation is that Parkinsonian dementia is not uniform, and the disorder comprises distinct subgroups or

stages. Different cognitive profiles in dementia may mean more than a single disease process at work, and therefore indicate the need for multiple treatment approaches (Chui, 1991). A study is proposed to address the question of uniformity of dementia in PD. As an introduction to the area, a brief review of Parkinson's disease is given in Appendix A, and a discussion of the neuroanatomical structures involved is to be found in Appendix B.

3.1 Dementia

Dementia was not identified as part of the PD symptom complex for many years, and was likely masked by the motor symptoms and early death of the patients (Cummings, 1988; Korczyn et al., 1986). After the introduction of levodopa therapy in the 1960's, which improved motor control and life expectancy for many patients, cognitive decline in some patients was more readily observable (Loranger et al., 1972). However, Parkinsonian dementia remained poorly defined (Mayeux and Stern, 1983) for several reasons. First, the motor symptoms of slowing, rigidity and tremor are not consistently and reliably obviated with drug therapy. In these patients any coexisting cognitive changes are masked. Therefore the prevalence of dementia could be obscured in such cases. Second, drug therapy itself, notably anticholinergics,

can have deleterious effects on cognitive processes (Dubois et al., 1990; Mohr et al., 1987, 1989; Newman et al., 1984) and thus confound the clinical picture. Third, up to half of all PD patients develop marked depression, that may also interfere with a diagnosis of dementia (Mayeux et al., 1981). Fourth, when dementia symptoms were first noticed in PD patients, it was thought that it was due to the most common cause of dementia, concurrent Alzheimer's disease. Later studies showed clear anatomic differences between Alzheimer's and Parkinsonian dementia: different brain regions were affected by dissimilar pathologies (Ball, 1984). Fifth, qualitative neuropsychological and behavioural similarities between dementias found in other neurodegenerative disorders of the basal ganglia, such as Progressive Supranuclear Palsy (PSP) and Huntington's disease, led to the development of a 'subcortical dementia' model (Albert et al., 1974). This concept has attracted considerable attention in the literature. Whereas cortical dementia of the Alzheimer type can be diagnosed by a specific list of criteria, such as are laid out in the Diagnostic and Statistical Manual (DSM III-R), subcortical dementia refers to nonspecific deficits of memory, personality and speed of thinking. It is not a diagnostic entity but a conceptual

model. There is consequently some confusion over the use of the word dementia. Any discussion over the existence of dementia in PD should take into account the criteria used to arrive at the diagnosis.

The clinical diagnosis of dementia of any type is generally based on either of two sets of widely used, independent criteria for dementia. These are the Diagnostic and Statistical Manual of Mental Disorders Third Edition-Revised (DSM III-R) (American Psychiatric Association, 1987) and the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). Many disease processes can lead to dementia, including Alzheimer's, Huntington's, multiple infarctions, and progressive supranuclear palsy; Parkinson's is also an accepted pathogenesis of dementia (Sagar and Sullivan, 1988).

The DSM III-R criteria are:

- Loss of intellectual abilities sufficiently severe to impair social or occupational function
- Memory impairment
- At least one of:
 - impaired abstract thinking
 - impaired judgment
 - aphasia
 - apraxia
 - agnosia
 - personality change

- State of consciousness not clouded
- Either of the following:
 - identified probable organic etiology
 - conditions other than organic factors excluded

The NINCDS-ADRDA criteria require evidence of intellectual decline on neuropsychological tests, and do not specify impaired work or social function, or require the exclusion of depression (Mohr et al., 1991). In both definitions there are limitations for the diagnosis of dementia in Parkinson's patients. PD patients, when demented, often do not display symptoms of apraxia, agnosia, or aphasia, that are more common in Alzheimer's disease, and depression is frequently found in PD patients whether demented or not. Another limitation is related to the motor symptoms of PD, that in themselves can interfere with social and occupational function (Mayeux, 1989). Careful testing of cognitive function that limits reliance on motor function might address this difficulty. With these problems in mind, the DSM III-R criteria can still provide a valid basis for the diagnosis of dementia in PD. In summary, diagnostic criteria for dementia generally require a progressive loss of intellectual abilities severe enough to interfere with social or occupational function, without clouding of

consciousness (Brown and Marsden, 1988), and which exceeds the decline expected with normal aging (Chui, 1989).

Studies of dementia in Parkinson's often fail to define dementia, or control for degree of cognitive disability, so that inferences cannot be drawn and generalized to populations of demented patients. For example, a study of dementia in Parkinson's and Huntington's diseases by Massman et al. (1990) fails to define, operationalize, or specifically test for dementia in the subjects. Frequently, dementia is grouped with other cognitive deficits (Growdon and Corkin, 1986). Therefore, conclusions drawn about neuropsychological function in 'dementia' may not apply specifically to samples selected for the presence of dementia according to the criteria presented above.

The following review of literature on dementia in PD illustrates this point. Table 1 contains information taken from recent studies on dementia. No review papers have been included. The following questions were applied to each paper: Was dementia defined in terms of independent criteria, e.g., the DSM III-R? If it was so defined, was the definition applied to arrive at a diagnosis of dementia in the sample? How many cognitive

domains were tested in the demented population? Were absolute results reported or were they reported as relative to another dementia group? Of twenty recent studies, only six meet these criteria for selection of a dementia sample. Standard abbreviations for Alzheimer's Disease (AD), Huntington's Disease (HD) and Progressive Supranuclear Palsy (PSP) are used.

Table 1. Studies of Dementia in Parkinson's Disease

Authors	Define	Diagnose	Domain	Groups
Albert et al., 1974	no	no	4	PSP
Cedarbaum et al., 1991	yes	no	0	no
Huber et al., 1986a	no	no	6	AD
Huber et al., 1986b	yes	no	1	no
Huber,Shuttleworth 1990	yes	yes	5	AD
Korczyn et al., 1986	no	no	N/A	no
Levin et al., 1991	no	no	1	no
Litvan et al., 1991	yes	yes	3	AD
Massman et al., 1990	no	no	1	HD
Mayeux et al., 1990	yes	yes	N/A	N/A
Mayeux et al., 1983	yes	no	MMSE	HD, AD
Mohr et al., 1990b	yes	yes	2	AD
Mortimer et al., 1982	no	no	4	no
Oyebode et al., 1986	no	no	N/A	AD
Piccirilli et al., 1989	yes	yes	3	no
Pillon et al., 1986	yes	yes	4	PSP,HD,AD
Pillon et al., 1991	no	no	6	PSP,HD,AD
Pirozzolo et al., 1982	no	no	6	no

Portin and Rinne, 1986	no	no	N/A	no
Sullivan et al., 1989b	yes	yes	3	AD

Applying constraints of definition, diagnosis, domains, and comparison groups, resulted in six studies wherein dementia was diagnosed in PD patients according to generally accepted, independent criteria, and cognitive domains were surveyed for deficits in the demented group. Deficits were found in memory and executive function (Huber & Shuttlesworth, 1990; Litvan et al., 1991), mental status (Piccirilli et al., 1989), motor and frontal functions (Piccirilli et al., 1989), and memory, vocabulary and visuospatial skills (Mohr et al., 1990b; Pillon et al., 1986; Sullivan et al., 1989b). Because these studies tend to focus on particular domains, it is difficult to ascertain from them if there is a single typical cognitive profile in PD dementia. Furthermore, clinical studies are subject to selection bias (Davidson-Saunders and Trapp, 1990). Therefore it is also difficult to determine if patient groups are comparable across groups.

Neuropsychological performance can vary with age, education, general state of health, among a number of factors (Lezak, 1983). With the aim of understanding the

dementia profile in PD, it may be useful to examine the associated demographic variables, and how the expression of this disease interacts with them.

Because of the difficulties with the identification and diagnosis of dementia discussed above, basic descriptive information as to the incidence, prevalence, and demographics in PD dementia has only recently emerged. The estimates of incidence of dementia in PD vary widely. Recent estimates range from 10% (Mayeux et al., 1990), 20% (Brown and Marsden, 1984; Litvan et al., 1991), to 60% (Cummings, 1988). The cumulative incidence of dementia increases with age; by age 85, 65% of PD patients are demented (Mayeux et al., 1990). In that study, the patient sample was partitioned by age group. To differentiate incidence, the number of patients who eventually dement, from prevalence, the number of patients who currently are demented in a sample, Mayeux and colleagues looked at overall occurrence rate by age group. The highest increase in risk for dementia occurred between the ages of 65 and 75. Other estimates of the incidence rate of dementia have ranged from 10% to 15%, but the incidence rate in this study was 10.9%. In other studies, the application of precise diagnostic criteria, such as the DSM III-R, have resulted in incidence

estimates of about 20% (Litvan et al., 1991).

Additional factors have been associated with PD dementia. Although dementing patients tend to be older (Portin and Rinne, 1986), age at disease onset does not significantly differentiate between demented and nondemented patients (Cedarbaum et al., 1991, Korczyn et al., 1986; Portin and Rinne, 1986). Rather, the length of disease is associated with the appearance of dementia. Mayeux (1989) states that "...dementia increases in prevalence and severity as the disease continues" (p. S51). Increasing bradykinesia and rigidity are also associated with cognitive decline (Mayeux and Stern, 1983; Mortimer et al., 1982; Portin and Rinne, 1986; Riklan et al., 1989). Such decline may include deficits in visuospatial reasoning (Mortimer et al., 1982) and high speed memory scanning (Ransmayr et al., 1990) as well as a more rapid progression of physical disability (Mayeux et al., 1988). Not only do the patients who develop dementia tend to have more pronounced slowing and rigidity, they also show a poorer response to levodopa therapy (Mayeux et al., 1988; Portin and Rinne, 1986). However, in contrast to the deficits associated with rigidity and bradykinesia, a better intellectual status is associated with increased severity of tremor (Mortimer

et al., 1982). This implies at least two possible separate courses of this disease: increased tremor with less impaired cognitive function, and increased rigidity and bradykinesia with a greater decline in cognition.

Although factors such as the presence of rigidity and bradykinesia are associated with dementia, no causal relationships have been identified. Moreover, Parkinsonian motor signs display a significantly different progression than that of cognitive changes, and the one factor is not a useful predictor of the other (Portin and Rinne, 1986). More recently it has been suggested that deficits in tests of motor perseveration and the ability to switch motor programs correlate significantly with cognitive decline measured four years later. The presence of motor program dysfunction, such as rapid alternating manual movements, may have some value in predicting the development of dementia (Piccirilli et al., 1989).

The initial descriptions of PD did not mention mental changes (Parkinson, 1817, cited in Mayeux and Stern, 1983). The introduction of levodopa therapy made it clear that a dementia might be uncovered even when motor symptoms were alleviated, but the source of that dementia remained unknown. Parkinsonian dementia has been

attributed to a co-existing Alzheimer's disease (Korczyn et al., 1986; Mayeux and Stern, 1983; Mortimer, 1988). There is some overlap between morphological changes found in the brains of Alzheimer's and Parkinson's patients who come to post mortem examination, so that some, but not all, cases of dementia in PD show the neurofibrillary plaques and tangles of Alzheimer's disease (Ball, 1984). As well, the rate of dementia in Parkinson's is much higher than that for Alzheimer's in nonparkinsonian populations (Mayeux et al., 1990). Some, but not all, cases may be attributable to dementia of the Alzheimer type. Finally, the neuropsychological profile of PD dementia generally does not conform to that of Alzheimer's (Cummings, 1988; Huber et al., 1986, 1989; Pillon et al., 1986, 1991). It is reasonable to assume that all cases of dementia in PD are likely not due to coexisting Alzheimer's disease (Mortimer, 1988).

In contrast, it was noted that the dementia of PD, as well as Huntington's disease, was similar to the original description of dementia in progressive supranuclear palsy (PSP). The symptom complex common to all three groups was termed 'subcortical dementia' (Albert et al., 1974). The characteristic pattern of cognitive loss in PSP patients thought to be similar to that in PD and HD included

forgetfulness, bradyphrenia, apathy or depression with outbursts of irritability, and impaired ability to manipulate acquired knowledge. Bradyphrenia refers to a group of symptoms including diminished voluntary attention, spontaneous interest, initiative and the capacity for effort and work, with increased fatigability and slight memory loss (Brown and Marsden, 1990). PD dementia patients have been described as collectively having symptoms of bradyphrenia, memory disorder, and depression (Brown and Marsden, 1987).

Although the concept that different subcortical neurodegenerative disorders could produce the same profile of cognitive changes had some appeal, it has been subject to considerable criticism (Brown and Marsden, 1988; Mayeux et al., 1983; Pillon et al., 1991; Whitehouse, 1986). The generalization of a symptom grouping from PSP to other neurodegenerative disorders has been criticized for several reasons. A careful description of the dementia of PD has not been carried out (Brown and Marsden, 1987b), and therefore to describe it as being of a similar nature to the dementia of PSP is premature. Comparisons between subcortical dementias (Huntington's, Parkinson's) and cortical dementias (Alzheimer's) have not produced coherent group patterns

on brief mental status examinations (Mayeux et al., 1983). The 'subcortical' name emphasizes differences between cortical and subcortical function, where separation of the two morphological zones may not be of great import, and the distinction between the two zones in functional terms has not been established (Brown and Marsden, 1987). Designating Alzheimer's disease as 'cortical' and Parkinson's disease as 'subcortical' implies that the differences in cognitive changes in the two populations are a result of cortical or subcortical pathology. However both anatomical regions are affected in the two diseases (Sagar and Sullivan, 1988). This type of morphological designation also implies that cortical dementia is a homogeneous entity, which it is not (Mohr et al., 1990c), in addition to implying that PD dementia is also a homogeneous entity, which has not been thoroughly investigated. Finally, the implied independence of the two regions has not been demonstrated as important in dementia, and excessively simplistic associations between anatomy and neuropsychological function may be problematic (Whitehouse, 1986).

Diagnostic criteria and theoretical models are not uniform in the PD dementia literature. Consensus on the symptom complex of dementia in PD is also not widespread

(Brown and Marsden, 1988). Memory loss, bradyphrenia, and apathy or depression were originally considered elements of 'subcortical' dementia (Albert et al., 1974), while executive and visuospatial deficits were not, but some authors now include the latter functions as well in subcortical dementia (Cummings, 1986). The following symptoms of PD dementia are widely reported:

Table 2. Reported Symptoms of Dementia in Parkinson's Disease

Memory loss	Cummings, 1988; Cummings and Benson, 1984; Huber and Paulson, 1985; Huber et al., 1986, 1989; Litvan et al., 1991; Pillon et al., 1986
Visuospatial loss	Cummings, 1988; Huber et al., 1986, 1989; Levin et al., 1991; Pillon et al., 1986; Sullivan et al., 1989b.
Bradyphrenia	Cummings, 1988; Cummings and Benson, 1984; Huber and Paulson, 1985.
Apathy/ Depression	Cummings 1988; Cummings and Benson 1984; Huber and Paulson, 1984; Huber et al., 1986, 1989.
Executive function	Cummings, 1988; Litvan et al., 1991.

This lack of agreement in symptoms is due in part to the inappropriate use of a descriptive model, i.e., subcortical dementia, for diagnostic purposes. It may also be that PD dementia is not homogeneous, but an

aggregate of different symptomatic presentations at separate stages of the disease, or in different subgroups. It may also be that at least two types of dementia, both Alzheimer's, and 'subcortical', may be present in the population of demented PD patients (Agid et al., 1986).

Several authors have suggested that the PD population as a whole may be divisible into subgroups, based on pathological, neurochemical, symptomatic and neuropsychological grounds (Chui, 1989; Cummings, 1988; El-Awar et al., 1987; Mortimer et al., 1982). For example, those PD patients who do develop dementia constitute a subgroup defined by specific criteria. According to Chui (1991), while the expression of dementia may be affected by a variety of factors, the most important ones are etiology and pathogenesis, both of which are incompletely understood in Parkinson's disease. Consequently there are multiple possible etiologies for PD (Marsden, 1982), and while this particular study screens for idiopathic cases only, that is not to say that the source of disease in each case is known. Within the category of 'idiopathic' cases, further subdivisions may be possible.

Two theories are often applied in dementia subgroup research. One is that the clinical heterogeneity reflects a stage model, in which the disease profile changes as time goes by and the disease progresses, or a subgroup model, in which the interplay of factors leads to different presentations independent of time (Martin et al., 1986). As Mohr et al. (1990c) have pointed out, different subgroups may not even represent different etiologies, but the influence of modulatory effects.

"Intellectual deterioration...is particularly complex and variable in its manifestations" (Agid et al., 1986, p.26). For example, Alzheimer's disease can be subdivided by rate of decline (Nyth et al., 1991), and neuropsychological features (Mohr et al., 1990c). Combinations of varying motor signs and neurocognitive changes may mean that PD can be divided into subgroups based on these variables, which in turn might reflect differences in etiology and pathogenesis (Chui, 1989, 1991). It has been demonstrated that better cognitive status is associated with greater tremor, while bradykinesia and cognitive impairment increase in tandem (Hershey et al., 1991; Mortimer et al., 1982).

The effects of medications upon the PD population have revealed possible neurochemical bases of dementia.

Anticholinergics have been implicated in disordered memory (Koller, 1984). A study by Dubois et al. (1990) suggested that anticholinergics were a factor in lowered scores on Digit Span, Similarities, and Arithmetic, all subtests from the WAIS-R. Unfortunately, the subjects and controls were not matched for global intellectual function, so that it is not possible to conclude that medication, and not level of dementia, was the important factor in neuropsychological function. Levodopa can cause confusion and hallucinations, or intellectual excitation and euphoria (Agid et al., 1986). On the other hand, Gotham and colleagues (1988) have demonstrated that patients who were off levodopa did more poorly on measures of verbal fluency than when on, and conversely, were more impaired on associative conditional learning when on levodopa. This variety of effects argues for complex neurochemical processes underlying the cognitive changes in PD and PD dementia. The fact that dopamine replacement therapy does not compensate for the cognitive deficits in PD also indicates that other neurochemical changes may be interfering with cognitive function (Taylor et al., 1990).

Cummings (1988) proposed, based on pathological and neurochemical changes in PD brains, that there are three

dementia syndromes: one derived from the effects of depleted dopamine, one based on disturbances in acetylcholine, and one based on coexistent Alzheimer's disease. It has been demonstrated that some demented PD patients show Alzheimer-type neuropathological changes, but only in a minority of the cases (Ball, 1984). However, PD dementia may be more severe when DAT is present (Cummings, 1988). Growdon and Corkin (1986) present data summarized from numerous investigators to suggest that neuropathological changes in PD dementia fall into three patterns: 1) senile plaques and neurofibrillary tangles; 2) no senile plaques or neurofibrillary tangles; and 3) an atypical presentation with diffuse Lewy bodies throughout the cortex. Cognitive changes in MPTP-induced Parkinsonism, a pure dopamine depletion model, include intellectual decline, disorders of naming, construction and frontal lobe function, but no memory disorder (Stern and Langston, 1985). However, PD dementia typically includes memory disorders, which might be the result of other disordered neurotransmitters (Cummings, 1988). Mortimer et al. (1982) proposed that the cognitive changes in PD could be clustered into four areas: 1) fund of information, such as Information and Vocabulary on the WAIS-R; 2) verbal memory, such as

tested on the Logical Memory passages of the WMS; 3) psychomotor speed; and, 4) visuospatial skills, such as are tested with Block Design and Digit Symbol of the WAIS-R. Therefore there are several possible ways to partition PD dementia. This study has focused on the neuropsychological variables and eliminated several confounds that are part of the clinical presentation: depression and medication effects. However, the final results, based on attempts to define subgroups based on neuropsychological variables, may not reflect distinct etiologies, but only modulatory effects of as yet unknown factors (Mohr et al., 1990c).

This study will extend the research into dementia in Parkinson's Disease, in that it will both attempt to replicate the neuropsychological descriptions of PD dementia given earlier, and examine the PD sample for homogeneity. The first hypothesis is that statistically significant deficits in frontal lobe function, memory and visuospatial skills will be found in a single sample of demented PD patients when compared to nondemented patients and normal controls. The second hypothesis is that multiple subgroups with neuropsychologically distinct profiles will be found within the dementia sample.

4 Method

4.1 Subjects

Three groups of subjects were included in this study: 23 demented PD patients, 23 nondemented PD patients, and 23 normal controls. The PD dementia group consisted of 23 idiopathic Parkinson's disease patients, diagnosed by a neurologist, based on the presence of the three cardinal signs of Parkinson's: bradykinesia, rigidity and tremor. The subjects were collected under the auspices of the Ottawa Civic Hospital Parkinson's Disease Clinic and the Neurodegenerative Disorders Branch of the Institute of Mental Health Research, as part of a larger research project. In cases where a neurologist determined concurrent neurological illness on clinical examination, a Computerized Tomography (CT) scan was performed. Pertinent medical data on the patient group was gathered on the Ottawa Civic Hospital Parkinson's Clinic Assessment Sheet by clinic personnel, and was used to assess inclusionary and exclusionary criteria. The Unified Parkinson's Disease Rating Scale (UPDRS) (Stern, 1988) provides precise documentation of motor signs and symptoms and was completed by a neurologist at the Ottawa Civic Hospital Parkinson's Clinic during screening for the study. A copy of the Clinical Assessment form has

been reproduced in Appendix I. The Rating Scale, which contains the guidelines used in scores on the Clinical Assessment form, is to be found in Appendix J. The modified Hoehn and Yahr (Hoehn and Yahr, 1967; Fahn et al., 1987) Scale, used to describe stage of disease, is widely used in the clinical assessment of this disorder, and is included in these rating scales. Because depression may be a factor in neuropsychological performance (see Appendix C for a discussion of this issue), the Hamilton Depression Index (Ham-D) (Hamilton, 1960) was also be administered by clinic personnel. Patients with a score of 16 or greater on the Ham-D were be deemed to be depressed and excluded from the study.

All patients were on stable antiparkinsonian medication regimes at least 6 weeks prior to the beginning of the study. None of the participants received anticholinergic medication and none were on Deprenyl. Patients refrained from taking dopaminomimetic medications immediately before testing. Once a patient was deemed 'off', testing proceeded. Medications were reinstated immediately after testing. The alterations in medication schedules were monitored by the supervising neurologist of the study.

All PD patients conformed to the following inclusion and exclusion criteria:

Inclusion Criteria for Patients

- age 40 to 80 years
- meet DSM III-R criteria for dementia (see Section 1.1)
- score of 136 or less on Mattis Dementia Rating Scale (MDRS)

Exclusion Criteria for Patients

- any unstable medical problems such as liver, kidney or heart disease, or cancer
- alcoholism
- pseudoparkinsonian syndromes
- psychiatric disorders, including depression
- noncorrected visual or auditory impairment

In clinical studies such as this one, the inclusion of patients is subject to many factors that can be the source of a selection bias (Dawson-Saunders and Trapp, 1990). The final selection of patients reflects several sources of bias. Variables such as stable control of Parkinsonian symptoms, lack of depression, ability to travel, or the availability of a companion with whom to travel, lack of other disease that might affect neurocognitive function, and the self selection process

by which patients volunteered time for a project with no direct benefit to themselves, may have contributed to a selection bias.

There was a second group of 23 PD patients who met the above criteria, with the exception of the presence of dementia; in this group, the MDRS score was 137 or greater. A third group of 23 healthy age and education matched individuals served as normal controls. They were solicited through advertising placed with publications from the Ottawa Civic Hospital, the Royal Ottawa Hospital, and The Parkinson Society of Ottawa. Aside from the items concerning dementia (DSM III-R, MDRS), and the presence of Parkinson's disease, they conformed to the inclusion and exclusion criteria set out above.

4.2 Tests

In the Introduction section several papers were presented as having met satisfactory criteria for valid diagnosis and assessment of dementia in PD. From these sources the following list of tests sensitive to PD dementia was extracted:

Table 3. Neuropsychological Tests Sensitive to PD Dementia

Domain	Test	Author
Visuospatial	Rey Osterrieth Figure; WMS Visual Reproduction:	3
	Block Design (WAIS-R):	1
	Picture Arrangement (WAIS-R):	6
	Raven's Progressive Matrices:	1,5
Memory	WMS Paired Associates:	1
	WMS Logical Memory, Visual Memory, MQ:	2,5
Executive	Wisconsin Card Sorting Test	2,5
	Verbal Fluency:	1,2,5
	Motor Sequences:	4,5
	Similarities (abstraction):	1
Global Intellectual	MiniMental State Exam	1
	Mattis Dementia Rating Scale, WAIS-R:	2

- 1 Huber & Shuttleworth, 1990
- 2 Litvan et al., 1991
- 3 Mohr et al., 1990b
- 4 Piccirilli et al., 1986
- 5 Pillon et al., 1986
- 6 Sullivan & Sagar, 1989b

From this a set of tests was selected for their reliability and validity in demonstrating cognitive changes in PD dementia. The Initiation and Perseveration scale from the MDRS was chosen as a test of frontal function because it encompasses several sensitive tests: verbal fluency, rapid alternating hand movements, and alternating graphomotor sequences. The Logical Memory Passages (Immediate Recall) from the WMS-R, as opposed to the entire test, were selected because they specifically

have been cited for sensitivity to memory disorders in PD, and because limiting testing time in an elderly and often infirm population was a goal, where possible. The final selection of tests includes:

Global	Mattis Dementia Rating Scale (MDRS)
Intellectual	Wechsler Adult Intelligence
Function:	Scale-Revised (WAIS-R)
Memory:	Logical Memory Passages from the
	Wechsler Memory Scale-Revised (WMS-R)
Language:	Vocabulary (WAIS-R)
Attention:	Digit Span (WAIS-R)
	Attention scale (MDRS)
Visuospatial:	Block Design, Picture Arrangement,
	Picture Completion, Digit Symbol
	(WAIS-R)
Executive	Similarities, Object Assembly (WAIS-R)
Function:	Initiation and Perseveration scale
	(MDRS)

MDRS: Mattis Dementia Rating Scale (Mattis, 1976)

WAIS-R: Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981)

WMS-R: Wechsler Memory Scale - Revised (Wechsler, 1987)

4.3 Procedure

Patients seen in the Ottawa Civic Hospital Parkinson's Clinic who were diagnosed with idiopathic Parkinson's disease and who met inclusion and exclusion criteria listed above were approached for recruitment. Subjects provided fully informed consent after being advised of the potential risks and benefits of this study by one of the permanent staff of the clinic (see Appendices G and H). Because of the possibility that some

study subjects who, because of their dementia, would be unable to appreciate the content of the information sheet or the consent form, the consent of the subject's next of kin or guardian was also sought. Testing was carried out by either the principal investigator or a trained and experienced psychometrist. The testing site is a quiet and well lit office. To minimize fatigue in the subjects, testing was carried out in a series of one and a half hour sessions. The testing sessions required a two to three hour discontinuation of antiparkinsonian medications to avoid the confound of medication effects on cognitive function (Mohr et al., 1987, 1989). Medications that were discontinued for testing were reinstated immediately following each testing situation. Medication withdrawal and reinstatement was supervised by one of the neurologists at the Ottawa Civic Hospital Parkinson's Disease Clinic. All study results were letter coded to ensure confidentiality. Hospital staff involved in the recruitment and testing, and the principle investigator, had access to the medical records of the patients involved. Ethical approval was granted both by Ottawa Civic Hospital and Carleton University Department of Psychology Ethics Committee.

4.4 Analyses

Statistical analyses have been run using two statistical packages: SPSS/PC+ version 4.0 and NCSS version 5.01 (Hintze, 1987), for validation purposes. Where only one package was used in analysis (Cluster Analysis, Discriminant Function Analysis), validation procedures were run using both programs.

Statistical analyses were organized into two sections. The first examined differences between the PD demented, PD nondemented, and the Normal Controls. Demographic variables on dependant variables were examined with series of t-tests to look for significant differences on individual tests. Then a comparison of neuropsychological profiles among the three groups was carried out with a Profile Analysis. Second, the PD demented group was examined for internal homogeneity. Dependant variables were regressed on age, length of disease, and total MDRS score, which served as an index of dementia. An absence of linear relationships between any of these variables led to further investigation with Cluster Analysis. Three subgroups were identified. These results were subjected to discriminant function analysis and ANOVA in order to determine which variables were active in separating out the subgroups.

5 Results

The results of analyses will be presented in two sections to reflect the order of hypotheses presented in the Introduction. The first part examines the differences between the demented PD group (PDD), the nondemented PD group (PD) and the normal controls (NC). The second part examines the homogeneity of neuropsychological performance within the demented group.

5.1 Differences Between Groups

The following table presents data on the age, sex, education, and Hoehn and Yahr score for each group. Group 1 subjects have Parkinson's disease with dementia (PDD), group 2 subjects have Parkinson's disease but do not have dementia (PD), and group 3 subjects are the normal controls (NC). The NC group have been arbitrarily rated as '0' on the Hoehn and Yahr scale so as not to be excluded from computer analysis. Two tailed t-tests have been run between each group for each demographic variable.

Letters in superscript refer to probability levels for the t-tests. The letter ^a refers to a p value of 0.01 or less between the PDD and PD groups; ^b refers to a p value of 0.01 or less between the PD and NC groups; ^c refers to

a p value of 0.01 or less between the NC and PDD groups. When the superscript letter is doubled i.e., aa, then the p value drops to 0.001 or less.

Table 4. Demographic Data for Three Groups

	Group 1 PDD Mean (SD)	Group 2 PD Mean (SD)	Group 3 NC Mean (SD)
age (years)	66.22 (7.95)	61.61 (8.93)	61.12 (6.33)
sex (M/F)	18/5	14/9	12/11
education	14.86 (3.61)	15.09 (3.40)	15.39 (2.90)
Hoehn & Yahr	2.33 (0.92)	2.28 (1.02)	0

For clarity, in the next series of tables the scores on dependent variables have been grouped by cognitive domain. Two tailed t-tests were run on all dependent variables between all groups. As above, superscript letters (a, aa) refer to p values from t-tests run between groups. All WAIS-R subtest scores are age scaled.

Since there are twenty-two comparisons in tables 5 through 10, an experimentwise overall significant alpha level is maintained if individual comparison levels are set at $p = 0.001$; these are indicated with double superscript letters (aa, bb, or cc).

Table 5. Intellectual Function

	Group 1 PDD Mean (SD)	Group 2 PD Mean (SD)	Group 3 NC Mean (SD)
FSIQ	95.39 ^{aa} (10.6)	116.91 (12.1)	125.08 ^{cc} (14.3)
MDRS total	128.08 ^{aa} (8.7)	142.09 (1.8)	142.70 ^{cc} (1.3)

note: Group 1 selected for MDRS <137; Group 2 MDRS >136

Table 6. Memory

	Group 1 PDD Mean (SD)	Group 2 PD Mean (SD)	Group 3 NC Mean (SD)
Logical Memory	13.87 (6.9)	14.72 ^{bb} (4.1)	23.45 ^{cc} (5.5)
Memory scale (MDRS)	21.23 ^{aa} (3.1)	24.52 (0.8)	24.56 (0.8)
Information (WAIS-R)	11.87 (2.3)	13.04 (2.8)	13.56 (2.0)

Table 7. Language

	Group 1 PDD Mean (SD)	Group 2 PD Mean (SD)	Group 3 NC Mean (SD)
VIQ (WAIS-R)	102.56 ^{aa} (12.3)	120.17 (13.9)	124.00 ^{cc} (14.1)
Vocabulary (WAIS-R)	11.78 (2.7)	13.78 (2.6)	14.52 ^{cc} (2.5)
Comprehension (WAIS-R)	10.17 ^{aa} (2.2)	13.74 (2.8)	14.52 ^{cc} (3.1)

Table 8. Attention

	Group 1 PDD Mean (SD)	Group 2 PD Mean (SD)	Group 3 NC Mean (SD)
Digit Span (WAIS-R)	9.69 ^a (2.8)	12.35 (2.5)	12.65 ^{CC} (2.6)
Arithmetic (WAIS-R)	8.96 ^{aa} (2.3)	12.69 (3.2)	13.26 ^{CC} (3.1)
Attention (MDRS)	35.95 ^a (0.9)	36.65 (0.9)	36.78 ^{CC} (0.5)

Table 9. Visuospatial Skills

	Group 1 PDD Mean (SD)	Group 2 PD Mean (SD)	Group 3 NC Mean (SD)
PIQ (WAIS-R)	85.96 ^{aa} (12.2)	108.48 (10.5)	120.69 ^{CC} (14.9)
Picture Completion	8.43 ^{aa} (3.0)	12.00 (1.7)	12.73 ^{CC} (3.0)
Picture Arrangement	8.04 ^{aa} (2.7)	11.35 ^b (2.3)	13.30 ^{CC} (2.5)
Block Design	7.30 ^{aa} (3.0)	12.00 (2.2)	14.39 ^{CC} (3.1)
Digit Symbol	7.35 ^{aa} (3.2)	11.26 (2.2)	12.65 ^{CC} (2.4)
Construction (MDRS)	5.13 (1.2)	6.00 (0)	6.00 (0)

Table 10. Executive Skills

	Group 1 PDD Mean (SD)	Group 2 PD Mean (SD)	Group 3 NC Mean (SD)
Init. & Persev.	31.39 ^{aa} (5.0)	36.65 (0.6)	38.91 ^{cc} (0.3)
Concept	34.21 ^{aa} (3.4)	38.26 (1.1)	38.49 ^{cc} (1.0)
Similarities	10.26 ^{aa} (2.4)	13.7 (2.7)	13.78 ^{cc} (2.0)
Comprehension	10.17 ^{aa} (2.2)	13.74 (2.8)	14.52 ^{cc} (3.2)
Object Assembly	7.04 ^{aa} (3.4)	10.83 (2.0)	13.26 ^{cc} (3.2)

Although individual tests reveal areas in which each group differed from the others, they do not address the issue of relative patterns of impaired and intact function. Does the demented group exhibit the same pattern of deficits as the nondemented group? The next step was to assess the extent of difference between groups across all dependent variables. To compare dependent variables in this respect, all raw scores were pooled across groups, within dependent variables, and transformed to z-scores.

Raw scores on all dependent variables were first plotted by groups onto histograms, and the score distributions were checked for normality. While assumptions of normality are met in most variables, the Mattis Dementia Rating Scale (MDRS), and each of its subscales (attention, initiation and perseveration,

construction, conceptualization, and memory) all showed a pronounced skew towards higher scores in the normal and non-demented groups, and to a lesser degree in the demented group.

The MDRS, and its subscales, were examined separately from the other dependent variables. This was done because membership in either the demented (PDD) or nondemented (PD) patient groups was determined in part by the MDRS score. Therefore it is not helpful to use the total MDRS score to examine between group differences. However, an examination of the subscale scores might reveal different patterns of neuropsychological performance that could be of interest.

The question of relative impairment across multiple domains, as discussed above, was addressed with Profile Analysis (Repeated Measures MANOVA). This is a procedure which examines multiple independent variables tested across multiple, commensurate dependent variables. The dependant variables must all be scaled identically, as in the case of z-scores, which are all based on a mean of zero and a standard deviation of 1. It can be used in cases where several groups are tested several times with the same instrument, or when several tests, all scaled alike, are administered to several groups. It addresses

the question of whether each group shows the same pattern, or profile, across multiple measures. The analysis yields three effects: Profile, Group, and Test. Test of the Profile effect (also known as parallelism) asks the question whether the groups have parallel patterns of high and low scores. The Group effect (also known as levels) refers to overall significant differences in levels between the groups, all tests combined together. The Test effect (also known as flatness) tests for significant differences between tests, when all groups are collapsed together. That is, when all groups are combined, do the segments between any two variables deviate significantly from a zero slope. If there are significant profile effects, then the groups are not parallel, and by necessity at least one of the profiles is not flat. In such a case the Test effect, or flatness, is irrelevant (Tabachnick and Fidell, 1989).

As mentioned in the Introduction, previous findings indicated that demented PD patients showed deficits, relative to controls, in memory, visuospatial, and frontal functions, but not in other domains such as language. Therefore it was expected that profiles of PDD and NC groups would not be parallel. It was expected that in the PD group memory, visuospatial, and frontal domains

would be impaired while others would be spared. It was further expected that a Group effect would show a significant overall decline in PDD scores, compared to both the PD and NC groups.

Several scores were omitted from this level of analysis. The Full Scale IQ, Verbal IQ, and Performance IQ are all composite scores incorporating the subscale scores. Because the IQ scores are composites, their relationship to the subscores reflects overlap, or singularity. In order to reduce singularity the subscales, and not the IQ scores, were included. As mentioned above, the MDRS scores and subscale scores were analyzed separately, also using Profile Analysis. The consequent set of dependent variables is composed of Logical Memory (Immediate Recall) (WMS-R), Information, Digit Span, Vocabulary, Arithmetic, Comprehension, Similarities, Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Digit Symbol (all WAIS-R subtests). The grouping variable was membership in any of three groups: Group 1, PD patients with dementia (PDD); Group 2, PD patients without dementia (PD); and Group 3, normal controls (NC).

Each group consisted of twenty-three subjects, with no data missing. Data were screened for outliers using bar

plots and histograms on NCSS, and none were detected beyond three standard deviations. A correlation matrix was used to examine the degree in correlation between the above set of dependent variables, all groups combined. In any MANOVA procedure it is inadvisable to include variables that have intercorrelation greater than 0.70 (Tabachnick and Fidell, 1989). The following variables showed correlations to other variables greater than 0.70, and were therefore excluded from the Profile Analysis: Comprehension (r^2 with Similarities, 0.7328; with Vocabulary, 0.7658), Vocabulary (r^2 with Information, 0.7641), and Block Design (r^2 with Digit Symbol, 0.7506; with Object Assembly, 0.8508; with Picture Arrangement, 0.7524) (Appendix K). Otherwise, assumptions of normality of sampling distributions, homogeneity of variance-covariance matrices, linearity, singularity, and multicollinearity were met.

The MDRS subscales were analyzed first using Profile Analysis. The subscales are Initiation and Perseveration, Conceptualization, Memory, Construction, and Attention. The sole significant finding was in the Group effect ($p = 0.0000$). None of the groups diverged significantly from flatness or parallelism, but the demented group, with all

subscale scores combined, had significantly lowered scores than either the PD or the NC groups. All subscale scores were uniformly depressed in the demented group.

The profile analysis for the balance of the dependant variables yielded Profile, Group, and Test effects. The profiles of each group, over 9 dependent variables, are graphed in Figure 1. For ease of interpretation, variables have been ordered from the lowest scores in the PDD group to the highest. MANOVA results for each effect are presented in Table 11. The profiles deviated significantly from parallelism according to Wilks' criterion ($F = 6.006$, $p = .0000$). According to the criterion of Hotelling's T ($F[12,55] = .0003$, $p = 1.00$) there was no significant Test effect, indicating that, averaged over the three groups, no test score means were significantly higher or lower than the overall mean of test scores. However, because of the significant parallelism effect, the Test effect (i.e., deviation from flatness) is redundant. There was, however, a significant Group effect ($F[2,66] = 31.07$, $p = 0.000$), indicating that the means of all test scores together differed significantly between groups.

Figure 1. Profile Analysis for PD, PDD, and NC Groups

Table 11. MANOVA Results for Profile Analysis in Three Groups

Effect	DF	Sum Squares	Mean Squares	F	p
Group	2	156.96	78.48	(2,66) 31.07	0.0000
Test	8	3.12E-04	3.90E-05	(8,66) 0	1.0000
Profile	16	29.92	1.86	(24,792) 3.82	0.0000

Simple effects for Group were calculated using one-way ANOVA and are presented below in Table 12. An examination of simple effects for Group required that the alpha level be reduced to $p = (0.05/9) = 0.005$ for multiple comparisons. At this level, only Information failed to differentiate among the three groups.

Table 12. Simple Effects for Group * $p < 0.005$

Test	DF	Sum Squares	Mean Square	F (2,66)	p
Logical Memory	2	25.89	12.95	20.31	0.000*
Information	2	2.85	1.42	1.45	0.242
Similarities	2	18.89	9.44	12.64	0.000*
Obj. Assembly	2	27.48	13.74	22.38	0.000*
Pic. Completion	2	21.39	10.69	15.1	0.000*
Pic. Arrangemt.	2	28.66	14.33	24.03	0.000*
Digit Symbol	2	29.06	14.53	24.69	0.000*
Digit Span	2	13.25	6.62	8.0	0.001*
Arithmetic	2	19.37	9.68	13.18	0.000*

A series of intergroup comparisons were then carried out to explore deviations from parallelism and levels in the three groups. Individual profile analyses were run using groups 1 and 2, groups 2 and 3, and groups 1 and 3. Results are reported in Tables 13, 14, and 15, respectively. Effects for Group, Test, and Profile generate a total of nine tests. Therefore, the alpha level was accordingly reduced to $p = (0.05/9) = 0.005$.

Table 13. Profile Analysis PDD and PD * $p < 0.005$

Effect	DF	Sum Squares	Mean Squares	F	p
Group	1	140.85	140.85	42.7	0.0000*
Test	12	7.10	0.65	1.34	0.2000
Profile	12	14.40	1.31	2.71	0.0020*

Table 14. Profile Analysis PD and NC * $p < 0.005$

Effect	DF	Sum Squares	Mean Squares	F	p
Group	1	7.06	7.06	2.94	0.0934
Test	8	3.77	0.47	1.06	0.3933
Profile	8	18.68	2.33	5.24	0.0000*

Table 15. Profile Analysis PDD and NC * $p < 0.005$

Effect	DF	Sum Squares	Mean Squares	F	p
Group	1	142.37	142.37	50.78	0.0000*
Test	8	5.39	5.67	1.35	0.2154
Profile	8	13.72	1.71	3.44	0.0008*

As in the original profile analysis for all three groups, no Test effect was found to be significant in any

of these three comparisons. That is, with any two, or all three groups compared, no significant deviation from flatness was detected.

Examination of Group effects revealed that, averaged across all tests, Group 1 (PDD) differed from Groups 2 (PD) and 3 (NC), but that Groups 2 (PD) and 3 (NC) did not differ significantly from each other.

Examination of Profile effects showed that all three profiles differed significantly from each other; each profile was unique.

5.2 Homogeneity Within PD Dementia Group

The next level of analysis addresses the question of homogeneity of neuropsychological performance within the dementia group. This was carried out in two parts. First, regression analyses were used to investigate relationships between age, disease length, and MDRS (Mattis Dementia Rating Scale) and the test scores. Second, a cluster analysis examined to what extent the formation of neuropsychologically distinct clusters could meaningfully account for score variation. This cluster analysis was examined through a series of one-way ANOVAs, and a discriminant function analysis.

Repeated regression analyses were run between MDRS as the index of degree of dementia, and all other variables. For twenty-two comparisons, an experimentwise alpha was set at $p = (0.05/22) = 0.002$. Only two variables met this criterion for significance, both subscales of the MDRS: Initiation and Perseveration, and Memory. The MDRS subscale Conceptualization approached significance, but no other variable produced a p value below 0.05. Therefore MDRS scores linearly reflect changes in Memory, and Initiation and Perseveration subscales, but do not vary directly with any other variables. Similar regressions run with age, and length of disease, yielded no significant results. The index of cognitive deficit in dementia in this sample does not show straight line relationships with length of disease, or age. One possible explanation for this lack of correlation is that several different processes account for the variation in cognitive function within the demented group.

To test this possibility, cluster analyses were then run. The analyses were iterated through various combinations of number of clusters and selection of variables. The choice of variables to be included was dictated by the overall percentage of variation in all the variables that is accounted for; the greater the

amount of variance accounted for, the better the 'fit' of the clusters. The choice of number of clusters should be chosen so that the addition of another cluster gives a relatively small reduction in the amount of variance accounted for. The resulting clusters were tested with one-way ANOVAs, to test the level of significance of separation between groups over the variables used, and Discriminant Function Analysis, to uncover those variables that function significantly to separate the clusters.

The cluster analysis that maximized variance accounted for and satisfied the above criteria most adequately separated all the dependent variables into three clusters. Use of all dependant variables, plus Years of disease and Hoehn and Yahr scores, but excluding Full Scale, Verbal and Performance IQs, maximized the percent of variance accounted for (68.6%), compared to any other sets of variables attempted. The addition of a fourth cluster only marginally reduced the percent of variance accounted for (to 62%). Each subject within the PDD group therefore received a cluster group designation (1, 2, or 3). A series of one-way ANOVAs were run to determine which, if any, variables were significantly different among the three cluster groups. The mean test scores, for

each group, are presented with the ANOVA results in Table 16 below. To achieve an experimentwise alpha of 0.05, alpha levels for each comparison were set at $p = (0.05/23) = 0.0022$.

Table 16. ANOVA Results in Cluster Analysis * $p < 0.0022$

Variable	Grp 1 N=9 mean	Grp 2 N=6 mean	Grp 3 N=6 mean	F 2,18	p =
Years of disease	11.4	12.8	17.2	0.98	.3962
Hoehn & Yahr	2.7	2.0	2.1	1.13	.3458
WAIS-R:Information	11.3	10.5	14.7	12.07	.0005*
Digit Span	8.5	8.8	12.2	5.66	.0124
Vocabulary	11.3	10.5	14.5	6.27	.0086
Arithmetic	7.5	8.8	11.5	12.52	.0004*
Comprehension	9.5	9.2	12.8	9.6	.0015*
Similarities	9.5	9.2	12.2	3.58	.0492
Pic. Completion	7	9.7	10.3	4.17	.0324
Pic. Arrangement	6.4	9.2	10	7.3	.0048
Block Design	5.4	10.2	7.8	7.8	.0036
Object Assembly	5.7	9.5	7.2	2.68	.0961
Digit Symbol	6.1	8.7	8.3	1.76	.1999
MDRS	123.9	133.7	131.3	5.49	.0137
Attention	35.7	36.7	35.8	2.44	.1159
Init. & Persev.	29.5	35	31.7	2.79	.0423
Construction	4.8	5.8	5.5	2.49	.1110
Concept	33.3	33.8	35.5	0.68	.5206
Memory	20.4	22.3	22.8	2.37	.1225
Logical Memory	10.8	20.1	14.2	4.12	.0336

A discriminant function analysis was then run to determine which variables act significantly to predict group membership. NCSS (Hintze, 1987) provides a stepwise variable selection process that permits the experimenter to enter as many variables as desired in descending order

of r^2 added. All dependent variable scores, plus Hoehn and Yahr score and Years of disease, were available for analysis. The number of variables entered was determined by several factors. Because the smallest subgroup size was six, the number of dependant variables was not to exceed six (Tabachnick and Fidell, 1989). However, the more variables added, the greater the reduction in percentage of classification errors. Since finding all the variables that would result in perfect classification was of interest, close to the maximum number of variables was preferred. Finally, the overall Wilk's lambda, a test of the significance of the ability of the combination of variables to predict group membership, declined with each variable entry, so again the maximum number of variables was desirable. The results for the consequent five variables, in order of entry into analysis, are given below; the value of Wilk's lambda is cumulative.

Table 17. Discriminant Analysis for Three Groups

Variable	R ² added	F	p	Wilks' lambda
Arithmetic	0.582	12.5	.0004	.4183
Pic. Arrangement	0.450	7.0	.0062	.2300
Init. & Persev.	0.456	6.7	.0077	.1251
Logical Memory	0.506	7.7	.0050	.0618
Pic. Completion	0.121	3.1	.4058	.0543

The homogeneity of the resultant variance/covariance matrices was tested using Box's Test, and not found to be significantly nonhomogeneous [$M = 76.67$, $p = 0.1033$].

The standardized discriminant function coefficients for each of the variables employed is given below.

Table 18. Standardized Discriminant Function Coefficients

Variable	Coefficient
Initiation & Perseveration	-.513
Logical Memory	-.165
Picture Completion	-.730
Picture Arrangement	-.647
Arithmetic	-.253

The following table gives the mean scores for each variable by group, as defined on the cluster analysis. The first five variables, Arithmetic through Picture Completion, are the variables that were significant in the formation of clusters. The variables following after them are presented for interest, but the reader is cautioned that they do not represent vectors that reliably separate these groups.

Table 19. Mean Scores for Dementia Groups from Cluster Analysis.

Variable	PDD Group 1 N=9	PDD Group 2 N=6	PDD Group 3 N=6
Arithmetic	7.5	8.8	11.5
Pic. Arrangement	6.4	9.2	10
Init. & Persev.	29.5	35	31.7
Logical Memory	10.8	20.1	14.2
Pic. Completion	7	9.7	10.3
Object Assembly	5.8	9.5	7.2
Similarities	9.5	9.2	12.2
Vocabulary	11.3	10.5	14.5
Information	11.3	10.5	14.7
Block Design	5.4	10.2	7.8
Digit Span	8.5	8.8	12.2
Digit Symbol	6.1	8.7	8.3
Concept.	33.3	33.8	35.5
Comprehension	9.5	9.2	12.8
Attention	35.7	36.7	35.8
Construction	4.8	5.8	5.5
Memory (MDRS)	20.4	22.3	22.8
Hoehn and Yahr	2.7	2	2.1
Years of Disease	11.4	12.8	17.2
MDRS	123.9	133.7	131.3

The five variables that separate this sample into subgroups were further analyzed with a series of ANOVAs to examine differences between the groups on those variables. The results are given in the table below.

Table 20. ANOVA Results for Dementia Subgroups

Variable	F (2,18)	p
Arithmetic	12.52	0.0004
Picture Arrangement	7.30	0.0048
Init. & Perseveration	3.79	0.0423
Logical memory	4.12	0.0336
Picture Completion	4.17	0.0324

The following figure represents means, transformed to z-scores, on the above five variables, for the three subgroups. The scores were transformed in order to clarify the relationships between group membership and variables.

Figure 2. Three Dementia Subgroups on Five Variables

6 Discussion

This study was carried out to determine two questions. Do demented PD patients have the same neuropsychological profile as nondemented PD patients? If so, this supports the idea that dementia represents a progression of the same deficits that affect the nondemented patients. If it is not so, then it may be argued that the demented group have experienced a separate pathogenetic course resulting in dementia. If the demented patients exhibit a different profile, then is there some pattern within this group to suggest what processes have been at work? Can it be described in terms of linear progression or different subgroups?

This section will first discuss the functioning of multiple cognitive domains in the PD and PDD groups in relation to controls. Then the profile analysis will be examined to illustrate the relative abilities and deficits in each group. Finally the question of homogeneity within the dementia group will be explored with the results from regression analyses, the cluster analysis, and discriminant function analysis. While the issue of cognitive changes in nondemented PD patients is not central to this study, it is nevertheless helpful to review the literature in this area

in order to place some of the following findings in context. Appendix D contains a summary of recent studies on this subject.

The three groups of interest (PDD, demented PD patients; PD, nondemented PD patients, and NC, normal controls) were compared on age, sex, education, and Hoehn and Yahr scores. The normal controls are younger than either patient groups, but the PD and PDD groups do not differ significantly on age. All three groups have similar male/female ratios and levels of education. Both patient groups have similar average Hoehn and Yahr ratings, that is, they have similar overall levels of motor impairment.

Global intellectual function was established a priori by assigning all patients with MDRS scores of 136 or less to the demented group, and those with scores of 137 or greater to the nondemented group. Therefore the significant differences between the PDD group and the PD group and controls (Table 5) on MDRS are set a priori. These differences were also reflected in another test of global intellectual function, the Wechsler Adult Intelligence Scale - Revised (WAIS-R). The Full Scale IQ of the demented group is significantly ($p < 0.001$) lower than that of the control group. This is consistent with the findings of Litvan and colleagues (1991). However, the actual scores of the PD

dementia group (average 95.39) are in the average range for national norms as established by Wechsler (Wechsler, 1981). The inconsistency in interpretation points out the differences in the national normative sample and the samples used in this study; this can be clarified by looking at the scores of the PD group. These patients have an average Full Scale IQ not significantly different from the control group, but significantly higher than the PDD group. One might argue that the high average mean Full Scale IQ of the controls represents a unique self selection bias, of individuals with higher than average intellectual function, and higher education, and therefore a greater appreciation for the value of research. The same logic could also be applied to both patient groups. The groups have been matched for age and education, and therefore these variables are not a likely source of confound. Note from Table 4 that all three groups have similar levels of education, approximately 15 years. If both patient groups (and all members self selected to participate in a time consuming research project) reflect a similar process of self selection, then it is reasonable to suppose that the relatively lower Full Scale IQs of the PDD group reflect a real decrement in comparison to the nondemented group. That is, there is no reason to assume that, except for the presence of dementia, the PDD group

would not demonstrate Full Scale IQs in the same high average range as the PD group and normal controls. Therefore there has been a significant drop in the full scale IQ of the PD dementia sample. This conclusion has also been reached by Dubois and colleagues (1991).

In the current study, both PD and PDD groups had equally impaired scores on Logical Memory Passages (immediate recall) in comparison to the normal controls. That is, the nondemented group showed an impairment on this task as great as that shown by the demented group. This is the only test in this study wherein the PD group was equally as impaired as the PDD group. The Wechsler Memory Scales (both original and revised, WMS and WMS-R) have previously demonstrated sensitivity to changes in memory in demented PD patients (Huber and Shuttleworth, 1990; Litvan et al., 1991; Pillon et al., 1986), especially on Logical Memory Passages and Paired Associates. However, a study by Sullivan and Sagar (1989b) did not find significant differences on these tests when comparing demented and non-demented PD patients. They attribute this result to small group size. While the Sullivan and Sagar (1989b) study found that their demented sample scored lower than the nondemented sample on immediate recall of verbal material on the WMS, their criteria for dementia were not equivalent to those in this study, and

their final group size of demented ($n = 3$) and nondemented ($n = 2$) make it impossible to draw firm conclusions about relative memory function. However, Taylor et al. (1986a) have also shown that nondemented PD patients scored significantly lower than normal controls on Logical Memory passages. Therefore these results are congruent with previous findings in that both demented and nondemented patients are impaired on Logical Memory. They extend the literature with the finding that both groups show an equal degree of impairment.

Generally, the types of memory disorders found in PD dementia fall in the category of 'effortful episodic' memory loss (Newman et al., 1984; Weingartner et al., 1984), which refers to recall of events embedded in time and place. Such memory dysfunction has been linked by some researchers to frontal lobe dysfunction, which provides a single 'frontal lobe' hypothesis to account for cognitive changes in Parkinson's disease (Taylor et al., 1990). Appendix F provides a review of these issues. In this case, both effortful episodic memory loss, as measured by Logical Memory, and frontal function, measured in part by Initiation and Perseveration, are impaired in the demented PD group, but not in the nondemented group. That is, the nondemented group does not show a significant deficit in Initiation and

Perseveration. If the two functions (effortful episodic memory and frontal) are linked, then it could be suggested that both domains would show similar impairment in whatever sample tested. However, this is not the case in the current study. It may be that a link between the two is too simplistic a test for the possible interactions between frontal lobe function and memory. However, the current study indicates that the performance on the two measures does not decline in tandem in the nondemented PD sample.

The Memory subtest from the MDRS did not exhibit the same pattern of scores as Logical Memory. The Memory test is composed of basic orientation to time and place, plus immediate recall of simple sentences, a word list, and figures. There is less emphasis on effortful episodic memory as compared to Logical Memory. While the demented PD patients had scores significantly lower than the PD group on Memory, the PD group was not significantly different from the normal controls.

Finally, the Information subtest of the WAIS-R was included in the memory section as it can reflect semantic memory and long term memory (Lezak, 1983). In this respect, the similar performance of all three groups on this test supports the contention of Cummings (1988) that long term recall is unimpaired in PD dementia, and previous findings

that demented PD subjects are not impaired on Information (Mortimer et al., 1982; Pillon et al., 1986). It is important to point out the distinction that effortful episodic memory is affected in PD, while semantic memory is intact.

Memory function has been found, in a nondifferentiated sample of PD patients, to distinguish among three subgroups: one that had no deficits, one that had both memory and global intellectual loss, and one group that had marked memory loss with less pronounced disorders in other cognitive domains (El-Awar et al., 1987). These results were partially replicated in the current study, when both demented and nondemented groups are reviewed: the demented group showed both memory and global intellectual loss, while the nondemented group had an isolated memory deficit and relatively intact performance on other tests.

While language deficits, such as naming, comprehension, reading and writing, are not typically included in the symptom complex of PD dementia (Brown and Marsden, 1988; Cummings, 1988; Dubois, 1991; Huber et al., 1985, 1989; Levin et al., 1989; Pillon et al., 1986), changes in Verbal IQ and Vocabulary from the WAIS-R have been reported. Mohr and colleagues (1990b) found a substantial reduction in VIQ in their demented PD group, which was comparable in extent

to the deficit in the Alzheimer group. As the subtest that has the highest correlation to Verbal IQ of all the Verbal tests (Wechsler, 1981), Vocabulary has been characterized by Brown and Marsden (1988) as "perhaps the simplest measure of language" (p.367). Normal Vocabulary scores have been documented in PD dementia (Huber et al., 1986, 1989; Sullivan et al., 1989b). In the present study the PDD group had Verbal IQs and Vocabulary scores in the average range as defined by Wechsler (1981). However, the same argument for a clear reduction compared to the nondemented and controls as was given for Full Scale IQ scores can also be applied here. The nondemented PD group, matched with the demented group in age, education, length of disease and motor symptom ratings, nonetheless show significantly higher VIQ scores than the demented group. The Vocabulary scores show a similar pattern. It has been proposed (Agid et al., 1986) that, because PD patients are very sensitive to interference, and do poorly on tests requiring conceptual manipulation, that such language losses in PD are a result of "defective manipulation of the material" (p.s24). This could account for the discrepancy between unimpaired basic language skills and deficiencies on the more complex Verbal subtests of the WAIS-R: Arithmetic, Digit Span, Comprehension and Similarities, which are more complex tasks than basic

naming, comprehension, reading and writing. However, the same argument does not necessarily apply to Vocabulary. This is a test which taps long term recall, and is related to level of education. (Lezak, 1983). Therefore the impaired VIQ scores in the demented group may in part be due to 'defective manipulation' (op.cit.), but may also reflect an actual language deficit in the demented group.

Attention measures in this study (Digit Span and Arithmetic from WAIS-R, Attention test from MDRS; see table 8) were all sensitive to impairment in the PDD group, while the nondemented PD group scored comparably to the normal controls. This is compatible with the findings of Litvan and colleagues (1991). Significant differences in attention were not detected in demented PD patients in another study (Pillon et al., 1986), but in that case it was likely due to the small sample size of 8. The magnitude of deficit found in the current study was comparable to that found on the language measures mentioned above. The same argument of "defective manipulation of material" (Agid et al., 1986, p.24), originally postulated by Albert et al. (1974) as a component of subcortical dementias, may also apply to the multiple functions of remembering, reversing and calculating required in Digit Span (especially backward) and mental Arithmetic. Deficits have been documented in Arithmetic in

undifferentiated PD samples (Boyd et al., 1991).

There is a consistent and marked visuospatial deficit in the PDD group in this study compared to normal controls (see table 9). 'Visuospatial' in this context comprises visuoceptive, visuomotor, and visuoconstructive skills as well as visuospatial reasoning. The Performance IQ and constituent subtest scores (Picture Completion, Picture Arrangement, Block Design and Digit Symbol), of the PDD group, are all significantly different from both the nondemented group and the normal controls. Object Assembly is discussed separately under Executive skills. The Construction test from the MDRS does not show this pattern, because of the lack of variance in scores in the PD nondemented and normal controls. Picture Arrangement is the only test that differentiates between the PD and normal controls. Finally, the scores of the PDD group on all the Performance IQ measures are also below average, by one to two standard deviations, compared to normative standards established by Wechsler (1981). Marked Performance IQ deficits in demented PD patients have been previously documented (Litvan et al, 1991; Mohr et al., 1990b), as well as impaired performance on Picture Arrangement (Sullivan et al., 1989b) and Block Design (Levin et al., 1991). Additionally, samples of mixed demented and nondemented, or

unspecified, PD patients have shown significant visuospatial disorders (Levin et al., 1990; Loranger et al., 1972; Oyeboode et al., 1986; Pirozzolo et al., 1982), including disorders of visuospatial reasoning (Huber et al., 1986a), deficits in Block Design (Huber et al., 1989), Picture Completion (Boyd et al., 1991). Visuospatial deficits can be demonstrated even in the early stages of PD (Levin et al., 1989).

Tests with both strong and minimal motor demands reflect this visuospatial deficit (Boller et al., 1984). Although it may be argued that bradyphrenia, rigidity, and tremor interfere with the manual manipulation required in many visuospatial tasks, an examination of these results indicates otherwise. The WAIS-R subtest Picture Completion, which has minimal motor demands, demonstrates the same pattern of scores as Block Design, Digit Symbol (both of which require speeded, fine motor manual responses) as well as the overall Performance IQ. In all cases, the demented PD patients score significantly lower than the nondemented PD group, and the normal controls. Further, the demented and nondemented groups are matched for degree of motor impairment.

Executive skills as used in the current study refer to the ability to abstract ideas, formulate concepts, and

initiate, organize and maintain behavioural sequences, including verbal fluency. These functions are often impaired after frontal lobe dysfunction, and are therefore frequently referred to as 'frontal' functions as well. The tests chosen to represent this domain were Initiation and Perseveration (MDRS) (verbal fluency, manual and graphomotor alternating sequences), Concept (MDRS) (abstraction and concept formation), Similarities (abstraction and concept formation), Comprehension (WAIS-R) (abstraction), and Object Assembly (WAIS-R) (abstraction). In this study PDD groups performed significantly more poorly in all these areas when compared to nondemented PD patients and normal controls. This is consistent with previous studies of demented PD patients that found significant impairments in verbal fluency (Pillon et al., 1986), manual and graphomotor sequences (Piccirilli et al., 1989; Pillon et al., 1986), and conceptualization and abstraction (Litvan et al., 1991; Mohr et al., 1990b). This study did not reveal differences between the PD group and normal controls on the Initiation and Perseveration scale at an alpha level of 0.01. However, previous studies have demonstrated significant decrements in executive skills in samples of mixed demented and nondemented patients (Benecke et al., 1987; Huber et al., 1989; Sheridan et al., 1987; Stern et al., 1983), which may

serve to demonstrate the robustness of executive skills loss in the more intellectually impaired patients. The literature in this area is extensive, and the reader is referred to Dubois et al., (1991) for an exhaustive review, which is beyond the scope and purpose of this study. However, the frontal lobes have been implicated in a wide range of activities, and a review of these can be found in Appendix E, along with a discussion of possible reasons for frontal lobe type dysfunction in PD.

In summary, these samples demonstrate very limited differences between nondemented Parkinson's patients and normal controls: these consist of Logical Memory passages (effortful episodic memory), and Picture Arrangement (visuospatial and sequencing). The differences between the demented PD and normal controls, by contrast, are extensive; only Information (long term recall) is unimpaired in the demented group. This does not support a model of simple progression of neuropsychological deficit leading to dementia. This impression was tested statistically, and verified, with a Profile Analysis.

Previous attempts have been made to describe the typical neuropsychological deficits in PD by testing across multiple domains, but some have not differentiated between demented and nondemented subjects (Boyd et al., 1991; Sullivan et

al., 1989b). Those that have preselected for dementia tend to report findings in a limited number of domains (i.e., Litvan et al., 1991; Mohr et al., 1990b; Pillon et al., 1986; Sullivan et al., 1989b). However, none have investigated the profiles of each group across multiple domains. In this study the profile analysis has addressed this issue and found that there are significant differences over all domains tested between group 1 (PDD) and both group 2 (PD) and group 3 (NC). However there was no overall significant difference between group 2 (PD) and group 3 (NC). Within each group no significant effect for test was found on the profile analysis. According to Tabachnick and Fidell (1989) this is a rare occurrence, and typically indicates that the highs and lows cancel each other out across the groups, leaving no significant overall effect. It cannot be deduced from this test whether, over all groups combined, one set of tests revealed more or less impairment than the others. However, when the interaction effects, or profiles, were examined, each group was found to have a unique constellation of intact and impaired functions. Group 3 (PDD) was impaired in virtually every domain except long term recall (Information), while the nondemented group 2 (PD) was impaired only on effortful episodic memory (Logical Memory) and a visuospatial/sequencing test (Picture

Arrangement). That neurocognitive function is so very disparate in these two groups may reflect different pathophysiological processes, and so support an argument that dementia in PD is a process distinct and separate from the cognitive changes associated with (nondemented) Parkinson's disease (e.g., El-Awar et al., 1987).

Having reported that the neuropsychological patterns of demented PD patients are distinct from nondemented PD patients, the current study then examined the PDD group alone. If dementia reflected a unique process, then how can it be described? Is it a single linear process, related to age, length or severity of disease? As reported in the results section, no correlations between MDRS, age, length of disease, or any dependent variable could be found. A similar lack of correspondence between length or severity of disease and dementia has been reported by Piccirilli and colleagues (1989). This argues against a model of dementia as a uniform progression of generalized cognitive decline over time or with severity of disease. Therefore a stage model, based on progressive decline, is not supported in this case.

If dementia is not a single linear process, could it be several processes? A subgroup model was explored with Cluster Analysis, and consequently the demented patients

were divided into three subgroups. The tests that served to separate the subgroups, derived from discriminant function analysis, were Arithmetic, Picture Arrangement, Initiation and Perseveration, Logical Memory, Object Assembly and Picture Completion; they represent memory, frontal, visuospatial, and attention functions. Picture Arrangement, Logical Memory, and Performance IQ, have all been described as impaired in PDD (Litvan et al., 1991; Pillon et al., 1986; Sullivan and Sagar, 1989b). In this case the cluster analysis indicates that there might be sufficient variability in these impairments to warrant separate subgroups. This could mean that different cognitive domains are differentially affected in PD dementia. This in turn suggests multiple pathogenetic mechanisms (Chui, 1991).

Although a series of ANOVAs examining differences among these three subgroups on the variables that served to separate the groups was not helpful in establishing significant intergroup differences, a preliminary review of the group means suggests some interesting possibilities. Those group means are reproduced below for ease of examination.

Table 21. Mean Scores in Dementia Subgroups.

	Group 1	Group 2	Group 3
Arithmetic	7.5	8.8	11.5
Picture Completion	7	9.7	10.3
Picture Arrangement	6.4	9.2	10
Object Assembly	5.7	9.5	7.2
Initiation & Perseveration	29.5	35	31.7
Logical Memory (WMS-R)	10.8	20.1	14.2

In terms of simple score contrasts, group 1 has the lowest scores in all tests, of all the groups. Comparisons between groups 2 and 3 are less straightforward. Scores on visuospatial measures, such as the Performance subtests from the WAIS-R, are very close. However, group 3 has relatively lower scores on Logical Memory, and Initiation and Perseveration. Finally, group 3 has a higher Arithmetic score. Further examination of other Verbal subtests (from table 17) shows that group 3 has higher scores on all Verbal subtests. In summary, the three groups might be characterized as follows: Group 1 has the most severe dementia; group 2 has relatively intact memory and frontal scores, mildly decreased visuospatial scores, and moderate verbal deficits. Group 3 has milder memory, frontal, and visuospatial deficits, with intact verbal scores.

It is tempting to speculate on the salience of subgroups in PD dementia. Because no linear relationships could be established between age, length or severity of disease, a stage or progression model, in which dementia follows a single, downward path of progression, is not supported. An alternate explanation is that PD dementia unfolds in several different courses. If the above groups represent meaningful differences in pathological mechanisms, then they might be characterized as (group 1) severe dementia, all modalities affected; (group 2) mild, Alzheimer-like dementia, with preserved frontal and memory functions but, verbal and visuospatial deficits, and (group 3) moderate Parkinsonian-like dementia, with frontal, memory and visuospatial deficits, but preserved verbal function.

Referring back to figure 2, the groups also break out to form three levels on Initiation and Perseveration, and Logical Memory. It is possible to speculate that these levels may represent degrees of frontal involvement, with the other three representing more posterior functions. The three groups could then be characterized as mild, frontal, and posterior dementias.

Whether or not these subgroups are a valid and reliable measure of differences within PD dementia will require replication in additional studies. Because it of the

difficulties controlling for all extraneous variables, validation in subgrouping research requires replication with other samples and investigators (Chui, 1991).

Previously, the use of anticholinergics has been implicated in disordered memory (Koller, 1984), as well as Digit Span, Similarities and Arithmetic (Dubois et al., 1990). The unmedicated status of this sample may help to clarify the role of anticholinergics. It has been reported that anticholinergics can act to exacerbate memory deficits (Agid et al., 1986). The poor performance of both PD and PDD groups on Logical Memory implies that memory deficits are not exclusively related to the use of anticholinergic medication; these patients were reliably 'off' at the time of testing. Similarly, the same degree of dopamine loss that can result in Parkinsonian motor symptoms does not necessarily result in dementia, and different degrees of dementia can exist at the same level of motor impairment, and length of disease. Therefore the presence or degree of dementia appears to have no linear relationship with Parkinsonian motor symptoms; in fact, current results suggest that there is no such relationship. Additionally, these patients were not depressed; their cognitive impairments cannot be ascribed to coexistent mood disorder.

In summary, Parkinsonian dementia affects virtually all domains; only long term memory (Information) was found to be intact in this group. Nondemented PD patients have mild visuospatial deficits and a marked effortful episodic memory deficit, equivalent to that found in the dementia group. All three groups, the normal controls, nondemented group, and demented group, showed neuropsychologically distinct profiles across multiple cognitive domains. This supports the idea that dementia represents a unique pathological process, separate and distinct from that affecting the nondemented group. Investigation of the demented group led to subdivision into three neuropsychologically distinct subgroups, according to performance on frontal, memory, and visuospatial tests. These groups did not differ on disease severity or length of disease. This suggests that multiple pathogenetic mechanisms are involved in the development of dementia in Parkinson's disease, leading to three neuropsychologically distinct presentations. This hypothesis should be further tested with replication in different and larger samples, as well as validation with biological markers such as CSF fluid assays for neurotransmitters and postmortem examination for pathological changes.

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8 Appendix A: Introduction to Parkinson's Disease

Parkinson's disease is a chronic, progressive debilitating, neurodegenerative disease with no known cure. The primary symptoms are motor: rigidity, tremor, and motor slowing. The disease also affects cognitive function through associated disorders such as depression, specific cognitive dysfunction of the frontal lobes, and dementia. In the 1960's the drug levodopa, which was useful in controlling the motor symptoms and progress of the disease, was introduced. In the 1980's, several events led to significant gains in the body of knowledge of this disease, and have opened up new areas of research. First, accidental poisonings from street drugs led to a disease entity that mimicked Parkinson's disease in all ways, except that the disease progression was much faster, on the order of days instead of years. The toxin was traced to a metabolic byproduct of MPTP, a contaminant in a designer street drug (D'Amato et al, 1986). This compound permitted researchers for the first time to develop a reasonably accurate animal model of the disease for research purposes. Second, several centers have attempted transplanting fetal or adrenal dopamine-producing tissues into the brains of Parkinsonian patients. This treatment route has received considerable media attention. Last, it has been found that

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electroconvulsive therapy, when administered for depression in Parkinson's patients, has been effective in ameliorating motor symptoms as well. Several centers are currently studying the possibilities of treating PD with electroconvulsive therapy. (Abrams, 1989; Burke et al., 1988; Douyon et al., 1989; Yudofsky, 1979).

Parkinsonism, in contrast to Parkinson's disease, refers to a number of syndromes that are comprised of rigidity, tremor, and a lack of spontaneous movements. Associated with these symptoms are a mask-like, expressionless face, stooped posture, and an unmodulated voice. Bradykinesia, which includes hesitancy in initiating movement, progressive difficulty in performing rapid, repetitive movements and poorly defined fatigue, is also found (Lees, 1990). Patients may also experience difficulty executing and sequencing learned motor programmes. Muscular rigidity, resting tremor and postural instability can be severe enough to be disabling. There can also be subtle changes in behaviour, such as lack of spontaneity, blunting of emotions, poverty of imagination, increasing apathy, lack of initiative and mild word finding difficulty (Gerstenbrand and Poewe, 1990; Hoehn, 1990; Pollock and Hornabrook, 1985; Stern, 1990). The label Parkinson's disease is reserved for

idiopathic cases, those of unknown origin. Known causes include encephalitis, coal gas poisoning, and drug side effects.

These represent the core symptoms of Parkinson's disease, but depression, dementia and cognitive impairments can accompany the physical findings. Variability in clinical presentation extends to alterations in cognitive function as well. Up to 50% of all patients develop depression (Mayeux et al., 1988), and approximately 20% of all patients develop dementia (Litvan et al., 19991). Disease onset typically occurs after the age of 50. The symptoms of PD develop as a consequence of degeneration of dopamine producing cells in the substantia nigra, which in turn reduces the amount of dopamine available in the subcortical ganglia. Other neurotransmitter systems may be affected. A more extensive discussion of the neuropathology in PD is to be found in Appendix B. Current treatments, such as anticholinergics and dopaminomimetics, aim to restore an optimum balance of affected neurotransmitter systems.

9 Appendix B: Neuroanatomical Structures Implicated in Parkinson's Disease

The symptoms of Parkinson's disease reflects the depletion of dopaminergic neurons in the substantia nigra, and consequently, the availability of dopamine in the brainstem and ascending dopaminergic tracts. There is associated severe neuronal loss in the substantia nigra pars compacta and the ventral tegmentum (Chui, 1989). The structures involved in Parkinson's disease include the dopaminergic tracts in the brainstem and basal ganglia. In the upper brainstem, the collection of cells known as the substantia nigra, so named for their black appearance in fixed specimens, produce the neurotransmitter dopamine. The neurotransmitter ascends via the nigrostriatal pathways, to the striatum, comprised of globus pallidus, putamen, caudate and thalamus (Agid et al., 1990; Ball, 1984). The proper function of motor systems, in reference to fluidity, smoothness, and sequencing, depends in large part on these structures (Cummings and Benson, 1984).

Although the failure of the dopaminergic system is the most prominent disorder, it is not the only neurotransmitter disorder in PD. There appears to be a further degeneration affecting noradrenergic and serotonergic systems, not only in the basal ganglia but also in neocortical and limbic

structures. The motor symptoms are most likely related to disorders of the basal ganglia and nigrostriatal dopaminergic system. Further impaired dopaminergic transmission may be the cause of akinesia, subtle cognitive defects and depression (Scatton et al., 1983). Treatment with levodopa may improve overall mental status, depression, and 'frontal' signs that might be a result of improved neocortical or limbic dopaminergic transmission (Dubois et al., 1990; Jayaraman, 1987), or even simply the alleviation of motor symptoms. It has been found that decreased dopamine in the putamen can lead to motor problems of the type found in Parkinson's, particularly akinesia, whereas a decrease in dopamine in the caudate may play a role in the pattern of cognitive impairment found in PD (Brown and Marsden, 1990). It has been hypothesized that the basic function of the basal ganglia is the automatic execution of learned motor programs, and that this is disrupted in Parkinson's disease (Marsden, 1982).

Cummings and Benson (1984) have tabulated neuropsychological deficits possibly associated with specific subcortical structures, presented in Table 22 below.

Table 22. Deficits Associated With Subcortical Lesion Sites

Subcortical Structures	Associated Deficits
Striatum	disorders of executive behavioral programming, reinforcement and conditioned learning, mood and motivation, language and attention.
Thalamus	deficits in arousal, attention, mood, memory, language, abstraction and categorization.
Brain stem nuclei:	deficits in arousal, attention, mood and memory

The deficits in executive motor programming secondary to striatal lesions noted above are similar to those found following frontal lobe lesions. By way of example, a case of striatonigral degeneration, verified by MR imaging, has been documented that presented with rigidity and bradykinesia. Neuropsychological examination revealed selective deficits in letter fluency, short term memory, motor speed, strength, and sequencing, all deficits associated with lesions to the primary motor and orbitofrontal cortices (Sullivan et al., 1991). It may be that subcortical structures are integrally involved in those cognitive functions previously thought to be cortical in origin. The cognitive deficits found in PD may be a reflection of the subcortical neurodegenerative processes in this disease.

10 Appendix C: Depression

The presence of depression in Parkinson's disease highlights several issues. Why does this depression occur? Is it a reaction to the debilitating effects of the disease, or is it a result of disordered neurochemistry? Does its presence indicate a variant of the PD pathological process? How does depression affect neurocognitive function and neuropsychological performance? These questions will be discussed in this section.

Depression frequently accompanies Parkinson's, but variability in diagnosis of depression has led to a range of prevalence estimates between 20% and 90% of all patients; current estimates are close to 50% (Mayeux et al., 1988). There has been some controversy as to the source of depression in this disease. For a long time it was believed that the depression was a reaction to the situation of being progressively, incurably ill (Huber et al., 1988). However, consequent work demonstrated that the presence of depression in PD does not correlate with disease severity; some of the most disabled patients did not become depressed. When compared to populations of other progressive, disabling diseases, such as arthritis, the PD population failed to show the same incidence or pattern of depression (Huber et

al., 1988; 1990). If exogenous factors could not entirely and satisfactorily account for the depression, could the depression be endogenous?

Neurotransmitter studies have demonstrated clear links between depression in PD and patterns of loss of neurotransmitter substances (Starkstein et al., 1990b; 1989). Studies tend to support the hypothesis that depression in Parkinson's is endogenous, a consequence of possibly several disordered neurotransmitter systems (Guze and Barrio, 1991; Mayeux, 1989). It has been suggested that disturbances of mesolimbic and mesocortical dopamine projections (Fibiger, 1984) or serotonergic systems (Mayeux et al., 1984) are involved in the emergence of depression in PD.

Diagnosis of depression may be difficult because of the confounds of motor slowing and bradyphrenia. However, specific complaints associated with depression in PD can be dissociated from motor signs. The following complaints are reported only in PD patients with depression (as compared to those with PD alone): worrying, brooding, decreased interest, hopelessness, suicidal tendencies, social withdrawal, self depreciation, ideas of reference, anxiety, decreased appetite, initial and middle insomnia and

decreased libido. Both depressed and nondepressed patients reported anergia, motor retardation and early morning awakening (Starkstein et al., 1990a).

Depression has been reported to occur significantly more frequently in patients with left hemisphere lesions than in patients with right hemisphere lesions. Since Parkinson's is a unilateral disease in the earliest stage, it is possible that side of onset might be correlated with depression. It has been found that in patients with unilateral disease, those with greater left hemisphere disease were significantly more frequently depressed than those with more right hemisphere involvement (53% vs. 21%). The imbalance in the depression scales was accompanied by cognitive decline on mental status examination, such that the predominant left hemisphere disease patients tended to show more impaired scores than the right hemisphere group. Not only was depression more frequent in the left hemisphere group, it was stronger (Starkstein et al, 1990c).

Depression in PD is associated with lowered scores on tests of cognitive function, especially calculation, digit span and visuomotor skills (Mayeux et al., 1981). Cognitive impairment can also be found in association with depression in non Parkinsonian populations. Cognitive changes have been found in both depressed and nondepressed patient groups, but

the impairments in the depressed patients were significantly worse than the nondepressed group (Starkstein et al., 1990). When only demented PD patients are studied, the intellectual impairment in dementia is greater than can be accounted for by depression alone (Martin et al., 1973; Sagar and Sullivan 1988). In summary, the presence of depression is associated with cognitive impairment in PD, but it does not account for all of the cognitive impairment, whether demented or not.

The associations between disease severity, intellectual impairment and depression are unclear. A relationship has been found between severity of depression and Mini Mental Scale scores, such that the more depressed PD patients also had lowered MMS scores. No relationship, however, was found in this study between depression and severity of illness, duration of motor symptoms, or age (Mayeux and Stern, 1983). A significant correlation between severity of disease and intellectual impairment, using a mental status exam as a measure of intellectual function, was shown in a later study in PD patients. Depression was not found to be correlated with either disease severity or intellectual impairment (Huber et al., 1988). Therefore, depression may be correlated with lowered MMS scores, and intellectual impairment may be correlated with disease severity, but no link has been established between depression and disease

severity.

In summary, depression occurs in roughly half the cases of Parkinson's disease. It is not associated with disease severity. It is thought to be endogenous, secondary to the disruption of one or several neurotransmitter systems. When both depressed demented, and nondepressed demented PD patients are compared, studies have indicated that the presence of depression alone is not a sufficient explanation for the cognitive changes found in demented patients.

11 Appendix D: Cognitive Changes

Although in the original description of Parkinson's disease, there was no indication of mental impairment (Parkinson, 1817, cited in Cummings, 1988), this assumption was challenged in the early 1970's as widespread declines on the Wechsler Adult Intelligence Scale (WAIS) were reported in PD patients (Loranger et al., 1972). As PD patients often displayed depression, the Loranger study also tested a control group of depressed patients. Comparison between the two patient groups revealed that the effect of depression alone on WAIS IQ scores was not as pronounced as that of PD. Since that time it has become generally accepted that mental status changes are ubiquitous in Parkinson's disease (Cummings, 1988). The greatest degree of impairment is seen on Performance measures. Full scale IQ scores generally remain in the normal range overall in the Parkinson's population, reflecting the relative preservation of verbal skills (Brown and Marsden, 1987). Intellectual changes in Parkinson's may be due to factors such as 1) lesions of the disease 2) confusion secondary to drugs 3) depression and 4) vascular lesions (Mortimer, 1988).

In many studies of cognitive changes and dementia in Parkinson's disease the two terms are used almost interchangeably. An example of the confusion between

dementia and intellectual changes is found in a study by Pirozzolo et al., (1982), in which the authors state that over 93% of the patients demonstrated some cognitive impairment, and that, because of the 'continuous nature' of cognitive impairment to dementia, it was difficult to determine a prevalence rate for dementia. Therefore any conclusions should be evaluated in light of the criteria used for determination of cognitive impairment and dementia. In this appendix, results based on populations of mixed demented and nondemented PD patients have been excluded where information on mental status is available.

In the two decades since the Loranger et al. (1972) study, there have been further descriptions of cognitive changes. However, in part due to confusion over the terms dementia and cognitive changes in the literature, no "...clear consensus of the cognitive profile associated with this disease [is available] from a review of the available literature " (Taylor et al., 1986b, p.847). However, some patterns have emerged. In studies that differentiate between cognitive changes associated with PD, and frank dementia (usually by way of a cut-off score on a dementia assessment tool), the nondemented cognitive impairments are usually found in the domains of memory, visuospatial skills, frontal/executive functions, bradyphrenia and psychomotor

function (Cummings, 1988; Huber and Paulson, 1985). Tests of the cognitive functions in high functioning Parkinson's patients and controls (IQs of 120 and higher) have revealed a pattern of deficits in the patients that was coherent and similar to other PD studies. Typical changes in this group consisted of impaired Performance IQ, verbal memory, visuospatial memory and visuospatial skills. The high functioning patients did not show deficits of executive function on the Wisconsin Card Sorting Test, of memory on the Wechsler Memory Scale, or global intellectual function on mental status examinations (Mohr et al., 1990a). If one takes the position that cognitive changes are ubiquitous in PD, it may be concluded that these tests are not sufficiently sensitive to detect declining cognitive functions in a sample of highly intelligent and still functioning PD patients.

On memory testing, Paired Associates and Logical Memory from the Wechsler Memory Scale have been found to be impaired in many studies (Hietainen and Teravainen, 1986; Huber et al., 1986b; Agid et al., 1986) and show improvement when motor symptoms are relieved on levodopa therapy (Mohr et al., 1989). However, the following memory tests do not show improvement with levodopa therapy: the CVLT (California Verbal Learning Test), verbal word list learning, The

Rey-Osterrieth Figure, and the figures from the Mattis MiniMental Status Exam (Mohr et al., 1989). Word list learning, as measured by the Buschke Selective Reminding Test, is impaired in PD, especially in patients over the age of 65 (Fischer et al., 1990). Over the age of 65, patients with longer duration of disease are at greater risk to develop this particular memory deficit, independent of dementia or depression (Fischer et al., 1990).

Memory deficits are specific in PD. The impairment for effortful episodic memory is selective for short term recall only, and disappears on long term testing (Taylor et al., 1990). When levodopa is given to normal elderly controls, they improve on free word recall tasks (Newman et al., 1984), and on recall of complex verbal materials (Mohr et al., 1989). Remote memory and immediate recall are not affected in PD (Agid et al., 1986; Huber et al., 1986), as well as generic or knowledge memory (Mohr et al., 1989). Impairment on the Brown-Peterson paradigm, which assesses the effect of proactive interference on memory, has been reported in PD patients (Cummings, 1988). In summary, effortful episodic memory is selectively impaired in Parkinson's on short term recall only.

Boller et al. (1984) have defined impairment in visuospatial ability as disorders of judging relative

positions of objects in space, integrating such spatial positions into a framework, and in performing mental operations involving spatial concepts (Boller et al., 1984). Some abilities decline in nondemented subjects as the disease progresses, such as face recognition, visual organization, and pattern construction (Levin et al., 1991). Performance on tests such as the Rey-Osterrieth figure, the Taylor figure, and Street Map do not show improvement with levodopa therapy (Mohr et al., 1989). In general, the Parkinson's population shows impairment in tests of visuospatial skills (Huber et al., 1986; Mohr et al., 1990b; Mortimer et al., 1982).

However, visuospatial deficits do not appear consistently and reliably in PD patients and intact visuospatial skills have been reported in patients who are only mildly affected by the disease and who show no other cognitive disorders or depression (Della Sala et al., 1986). It has been suggested that patients with mild motor symptoms show visuospatial deficits only when visuospatial skills are used to control movement (Brown and Marsden, 1987). It has also been stated that the visuospatial deficit often found in these patients is largely on tests requiring self generated replies, but that no such impairment is seen when a multiple choice format is used (Brown and Marsden, 1990).

Both perceptual and motor components can contribute to the deficit, which is independent of depression and degree of cognitive deficit (Boller et al., 1984).

Performance on frontal/executive type tests are frequently found to be impaired in PD. Increasingly, the cognitive deficits in PD are being characterized as frontal (Cummings, 1988; Taylor et al., 1990). Parkinson's patients are particularly impaired on tests sensitive to frontal lobe lesions, such as the Wisconsin Card Sorting Test, Stroop, delayed recognition test and verbal fluency (Taylor et al., 1986a). Neuropsychological studies of Parkinson's patients consistently demonstrate deficits on set shifting, such as on the Stroop test and Trailmaking A and B (Hietainen and Teravainen, 1986), as well as temporal ordering, recency and sequencing tasks (Brown and Marsden, 1990; Sagar and Sullivan, 1988; Sullivan and Sagar, 1989a). PD patients also show interference effects, similar to frontal lobe patients (Cummings, 1988), and endorse a great many 'frontal' type behaviors in a checklist format, such as inertia, stereotypy, indifference, disinterest, social dependence, indifference to rules, dependence on the physical environment, difficulty in programming, and loss of intellectual control (Pillon et al., 1986). Unfortunately, theoretical discussion of the relationship of these

'frontal' behaviours to the frontal lobes, and operational definitions of the same behaviours were not more clearly defined in the Pillon study, and so it is difficult to evaluate the usefulness of such a checklist. High functioning Parkinson's patients fail to show the typical deficits on the WCST (Wisconsin Card Sorting Test) (Mohr et al., 1990a), which may reflect test insensitivity, or some level of protection afforded this group by education, IQ, or life experience. When levodopa is given to elderly normal controls, they do not show increases on verbal fluency, which is usually associated with frontal lobe function (Newman et al., 1984). Parkinsonian patients have a disproportionate disability in dating past public events, compared to Alzheimer patients, when the study controlled for the content knowledge of those events (Sagar and Sullivan, 1988). Both dating ability and recency judgements are impaired in PD patients (Sagar and Sullivan, 1988), implying a disorder in ordering items in time. Disorders of temporal organization and recency judgements have been reported in patients with frontal lobe lesions (Milner, 1982). In summary, the frontal/executive deficits in PD may include sorting, abstraction, verbal fluency, freedom from distraction, set shifting, temporal ordering and recency judgement, and sequencing.

Another element of the cognitive changes reported in PD is a syndrome known as bradyphrenia. This refers to a slowing of thought processes, and many studies have commented on findings of slowing and hesitancy in higher cognitive functions that are independent of accuracy (Sagar and Sullivan, 1988). However, when slower reaction times have been accounted for, PD patients do not show slower 'cognition times' than normal controls (Mayeux et al., 1987).

Although motor signs such as rigidity, tremor and bradykinesia are hallmarks of this disease, higher order motor programming is also disrupted (Piccirilli et al., 1989; Marsden, 1982). Disorders of organized, sequential motor movements may reflect disruptions in perceptual, visuospatial, planning and sequencing processes (Sagar and Sullivan, 1988).

Cognitive changes in PD are widespread through the population, and tend to converge on memory, visuospatial, and frontal lobe functions. Factors that modify these changes are drug status, level of daily functioning, motor slowing and test format (i.e., multiple choice or subject-generated responses).

12 Appendix E: The Role of the Frontal Lobes in Parkinson's Disease

It has been suggested that the frontal type disorders seen in Parkinson's disease (PD) are a direct consequence of subcortical degeneration (Taylor et al., 1986a, 1990). This theory requires that plausible connections between the two areas be demonstrated, and that neurocognitive disorders after subcortical lesions mimic those found after frontal cortical lesions. If this can be demonstrated, this theory may supply a rationale for the types of frontal lobe deficits found in PD patients. This also presupposes that, in PD, there is little or no cortical degeneration, and that the pathophysiological process is limited to the basal ganglia. Such ideas were discussed in the Introduction, and various criticisms for the 'subcortical' model were presented. The 'subcortical loop' model is presented here in addition to other findings on the frontal lobes, in order to expand on the theoretical explanations for some of the cognitive deficits in PD.

Recent studies have demonstrated the presence of multiple anatomical circuits linking subcortical structures with specific and discrete frontal cortical sites (Alexander et al., 1986; Taylor et al., 1988). Each of these circuits integrates input from different cortical areas and directs

that back to a single zone of the frontal lobes.

The following description of five such subcortical-frontal circuits is taken from Alexander, DeLong, and Strick (1986). In primates five anatomical circuits can be demonstrated that link specific frontal cortical sites with other cortical input and basal ganglia. Each circuit has the same basic organization, that is, multiple cortical inputs are gathered at the levels of striatum, thalamus, pallidum and substantia nigra, which then loop back to a discrete and specific cortical site. The five cortical sites in the frontal lobes that are targets for each of the five circuits are 1) the supplementary motor area (motor circuit), 2) the frontal eye fields (oculomotor circuit), 3) the dorsolateral prefrontal cortex (dorsolateral prefrontal circuit), 4) the lateral orbitofrontal cortex (lateral orbitofrontal circuit), and 5) the anterior cingulate area (anterior cingulate circuit).

The supplementary motor area is one cortical source for the motor circuit that also takes input from the arcuate premotor area, plus the motor and sensory cortices. These are functionally integrated at the level of the putamen so that separate cortical areas for individual body parts are aligned. For example, sensory and motor fibres associated with the wrist are brought together at this level. From the

putamen these topographically organized fibres project to the globus pallidus and the substantia nigra, and through to the thalamus. Ultimately these fibres loop back to the supplementary motor area, which is comprised of Brodman's areas 6 and 8 on the mesial cortical surface. Two features of the supplementary motor loop are the specificity of neuronal responses to active and passive movements of individual body parts, and a consistent somatotopic organization throughout the circuit. The circuit is able to integrate information about body movement and position. The motor circuit is thought to have a role in control of movement direction and in modulating movement velocity or amplitude. The basal ganglia have been implicated in the preparation of movement, and clinical observation has shown that lesions to the supplementary motor area can affect the initiation of motor activity (Luria, 1973).

The frontal eye fields are the cortical endpoints of the oculomotor circuit, which integrates input from the frontal eye fields in addition to dorsolateral prefrontal cortex and posterior parietal cortex. This follows a course similar to the motor circuit, but instead of integration occurring in the putamen, it occurs at the level of the caudate. The result then passes through the globus pallidus and substantia nigra, to the thalamus and back to the frontal

eye field. The frontal eye field is found on the lateral frontal surface in the region of Brodman's area 8. This circuit appears to respond to passive visual stimulation, and is involved in fixation of gaze and saccadic eye movements.

The dorsolateral prefrontal circuit combines input from the dorsolateral cortex, the posterior parietal cortex, and the arcuate premotor area. Because of the parietal input it has been characterized as an association loop. As above, the fibres are integrated at the level of the caudate, then progress on to the globus pallidus and the substantia nigra, then to the thalamus and return to terminate in the dorsolateral cortex. Dorsolateral cortex consists of parts of Brodman's areas 9, 10, 44, 45 and 46. The dorsolateral circuit has not been functionally characterized as well as the supplementary motor or oculomotor circuits, but it may be involved in processes subserving spatial memory.

The second association loop is the lateral orbitofrontal circuit. This combines input from the lateral orbitofrontal cortex, the superior and inferior temporal gyri, and the anterior cingulate area. This combines at the level of the caudate, passes on to the globus pallidus and substantia nigra, next to the thalamus, and circles back to the lateral orbitofrontal cortex. Lateral orbitofrontal cortex is found

in Brodman's areas 11 and 47. Bilateral lesions to this cortical area in primates is demonstrated behaviourally by perseverative tendencies that interfere with switching behavioural sets.

The last of the five circuits is the anterior cingulate circuit. Input from the anterior cingulate area, hippocampus, entorhinal cortex, and inferior and superior temporal gyri are combined in the ventral striatum, which includes nucleus accumbens and the olfactory tubercle, and then pass on to the globus pallidus, ventral pallidum, and substantia nigra, to the thalamus and project back to the anterior cingulate area. The anterior cingulate area includes Brodman's areas 32 and 12. This particular circuit has strong limbic connections, but no functional speculations have been offered (Alexander et al., 1986).

The cortical termination points of these five circuits can be grouped according into three traditional anatomical areas: mesial, dorsolateral, and orbitofrontal. The mesial surface comprises Brodman's areas 6 and 8 on the mesial surface of the lobe. The dorsolateral surface includes areas 9, 10, 11, 12, 46 and 47. Orbitofrontal cortex includes areas 10, 11, 12, 14, 15, and 47 (Stuss and Benson, 1984).

The supplementary motor and anterior cingulate circuits terminate on the mesial surface of the frontal lobe. Tests

which are sensitive to lesions in this region are verbal fluency (FAS, or shopping list from the MDRS), and the Initiation and Perseveration scale on the MDRS. Since this area has been implicated in programming motor sequences, as well as initiation and maintenance of those sequences, any test requiring planned, sequential motor programs, such as drawing sequential squares and triangles (from the MDRS), and Trailmaking A and B, should also be sensitive. Mesial lesions have also been associated with attentional deficits, and may be demonstrated on tests of distractibility, such as the Stroop and consonant trigrams (Stuss and Benson, 1984; Stuss, 1988).

The frontal eye fields and the dorsolateral prefrontal circuits terminate on the dorsolateral surface of the frontal lobe. This area has been implicated in deficits on motor sequencing, such as the manual and graphomotor sequencing tasks on the MDRS; deficits in planning, sorting, and abstraction, which can be found on the Halstead Category test, the Wisconsin Card Sorting Test, and Similarities from the WAIS-R; and deficits in verbal fluency, such as on the FAS test. Because the frontal eye fields are included in this area, deficits may also be found on tests of visual search, such as embedded pictures (Stuss and Benson, 1984; Stuss, 1988). The overlap of deficits between mesial and

dorsolateral areas may be due to lesion studies which include large areas of cortex, often overlapping cortical boundaries as described here.

The lateral orbitofrontal circuit terminates largely in the orbitofrontal area. Lesions in this regions have been associated with personality changes such as disinhibition and increased rule-breaking, a verbal-behavioural dissociation such that verbal input or instruction does not alter behaviour, and an absence of motor slowing (Luria, 1973; Stuss, 1988; Stuss and Benson, 1984).

The relevance of these circuits lies in functional differentiation of frontal cortex: [it]"...provides a framework whereby relatively selective disturbances of 'motor' or more 'complex' behavior may occur from damage to different portions of the basal ganglia." (Alexander et al., 1986, p.373). This author makes the further connection that "...certain motor disturbances characteristic of Parkinson's disease have occasionally been observed in patients with lesions that involve the supplementary motor area" (op. cit., p.374), such as akinesia. Such loops may mediate the relationship between the functions of the basal ganglia and the prefrontal cortex (Alexander et al., 1986).

A simpler version of these circuits, involving a complex loop and a motor loop, has also been described (Taylor et

al., 1988). The former integrates association cortex with basal ganglia and the frontal lobe. The latter primarily organizes motor functions. This association loop is comprised of two separate circuits described by Alexander et al. (1986), i.e., the dorsolateral prefrontal and the lateral orbitofrontal.

Because the caudate and the prefrontal cortex in animals has been shown to be involved in tasks which require the development of an internally ordered, subject directed, plan of action, it has been suggested that these structures may act to 'prime' the frontal cortex about the significance of an event to come. Without such priming the frontal cortex would require constant re-affirmation of the significance of stimuli, that is, would constantly require external cues and guidance to carry out a motor program (Taylor et al., 1988). Such a priming capacity could be integral to internally generated motor programming and behavioral planning.

The hypothesis that the basal ganglia are part of a striatal-cortical system which is involved in planning and modulating ongoing activity in the absence of external stimuli has also been explored in a paper by Stern (1987). That is, the functions of the basal ganglia are thought to be similar to those hypothesized for prefrontal cortex. For

instance, performance on a delayed response task can be affected by lesions in either striatum or frontal cortex in animals (Stern, 1987).

The possibility that disturbed caudate outflow in PD will give rise to impairments in functions which are also dependent on the integrity of the prefrontal cortex has been investigated, based on the supposition that the outflow of the caudate to prefrontal cortex is disturbed by the hypodopaminergic dysfunction in PD (Taylor et al., 1986a). In this study, it was hypothesized that nondemented parkinsonian patients would demonstrate deficits in functions dependent on the two frontal loops, the motor and association. Four clusters of tests were administered: psychomotor, memory, visuospatial and executive. Only five tests distinguished PD patients from controls: the Wisconsin Card Sorting Test (WCST), the Rey Auditory Verbal Learning Test (RAVLT) free recall, a delayed memory recognition test, a multiple manual set performance task, and immediate, but not delayed, recall of the logical memory on the WMS. In addition, the experimental group was slower, but not less accurate, on the visuospatial tests, than the controls. The types of cognitive deficits found in these patients were interpreted to be those which required the ability to spontaneously generate efficient strategies in self directed

task specific planning. This is concordant with the model in which the prefrontal cortex and caudate are viewed as critical structures in motor programming and planning. The results were related to defective frontal lobe function by way of several arguments. The visuospatial results indicate that visual and perceptual processes were intact but slow in the patients. Slowing of rapid visual scanning is known to be defective in PD. Memory functions of encoding, consolidation, and retrieval processes were all demonstrated to be intact. The other tests in the study have demonstrated sensitivity to frontal lobe lesions. A common element underlying the significant test; in this study was the requirement of spontaneous generation of task-specific strategies. Therefore correct performance relied on the constant formation and changing of mental strategies. "The presence or absence of impaired performance in the PD group appeared to hinge on the degree to which internally, that is, subjectively organized guidelines, are required for success" (Taylor et al., 1986a, p.872). Tests requiring access to semantically stored information (Trails B and verbal fluency) were not impaired in this group. "This profile of cognitive strengths and weaknesses strongly suggests that the deficit which characterizes PD is neither global nor broadly regional in nature... Execution of even

highly challenging executive abilities was not impaired where rules were explicit...only those tests which maximized the need for self-directed planning in forming context dependent associations or strategies were affected" (op. cit., p.872-3). Caudate and prefrontal lesions, like cognitive deficits in PD, are associated with deficits in self generated motor programmes and behavioural planning.

The following review of the literature on frontal lobe lesions and behaviour emphasizes the similarities between PD deficits and those associated with frontal lobe disorders. The function of frontal lobes in humans has been surmised largely from lesion studies. Results from such studies do not necessarily indicate what the functions are of the intact frontal lobe. They instead describe behavioural deficits which result from frontal lobe lesions (Ellis and Young, 1988). The most extensive series of studies arise from the surgical excision groups tested at the MNI (Montreal Neurological Institute). The contribution of these studies lies in the detailed information about surgical lesion sites and follow up neuropsychological assessments. These cases tended to have large excisions, including dorsolateral, orbital and mesial surfaces. While they are useful in describing frontal lobe dysfunction in general, they do not typically provide more precise

localization of function. In general, studies of localization of behaviour deficits following frontal lobe lesion are hampered by problems in accounting for variables such as lesion size, location, and even lateralization (Stuss and Benson, 1984).

The following frontal lobe lesion studies, undifferentiated to region, demonstrate a clear series of deficits. However, the majority of excisions carried out at the MNI spared the primary and secondary motor areas so that, in effect, those studies presented here refer to prefrontal cortex.

Some lesion studies demonstrate laterality effects. In general, left frontal patients tend to show more difficulties with language stimuli, while the right frontal subjects are more prone to errors with nonverbal, pictorial stimuli. However, both sides of the frontal lobes are sensitive to all tests reported (Jones-Gotman and Milner, 1977; Milner, 1963, 1964; Smith and Milner, 1988).

Emission of behaviours is reduced in some specific ways after frontal insult. Spontaneous speech, as well as verbal fluency, is affected by left frontal lesions. The Thurstone word fluency test, as well as similar verbal fluency tasks, are sensitive to this deficit (Milner, 1964). In an analogous fashion, right frontal lesions are associated with

impaired design fluency. This has been demonstrated with the Design Fluency Test which requires the patient to produce as many different, abstract designs as possible (Jones-Gotman and Milner, 1977; Milner and Petrides, 1984; Smith and Milner, 1988). It has also been noted that the production of spontaneous facial expressions is reduced after frontal lobe lesions (Kolb and Milner, 1981).

According to Luria (1973), the premotor cortex acts on the rapid and smooth transition of one component of a skilled act to the next. Therefore lesions of the premotor cortex affect the automaticity, smoothness and speed of movements. Animal studies suggest that this area programs motor acts involving the mouth and arm (Jayaraman, 1987).

Studies of undifferentiated frontal lobe lesions, involving all or some of the frontal cortical areas have shown consistent deficits in abstraction, planning, and behaviour modulation, such as on WCST (Milner, 1963, 1964; Milner and Petrides, 1984).

A consistent report in the literature is an impairment in using cues or feedback to alter behaviour, resulting in perseverative responses and errors. On the Wisconsin Card Sorting Test (WCST) this also leads to fewer categories achieved and difficulty in shifting set (Milner, 1963, 1964; Milner and Petrides, 1984). The perseveration scale on the

Mattis DRS also reflects this tendency (Janowsky et al., 1989). Perseverative errors may be associated with dorsolateral lesions only (Milner, 1975). However, close examination of the surgical diagrams of patients in this study indicates that surgical lesions often extend beyond dorsolateral surfaces. A similar type of disorder in a dichotomy between verbal response and behaviour has been noted. The patient may be able to say what the next correct response ought to be, but still is unable to effect the correct response (Luria, 1973). Such a response tendency may underlie perseverative behaviours.

Conditional associative learning tests, which pair a novel stimulus with a novel behavioral response, are very difficult for subjects with frontal lobe lesions. This deficit cannot be attributed to a failure to remember either the stimulus or the required response, as subjects are able to demonstrate that they have learned both. The impairment appears to lie in forming a new stimulus-response association (Milner and Petrides, 1984; Petrides, 1985).

With regard to the role of the frontal lobes in memory, Luria says that lesions of the frontal lobes do not result in primary disturbances of memory; rather the ability to effectively recall and maintain an active search effort, as well as to switch from one set of memory traces to another,

is impaired. This is similar to studies that demonstrate recall, but not recognition, memory, is impaired in PD patients, presumably due to frontal dysfunction. However, the difficulties with temporal sequencing which have been demonstrated in FL cases have led to the conclusion that such patients are impaired on memory tasks which require some temporal information and organization, while being relatively spared on memory tasks which do not make temporal demands (Fuster, 1985; Milner and Petrides, 1984; Schacter, 1987; Stuss and Benson, 1984). A more extensive discussion of memory deficits after frontal lobe lesions is to be found in Appendix F.

Both in spontaneous behaviour (Stuss, 1988) and on formal testing, a loss of inhibition has been reported after frontal lobe lesions (Milner, 1963). On the Wisconsin Card Sorting Test (WCST) such lack of inhibition leads to perseverative errors, because the patient does not seem to inhibit previous response tendencies in the face of cues to change strategies (Milner, 1963). This is also seen in eye movements if the lesion includes the frontal eye fields; the patient is unable to inhibit eye saccades to distracting stimuli, even when instructed to ignore the competing stimulus (Milner, 1982). A failure to inhibit has been demonstrated in both monkeys and humans with the delayed

alternation test (Freedman and Oscar-Berman, 1986; Milner and Petrides, 1984). In this test, the correct response in each trial is the alternate from the trial before, so that correct response cycles A -B -A -B, etc., with a delay between each trial. The delay element presents a difficulty for subjects. In delayed response testing, the subject is shown where an object, such as a penny, is hidden. After a delay, the subject is permitted to search for the object. Frontal lobe subjects frequently do not maintain a stimulus and place match over short time periods, and so make errors when searching (Freedman and Oscar-Berman, 1986). This is similar to the deficit seen on a delayed paired comparison task in which two stimuli, presented separately in time, must be judged as similar or different (Milner, 1964). There is agreement in the animal and human literature that dorsolateral lesions interfere with memory tasks requiring temporal coding, but not those tasks which are free of temporal context.

There is a loss of temporal organization and deficits in monitoring temporal sequences such that self ordered pointing tasks are impaired, as well as recency and frequency judgements (Milner, 1982; Milner and Petrides, 1982, 1984).

There is also a tendency towards increased rule-breaking after frontal lobe lesions, which some authors have postulated to also be a result of loss of inhibition. This is seen on Porteus Mazes and the stylus maze task, in which the patient may ignore the command to start and cross lines inappropriately (Milner, 1964, 1965; Milner and Petrides, 1984).

Another source of difficulty for frontal lobe patients lies in sorting and category formation. On the WCST, frontal lobe patients attain fewer categories than normals. Although this has been ascribed to the effect of perseverative errors (Milner, 1963), there appears to be in addition a specific difficulty in abstraction which is apparent on sorting tests (Incisa della Rocchetta, 1986). Another test of sorting and category formation is the Halstead Category test (Halstead, 1947), which requires the subject to discover a principle in a series of cards or slides which will suggest a number between one and four. In general, defective performance on this test reflects bilateral and left prefrontal pathology (Stuss and Benson, 1986).

The Tower of London test requires the planning and execution of novel strategies to solve a puzzle, which involves moving coloured rings from one peg to another within a set of rules. Left anterior frontally damaged patients show deficits on this test (Shallice, 1982).

Disturbance in frontal lobe function may lead to "disintegration of complex programmes of activity and to their ready replacement either by simpler and more basic forms of behaviour, or by the repetition of inert stereotypes" (Luria, 1973, p.199). In such patients, the "verbal command remained in their memory, but it no longer controlled the initiated action and lost its regulating influence." (op. cit., p.200). This is similar to the dissociation noted by Milner (1964) between verbal and behavioural responses to the WCST by patients with frontal lobe lesions. Such patients might be able to verbalize the correct move or strategy, but not use that verbalization to guide behaviour. Whereas deficits such as these are results of lesions to the prefrontal cortex, lesions restricted to the premotor zones will result in 'pathological inertia' to the initiation of action and leave the motor programmes intact. Behaviour becomes impulsive because "the retention of a complex and consecutive programme for the intellectual act is disturbed" (op. cit., p.212). Visuo-perceptual problems may result from a "profound

disturbance of the analysis of visual perception in massive lesions of the frontal lobes" (op. cit., p.217). Further, arithmetic problems are difficult because the patients cannot switch between the arithmetical and other operations required to come to the correct solution. Such patients who "replace the performance of a complex programme by an inert stereotype characteristically are not aware of their mistake" (op. cit., p.218-219).

What is missing in these patients is the ability to formulate and execute a programme to effect a goal. Simple problems may rely on simple, well learned plans to reach the desired goal; but if the problem is unusual or more complex, then a programme of action must be formulated, and this the frontal lobe patient finds difficult.

Organized conceptually, frontal lobe disorders include a loss of temporal organization in goal oriented behaviour and an impaired ability to plan sequential tasks or properly sequence behaviours (Milner, 1982). There can be a loss of the ability to establish, maintain or change a set, affecting attention, sorting, planning and perseveration (Stuss and Benson, 1984). A strong tendency to persevere in one response mode may occur, due to disruption of inhibition of competing responses (Milner, 1963, 1982). There is a notable dissociation between verbal and

behavioural response, such that a subject may say what the next appropriate behaviour should be, while at the same time continuing to make perseverate errors (Milner, 1963).

Therefore a frontal lobe lesion can affect the inhibition or regulation of motor responses while verbal responses are left intact. A patient can lose the ability to monitor behaviour, so that they are unable to use feedback to alter their actions (Stuss and Benson, 1984).

Tests showing most sensitivity to frontal lobe lesions include verbal and design fluency (Milner and Petrides, 1984), the Wisconsin Card Sorting Test (WCST), the Halstead Category Test (Stuss and Benson, 1986), the Initiation and Perseveration scales of the Mattis Dementia Rating Scale (Janowsky et al., 1989), conditional associative learning, recall memory for word lists, delayed alternation, response and judgement tests, mazes, self ordered pointing, ordering, frequency and recency tasks, and tests of abstraction (Fuster, 1985; Jones-Gotman and Milner, 1977; Milner, 1963, 1965, 1982).

Neuropsychological tests which are sensitive to known lesions of individual cortical areas may also be sensitive to disorders of the cortical-basal ganglia circuit which terminates in that cortical area. For instance, tests which demonstrate lesions to the frontal eye fields (FEF) are

thought to include visual search, the complex picture, and embedded figures. Lesions to the FEF interfere with control of saccadic eye movements. Lesions of the supplementary motor area (SMA) can lead to decreased verbal output, lack of spontaneous initiation of speech, and adynamia, which may include facial expression (Stuss and Benson, 1986). In Parkinson's, a subcortical degenerative disease, deficits on visual search, decreased verbal fluency, slowness to initiate action and speech have been well documented (Brown and Marsden, 1987, 1990; Cummings, 1988; Growdon and Corkin, 1986).

A more detailed description of localization of behaviour within the frontal lobe reveals similarities between that and the 'subcortical' syndrome of PD. The prefrontal cortex, as the association cortex of the frontal lobes, may act to organize behaviors in a goal oriented fashion with respect to time sequences, that is, past and future contingencies. "...the prefrontal cortex seems important for temporally extended behavioral structures that require selective attention, memory, foresight, and choice between alternatives." (Fuster, 1985, p.170). Excluded from this description are well established and stereotyped behavioural sequences, such as getting to work in the morning, where temporal discontinuities, such as waiting for the bus, do

not impose a cognitive challenge. Rather, it is the organization of behaviour in time in response to some novel input or stimulus, or the organization of new behaviours, which is subserved by the prefrontal cortex (Fuster, 1985).

Furthermore, within this model, deficits after frontal lobe lesions describe one basic and three subordinate functions. The prefrontal cortex performs temporal integration in its role in the programming of behaviour. Such a function may be carried out in three ways. First, short term memory reviews the recent past in order to monitor behaviours. Second, the frontal lobes develop a preparatory set to anticipate future behaviours, and third, a control function suppresses or inhibits interference which might disrupt "...the formation and execution of behaviour structures" (Fuster, 1985, p.175). These three functions, the anticipatory preparation, short term memory, and interference control may all be involved in the temporal control of behaviour. This functional organization is ascribed to the prefrontal cortex in general, without further localization. It has been reported that temporal integration can be disrupted after lesions to the prefrontal convexity, and deficits in interference control (i.e., loss of inhibition) are often associated with orbital-medial lesions (Fuster, 1985).

Luria (1973) says that "the lateral zones of the frontal cortex are very closely linked with the motor structures of the anterior parts of the brain;...lesions in the lateral frontal zones, and in particular, in the postfrontal region, as a rule give rise to particularly marked disturbances of the organization of movements and actions, to disintegration of motor programmes..."(p.221). On the other hand, the basal or orbital, and medial zones of the frontal lobes have a completely different functional organization. They are closely linked to the reticular formation and limbic system, "with no direct relationship to the motor cortex, the precentral gyrus or the premotor area" (p.222). Lesions of the basal, orbital zones lead to generalized disinhibition and gross changes in affective processes. The intellectual changes in these individuals also forms a different picture. Whereas in the lateral zones, lesions lead to potentially intact ability to carry out intellectual operations, the impulsiveness leads to fragmentation of motor programmes, in the medial zones have an effect on the "regulatory and modulatory influences which the frontal cortex exerts, through its descending connections, on the structure of the reticular formation" (p.224). This leads to a state of confusion, and lack of orientation, marked by confabulations.

Stuss' (1988) model of surface localization of lesion and correlation with frontal lobe disorders is most easily communicated by reproducing his table of surface localization and deficits.

Table 23. Cortical Localization and Behavioural Deficits
(Stuss, 1988).

	ORBITAL	LATERAL	MEDIAL
DEFICIT:			
PERSONALITY	facetious, puerile, disinhibited	apathy, indifference, restless, explosive, 'pseudodepressed'	slowness, apathy, pseudo depressed
MOTOR	not slow; poor goal direction; impulsive	restless, poor sequencing of motor tasks	akinetic, agestural; no initiative; possible gait disturbance
COGNITIVE	intact, but poor use in real life	possible IQ deficit; deficient planning, sorting, abstraction	slowing of initiation of processing
LANGUAGE	normal fluency, but verbal-action dissociation	language syndromes; diminished fluency; loss of verbal regulation	diminished fluency, slow initiation

According to the table above, motor signs which arise from frontal lesions are of two different types, arising from two different areas of the cortex. A restless, impulsive, childish and unreliable constellation of behaviours is seen with orbitofrontal lesions. Damage to the dorsolateral frontal convexity can give rise to a 'pseudodepressed', abulic, hypokinetic syndrome, associated

with a lack of drive. 'Pseudodepression' is a term which describes personality changes in frontal lobe patients, and is comprised of apathy, indifference, decreased initiative, interest in sex, overt emotional display and verbal output (Blumer and Benson, 1975). Akinetic mutism may be seen after lesions, usually bilateral, to the posterior medial-orbital surfaces. With diffuse right frontal or bilateral damage a disturbance known as motor impersistence can be seen, in which there is difficulty initiating and maintaining motor movements (Stuss and Benson, 1986).

Lesions of the supplementary motor area (SMA) can lead to speech arrest, speech retardation or arrest of voluntary movements (Stuss and Benson, 1986). Based on lesion, stimulation, and blood flow studies, it can be concluded that the SMA is the site of programming of motor subroutines, which consist of quick, isolated motor movements. Additionally, the SMA may also contribute to initiation of movement and execution of established patterns of fast motor activities, such as are involved in speech, finger and limb movements (Roland et al., 1980; Jayaraman, 1987).

In general, the frontal lobes can be regarded as tertiary association zones for both the limbic system and the motor cortex. This is reflected in the importance of the frontal

lobes in both regulation of attention and vigilance as well as control of highly complex motor programmes. By virtue of their limbic connections, the medial zones are particularly implicated in regulating the state of waking and appropriate level of attention for immediate tasks (Luria, 1973). The disorders seen after lesions to medial and lateral regions are similar to those seen in PD. One explanation for symptom site selectivity in PD may lie in differential deterioration of cortical-subcortical connections connecting different regions of frontal cortex with separate subcortical structures.

13 Appendix F: Memory Deficits and the Frontal Lobes in Parkinson's Disease

This section will first review how frontal lobe dysfunction from lesions, surgery, and trauma affect memory, then discuss the types of memory failures found in Parkinson's disease in order to compare the types of memory loss from each etiology.

In a thorough review of the literature, both human and animal, on the impact of frontal lobes on memory function, Schacter (1987) has argued that the frontal lobes contribute temporal and sequential organization to memory, and that deficits in these functions leads to specific types of memory impairments. Three important points are made in this article. First, that patients with discrete frontal lesions are impaired for memory of certain kinds of contextual or spatiotemporal information. For instance, tasks requiring recency or frequency judgements dependent on memory show impairments in frontal lobe patients. Second, lesion studies in nonhuman primates indicate that lesions to the principal sulcus impair performance on spatial memory tasks. Finally, encoding of spatiotemporal information in humans is accomplished relatively automatically, without effort or effect on concurrent cognitive processes.

Memory can be conceptually subdivided into declarative and procedural, the former encompassing episodic and semantic. Declarative memory can be consciously invoked. Episodic memory is embedded in context, so that the memory is associated with a specific place and time. Semantic memory does not have such contextual tags, but instead refers to knowledge of rules and general principles (Tulving, 1972). Procedural memory refers to acquired skills or procedures, usually motoric, which may not be conscious. It has been argued by other authors (Kinsbourne and Wood, 1975; Rozin, 1976; Schacter and Tulving, 1982a,b; Stern 1981; Tulving, 1983) that amnesic patients specifically have difficulty recalling the spatiotemporal context of events, and therefore show deficits in episodic memory. It has also been argued that amnesics exhibit a generalized deficit in memory for declarative information that encompasses the deficit in episodic memory (Mayes and Meudall, 1983; Squire and Cohen 1984; Zola-Morgan, Cohen and Squire, 1983). Schacter (1987) concludes that all arguments are correct for a subtype of amnesic. His position is that those who are free of frontal lobe involvement may have general impairment of declarative memory, while those with frontal lobe involvement have special difficulties with episodic memory.

An example of the influence of frontal lobe dysfunction on memory is seen in a study by Schacter, Harbluk and McLachlan (1984) (cited in Schacter, 1987). In this study, amnesics who performed poorly on the Wisconsin Card Sorting Test (WCST) and a word fluency test, both sensitive to frontal lobe dysfunction, were told fictional items about both well known and unknown people (e.g., "Bob Hope refuses to eat chicken"). Later, both controls and amnesics were tested for both item recall, and the source of the information. When recall levels were controlled, the amnesics showed a disproportionate poverty of recall for the source (the experimenters) of the information. The inability to recall the circumstances under which they acquired the information indicates a loss of space and time context in their memory.

Deficits in frontal lobe function on specific testing are well documented in Parkinson's patients, using such tests as the Wisconsin Card Sorting Test, Stroop, and verbal fluency (Cummings, 1988; Litvan, Mohr et al., 1991; Starkstein et al, 1987; Taylor et al., 1986). Parkinson's patients are also impaired in temporal sequencing, ordering and recency judgements (Brown and Marsden, 1990). Defective spatiotemporal deficits may underlie the episodic memory disorder in PD.

Highly specific memory deficits have been demonstrated in Parkinson's disease. Tests that have shown impairments in this population are the Paired Associates and Logical Memory passages from the Wechsler Memory Scale (Hietainen and Teravainen, 1986; Huber et al., 1986; Litvan et al., 1991; Mohr et al., 1987; Pillon et al., 1989; Taylor et al., 1986). In fact, the majority (71%) of nondemented patients in one report showed at least mild memory deficits on the WMS (Sullivan et al., 1989b). Short term memory is also reported to be impaired in PD while long term memory is intact (Sullivan and Sagar, 1989b). Recognition memory tends to be better than recall memory in PD (Brown and Marsden 1990; Flowers, Pearce and Pearce, 1984; Taylor et al., 1986). The levodopa therapy that ameliorates motor symptoms in PD is also associated with memory improvement on Logical Memory and Paired Associates (Mohr et al., 1989). Bradykinesia is positively correlated with recent memory impairment (Riklan et al., 1989). Increasing severity of the illness is associated with increasing deficits on memory for temporal order (Goldenberg, 1990; Sullivan and Sagar, 1991a). This disorder of temporal ordering is not a result of degraded memory for the individual stimuli (Vriezen and Moscovitch, 1990).

Parkinson's patients are sensitive to the effects of proactive interference (Tweedy et al., 1982), especially in episodic and semantic memory (Helkala et al., 1989). Even relatively high functioning PD patients show impairments on Logical Memory passages in addition to visuospatial memory for the Rey-Osterrieth figure (Mohr et al., 1990a). Word list learning, both on the Rey Auditory Verbal Learning Test (Taylor et al., 1986a) and on a selective reminding memory test similar to the Buschke Selective Reminding Test, has also been found to be impaired in nondemented patients (Fischer et al., 1990). Immediate and remote memory do not tend to be affected in this population (Agid et al., 1986; Huber et al., 1986), as well as generic or semantic memory, or memory for facts and information not embedded in time and place (Mohr et al., 1989). Visuospatial memory, as tested by the Visual Reproduction on the WMS, and the three minute delayed recall on the Rey-Osterrieth figure, indicate impairments even in high functioning Parkinson's patients (Mohr et al., 1990a). Greater impairments have been found on visuospatial tasks than verbal tasks when drawing on working, or immediate memory (Bradley, Welch and Dick, 1989) and on recognition memory (Sullivan and Sagar, 1989a).

Implicit memory, as tested with a pursuit rotor motor task and lexical priming task, may be impaired in demented,

but not nondemented, PD patients, and the deficits are correlated with degree of dementia and not motor dysfunction (Walicke and Butters, 1989). However, these results were not replicated in a later study, which found that difficulties on the rotor pursuit task were not associated either with general cognitive function or primary motor dysfunction (Harrington et al., 1990). A later study failed to replicate impairments on rotor pursuit, but found them on a different skill acquisition task (Bondi and Kaszniak, 1991).

Although it has been suggested from reaction time experiments that because PD patients do not show evidence of slowing of internal mental processing and therefore should not experience decrements in access to semantic memory (Hines and Volpe, 1985), deficits in semantic memory have been demonstrated in some conditions. When PD patients are impaired on confrontational naming, they are also impaired on verbal fluency in both single letter and category conditions. Such impairment of semantic access is not related to problem solving ability, generation of category labels, speed of verbal production (Beatty, Monson and Goodkin, 1989) or task switching (Gurd and Ward, 1989).

An interesting question is whether the memory deficits in Parkinson's disease can be credited to defective contextual or spatiotemporal processing and thus

attributable to frontal dysfunction as opposed to involvement of nonfrontal, temporal and diencephalic memory systems. Such a spatiotemporal encoding mechanism has been proposed to account for impairment in the ordering of remote memories (Growdon and Corkin, 1986). Although some authors have targeted effortful memory systems (i.e. episodic) (Newman, Weingartner, Smallberg and Calne, 1984; Weingartner, Burns, Diebel et al., 1984) as the essential memory deficit in PD, Schacter (1987) refutes this argument in a discussion of effortful versus automatic processing of spatiotemporal information. His position is that such processing is relatively noneffortful and automatic. Although episodic memory, which is encoded in a space-time context, is often impaired in Parkinson's patients, to differentiate memory systems on an axis of effortful/noneffortful implies a deficit in generalized cognitive ability. There is greater heuristic value in looking at episodic memory disorder as secondary to an underlying deficit of spatiotemporal organization.

Recall of the Wechsler Memory Scale Logical Memory Passages and Paired Associates may reflect deficits in sequencing and organizing verbal material, i.e., ordering items in a paragraph coherently, and pairing words, so that recall is inefficient. When memory involves conceptual

manipulation, or distraction is applied, memory function in Parkinsonian patients is affected (Agid, Ruberg, Dubois et al., 1986). It may be, as Schacter (1987) argues, that the 'effortful' component of memory actually reflects direct frontal lobe influences on memory. The difficulties in this area are due to a lack of detailed and specific information on cortex spared and affected in PD, in addition to problems in precise localization of function in frontal lobes in humans.

14 Appendix G: Information for Study Participants

Title: A Neuropsychological Analysis of Dementia in Parkinson's Disease

Principal Investigator: Lorraine McFadden, M.A.,
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Supervisor: Dr. Erich Mohr
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Purpose: Some people with Parkinson's disease develop pronounced difficulties with memory and thinking. This study will investigate these difficulties in detail in order to better understand their development and progression.

Procedures: All subjects who agree to participate will undergo the following procedures.

- 1) Neuropsychological testing of thinking and memory requiring 5 to 7 hours, in one and one half hour segments (separate appointments).
- 2) A brief physical and neurological examination to be conducted at the Parkinson's Disease Clinic at the Ottawa Civic Hospital.
- 3) Most medicines for Parkinson's disease will be discontinued 2 to 3 hours before testing, and will be restarted right after each testing session.

Risks and Discomforts: The testing procedures may involve minor fatigue during sessions.

Benefits: No immediate, personal benefit may be derived from participation.

Refusal and Withdrawal: You are free to refuse to participate, and are free to withdraw from this study at any time, without affecting your future treatment.

Confidentiality: Hospital staff involved in this project will have access to your medical records. All information collected regarding your participation will be identified by number only. Should the results of this study be reported or published, individual names or any identifying data will not be used.

Inquiries: All questions regarding the procedures of this study should be directed to:

Lorraine McFadden
Carleton University
Colonel By Drive
Ottawa, Ontario, K1S 5B6
(613) 724-6551 or

Dr. Erich Mohr
Ottawa Civic Hospital
1053 Carling Ave.
Ottawa, Ontario, K1Y 4E9
(613) 761-4000 extension 3260.

Date

Signature of Participant

Date

Signature of Next of
Kin/Witness

15 Appendix H: Consent Form

A Neuropsychological Analysis of Dementia in Parkinson's Disease

I, _____ agree to participate in the Neuropsychological Analysis of Dementia in Parkinson's Disease study. I have read, understood, and signed the information sheet describing this study attached to this consent form. I have been given the opportunity to discuss it with the investigator, and my questions have been addressed to my satisfaction. I understand that I may withdraw my participation at any time or refuse procedures without penalty or loss of any benefits to which I am otherwise entitled. I have been assured that all documentation regarding my participation in this study will be kept confidential.

Date Signature of Participant

Date Signature of Next of Kin

I have explained the above study and certify that to the best of my knowledge the subject/next of kin signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

Date Signature of Investigator

16 Appendix I: Ottawa Civic Hospital Parkinson's Disease

Clinic Assessment

Initial Visit _____ Routine Visit _____

Study Visit _____

Date of Admission to Clinic

Date of First P.D. Symptoms

First P.D.

Symptom _____ R _____ L _____ Indef _____

Family History of

P.D. Yes No Possible

Other Diseases

Family

Physician

Education

Treatment Duration

Time Since Last Medication

Falls

Rating Scale for Parkinson's Clinic

(0 if absent or normal, .5 if less than 1)

Rest Tremor

RUE _____ LUE _____ RLE _____ LLE _____

Action or Postural Tremor

(RT) _____ (LT) _____

Rigidity (Neck) _____ (RT) _____ (LT) _____

Finger Taps (RT) _____ (LT) _____

Bradykinesia _____

Arising from Chair _____

Gait _____

Postural Stability _____

Blood Pressure

Sitting _____

Standing _____

Pulse _____

Age _____

Today's Problems Are:

Slowness _____

Fluctuations _____

Dyskinesias _____

Sleep Upset _____

Confusion _____

Hallucinations _____

Bladder Diff. _____

Impotence _____

Constipation _____

G.I. Upset _____

Depression _____

Others 1) _____

2) _____

3) _____

Atypical Features (Yes or No)
Drug Aggravated _____
Possible _____
Postural Hypotension _____
Oculomotor Defect _____
Absent or Atypical Rest
Tremor _____
Early (< 3 years) Dysarthria
or Dysphagia _____
Neurogenic Bladder or
Impotence _____
Early (< 3 years) Postural
Instability _____
Atypical Gait _____
Pyramidal or Focal Neurologic
/Neuropsychologic
Signs _____
Longstanding Severe
Hypertension _____
Poor Levodopa
Response _____
Early Dementia (< 2
years) _____
Candidate for
Study? _____
Comments _____

Social History
Marital Status
 M W D S
 Other Living With Patient

Type of Residence
Occupation
 Working? Yes No
Knowledge of P.D.
 Yes No Partial
Member P.D. Society Y N

Health Teaching
P.D. Symptoms
Medications
Side Effects
Others

A.D.L.
Self Sufficient? Yes ___ No ___
Assistance With? _____
Mobility W/C Walker Cane _____
Community Resources
V.O.N. _____ Homemaker _____
Physio _____ Other _____

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Medication Record

Allergies _____

Medication History for P.D.

Initial	Date Y/M/D	Name of Drug	Dose	Administra tion Time	Star t	Sto p	Reason

Current Medication

17 Appendix J: Rating Scale for Parkinson's Clinic

(Score 0 if absent, or Normal and).5 if less than 1)
Hoehn and Yahr Scale:

- Stage 1: Unilateral involvement only
- Stage 2: Bilateral involvement without impairment of balance
- Stage 3: Mild to moderate bilateral involvement
- Stage 4: Severe disability; still able to walk or stand unassisted
- Stage 5: Wheelchair bound or bedridden unless aided

Resting Tremor 1: Slight and infrequently present; or frequently present and not bothersome to patient 2: Moderate; present most of time 3: Severe; interferes with many activities 4: Marked; interferes with most activities

Action or Postural Tremor 1: Slight ; present with action 2: Moderate in amplitude; present with action 3: Present with action with postural holding as well as action 4: Marked in amplitude, interferes with feeding

Rigidity 1: Slight 2: Mild to moderate 3: Marked, but full range of motion 4: Severe, range of motion achieved with difficulty

Finger Taps 1: Mild slowing and/or reduction in amplitude (11-14/ 5 sec.) 2: Moderately impaired; definite and early fatiguing; may have occasional rests in movement (7-10/ 5 sec.) 3: Severely impaired; frequent hesitation in initiating movements or arrest of ongoing movements (3-6/ 5 sec.) 4: Can barely perform the task (0-2/ 5 sec.)

Bradykinesia 1: Minimal slowness 2: Mild degree of slowness which is definitely abnormal 3: Moderate slowness, poverty of small amplitude of movement 4: Marked slowness, poverty or small amplitude of movement

Arising from Chair 1: Slow, or may need more than one attempt 2: Pushes self up from arm of seat 3: Tends to fall back and may have to try more than once 4: Unable to rise without help

Gait 1: Walks slowly, may shuffle with short steps 2: Walks with difficulty, but requires little or no assistance; may have some festination, short steps or propulsion 3: Severe disturbance of gait requiring assistance 4: Cannot walk at all, even with assistance

Postural Stability 1: Retropulsion, but recovers unaided
2: Absence of postural response, would fall if not caught by examiner 3: Very unstable 4: Unable to stand without assistance

Fluctuations/Wearing Off or On/Off 1: Slowing of gait with freezes and/or increase of tremor 2: Moderate increase of above disabilities but always able to function independently 3: Periods of complete immobility but mobile more than 75% of the day or patient has on/off 4: Mobile less than 75% of the day

Thought Disorder 1: Vivid dreaming 2: "Benign" hallucinations 3: Occasional to frequent hallucinations or delusions 4: Persistent hallucinations and delusions 5: Not able to care for self

Intellectual Impairment 1: Mild 2: Moderate memory loss with disorientation and moderate difficulty handling complex problems 3: Severe memory loss with disorientation for time and often to place; severe impairment in handling problems 4: Severe memory loss with orientation preserved to person only; unable to make judgements or solve problems; requires much help in personal care; cannot be left alone at all

Dyskinesia or Dystonia 1: Barely noticeable facial or limb involuntary movements or dystonic posture 2: mild involuntary movement or dystonic posture 3: moderate involuntary movements causing patient distress 4: Severe disabling involuntary movements

Akathisia 1: Looks restless, nervous, impatient, uncomfortable 2: Needs to move at least one extremity 3: Often needs to move one extremity or to change position 4: Moves one extremity almost constantly if sitting, or stamps feet while standing 5: Unable to sit down for more than a short period of time 6: Moves or walks constantly

Education 1: Gr. 13 = 13 B.A. = 16 M.A. = 18 M.D. or PhD = 20

18 Appendix K: Correlation Matrix for Profile Analysis

Table 24. Correlation Matrix of Dependent Variables in Profile Analysis: Three Subject Groups Combined

	LM	Info	DigSp	Vocab	Arith	Compn
LM	1.0000					
Info	0.2639	1.0000				
DigSp	0.3054	0.3512	1.0000			
Vocab	0.3661	0.7641	0.4111	1.0000		
Arith	0.4522	0.5977	0.6337	0.6088	1.0000	
Compn	0.3468	0.6667	0.3780	0.7658	0.6677	1.0000
Simil	0.2681	0.6069	0.5266	0.6348	0.6268	0.7328
PicCo	0.3418	0.3973	0.4682	0.3763	0.5962	0.4329
PicAr	0.4107	0.3028	0.4265	0.4725	0.5294	0.5307
BlkDes	0.5214	0.4155	0.5175	0.4990	0.6987	0.5906
ObjAss	0.4850	0.3882	0.4893	0.4415	0.6418	0.5614
DigSym	0.3912	0.3320	0.4368	0.4265	0.5796	0.4911

	Simil	PicCo	PicAr	BlkDes	ObjAss	DigSym
LM						
Info						
DigSp						
Vocab						
Arith						
Compn						
Simil	1.0000					
PicCo	0.5100	1.0000				
PicAr	0.5297	0.6162	1.0000			
BlkDes	0.5646	0.6688	0.7524	1.0000		
ObjAss	0.4652	0.6441	0.6510	0.8508	1.0000	
DigSym	0.4798	0.5928	0.6743	0.7506	0.6664	1.0000

END

09-12-93

FIN